Review

RM1 Semiempirical Model: Chemistry, Pharmaceutical Research, Molecular Biology and Materials Science

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In this review, we show improvements to the semiempirical quantum chemical method RM1 and present a wide range of its applications as reported by researchers of various areas, such as theoretical, organic, physical, analytical, and inorganic chemistry, as well as their interfaces with medicinal chemistry, biology, and materials science. Success of RM1 is seemingly due to its ability to predict structural, energetic, electronic and wave function dependent properties of the investigated systems, coupled with its low computational demand required to perform calculations when compared to *ab initio* and density functional methods. Moreover, RM1 is widely available in several computational chemistry softwares, such as MOPAC, GAMESS, Amber, Spartan, HyperChem, and AMPAC. This review describes various case studies that perhaps can be of interest to researchers who might need a more solid basis from which to expand the frontier of applicability of RM1 to even more complex problems on larger systems.

Keywords: RM1, Recife model 1, semiempirical methods, computational chemistry, quantum chemistry

1. Introduction

Semiempirical models for the quantum-chemical calculation of molecules have greatly developed since the seminal work by Hückel[1-3] in 1931 for the treatment of organic molecules with conjugated π systems. In 1963, Hoffmann[4] extended the Hückel method for non-planar molecules, and in 1965, Pople *et al.*[5,6] introduced the first semiempirical formalism that used an all valence electron antisymmetric wave function: complete neglect of differential overlap (CNDO). However, because CNDO was unable to differentiate between singlet and triplet systems, Pople *et al.*[7] then introduced a new formalism with fewer approximations: intermediate neglect of differential overlap (INDO). The most successful INDO parameterizations were those aimed at reproducing electronic spectra, such as Zerner's INDO (ZINDO).[8] Finally, Pople *et al.*[6,9] introduced NDDO (neglect of diatomic differential overlap), the most sophisticated of these Hartree-Fock based formalisms,

which includes all electron repulsion two-center integrals between charge distributions on two different atoms.

NDDO was the forerunner of many of the most successful semiempirical methods in current usage. There was even an ongoing discussion on whether some more fundamental aspects of quantum chemistry could be discovered through parameterization of the semiempirical equations,[10-14] although the debate was somewhat inconclusive. Nevertheless, one can always argue that, since the parameters are obtained from fitting the equations to reproduce experimental results, the parameters had to contain some chemical meaning. A multitude of semiempirical methods emerged at a time when the algebraic structure of quantum mechanics was already well defined, but, on the other hand, the processing power of computers was still 2 million times slower than today's computers, which limited the application of such methods to the study of chemical systems that contained only a few dozen atoms. From then on, the most successful ones were the NDDO semiempirical methods developed in Dewar's group:[15] MNDO (modified neglect of differential overlap), still widely used in different research fields, and

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AM1,[16] introduced in 1985, the most extensively used of the NDDO methods, which ensured a useful compromise between computing time and method accuracy. James Joseph Patrick Stewart, a former member of Dewar's group who also developed AM1,[16] later developed PM3,[17] which was also widely used because both methods were popularized by his MOPAC software,[18] which was distributed on a worldwide basis. Other attempts at developing other semiempirical methods were not as successful, if by success we mean worldwide usage coupled with widespread acceptance as a valuable technique in several research fields.

The next two decades saw a large increase in the processing capacity of computers together with the development of more computationally efficient and parallelized algorithms for first principles calculations. During this period no other semiempirical methods that were freely available and more accurate than AM1[16] or PM3[17] experienced a widespread usage on a worldwide basis. Part of this was perhaps due to opposition to these methods by the first-principles advocates. These combined factors created a vacuum in the semiempirical model research leading to a decrease of interest on the part of the scientific community in such methods.

However, it was this very increase in the processing capacity of computers and the development of more computationally efficient and parallelized algorithms that provided the necessary conditions for the more recent resurgence of semiempirical calculations of systems containing hundreds and even thousands of atoms such as proteins and solid phase structures, such as zeolites and metal-organic frameworks (MOFs): systems that are still completely outside the realm of contemporary density functional theory (DFT)/*ab initio* methods. Besides, pharmaceutical research started to require calculations on thousands of slightly different chemical structures for their combinatorial chemistry. Thus, accuracy of the extant semiempirical methods became an issue. Indeed, the most widely used methods in the early 2000s were still AM1[16] and PM3,[17] both developed a decade earlier.

In 1999, James Stewart attended the X Simpósio Brasileiro de Química Teórica, SBQT, in Caxambu, Minas Gerais, Brazil, and, immediately after, visited us in Recife. At the time, PM3 was already seven years old, and we felt that it was time to present a freely-available new and more accurate method to the worldwide scientific community: the RM1 (Recife model 1) project was born.

2. The RM1 Project

Generally, when trying to develop a new semiempirical model, researchers tend to focus on the algebraic structure of the method, usually attempting to increase the complexity of the formalism towards an increasing resemblance to the Hartree-Fock equations, including, for example, orthogonalization corrections. Sometimes attempts are made to develop semiempirical models that include concepts from even higher-level theories such as configuration interaction, propagators, and so on.

The decision was to maintain the AM1 formalism and focus, instead, on the parameterization procedure, using modern non-linear optimization techniques as well as some others developed by Stewart, all coded to tackle large multidimensional problems assessed by statistical techniques.

Due to the great complexity of the quest before us, the decision was also to consider systems composed only of the atoms H, C, N, O, P, S, F, Cl, Br and I. Most of the molecules of importance in biochemistry are made up of only six atoms: H, C, N, O, P and S. By adding the halogens, F, Cl, Br and I, the applicability of the method was greatly expanded, encompassing most systems of interest to organic and pharmaceutical chemistry research. RM1 was parameterized to reproduce the following experimental properties: enthalpies of formation, dipole moments, electronic charges, ionization potentials, and geometries (bond lengths and angles).[19] For that purpose, we used a parameterization set of molecules comprised of 1,736 species, including atoms and molecules of great importance for organic chemistry, pharmacy and especially biochemistry.

A significant advantage of retaining the complete formalism of AM1 is that the new parametrization could be instantly implemented in the myriad of extant computational chemistry programs by only changing the parameters associated with each of the atoms. Accordingly, from the year 2000 to 2006, lengthy parameterizations were tried by our group, albeit with little success.

Suddenly, a new parameterization led to consistent results that proved to be impossible to perfect at the time. The new parameters were sent to James Stewart for assessment and, having passed all the very stringent tests at the time, became the RM1 set of parameters. According to our original article,[19] "the problem of the net charge in nitrogen extant in PM3, is corrected in RM1. As is well known, PM3 net charges for amines are close to zero, whereas for nitro compounds they are too positive. Indeed, PM3 nitrogen charges for methylamine and nitromethane are, respectively, $-0.03e$ and $1.24e$, whereas the corresponding values for RM1 are $-0.44e$ and $0.40e$", where e stands for the elementary charge.

RM1 displays overall smaller average unsigned errors (AUE) associated to these properties when compared

to the previous Dewar semiempirical methods that only use monatomic parameters. For example, the AUE for the enthalpy of formation of AM1[16] and PM3[17] methods average, respectively, 11.15 and 7.98 kcal mol^{-1}, whereas for RM1 this value is only 5.77 kcal mol^{-1}. Likewise, the AUE in the dipole moments are 0.37 and 0.38 D, respectively, for AM1 and PM3, whereas for RM1 it is only 0.34 D. Similar AUE for the ionization potentials average 0.60 and 0.55 eV, while for RM1 this is only 0.45 eV. Further, the AUE in the interatomic bond distances are 0.036, 0.029, and 0.027 Å for AM1, PM3, and RM1, respectively. AM1 displayed the smallest error in the bond angles, 5.88°. Nevertheless, the RM1 bond angle error is 6.82°, smaller than the bond angle error of PM3 (6.98°).

As expected, the RM1 method was quickly implemented in several well-distributed programs, such as MOPAC,[18] Spartan,[20] GAMESS,[21] Amber,[22] HyperChem,[23] AMPAC,[24] MATEO,[25] eLBOW,[26] pDynamo[27] and ConGENER.[28] Of course, the advantage of RM1 over DFT and *ab initio* methods is the much reduced computation time for performing simulations.

To accelerate RM1 and other semiempirical calculations even more, Rocha and co-workers[29] recently developed a new version of MOPAC capable of performing the quantum chemical calculations in a parallel manner. In this investigation, some modifications to the MOPAC program source code were introduced to boost single-point energy calculations (1SCF) of medium-sized molecular systems (up to five thousand atoms) using GPUs. The authors used a combination of highly optimized linear algebra libraries for both GPU (MAGMA and CUBLAS) and CPU (LAPACK and BLAS from Intel MKL), with new GPU codes to accelerate some parts of the MOPAC2009 program that are time consuming, such as: pseudo-diagonalization (DIAG subroutine), full diagonalization (RSP subroutine) and assembly of the density matrix (DENSIT subroutine). For example, a 1SCF calculation for a methanol simulation box containing 2400 atoms and 4800 basis functions running serially took about three hours. When the authors adopted their strategy and used parallel procedures on the GPU with the same CPU (GPU, GTX-580), the same calculation took about four minutes, resulting in a speedup of about 44 times.[29]

The increase in computational power the scientific community is experiencing these days has allowed the complete quantum chemical computation of molecular systems containing more than a thousand atoms in conventional computers, and more than two million atoms in computer clusters. This fact creates the real possibility of studying and presenting new understandings of important phenomena in biochemistry, biotechnology and nanotechnology that require a wave function.

This review presents the improvements made to RM1 since its release in 2006, as well as its usefulness and applications to areas ranging from organic, physical, analytical, and inorganic chemistry, and to their interfaces with medicinal chemistry, biological chemistry and materials science.

3. RM1 Improvements

Since its publication, other research groups have significantly widened the scope of RM1[19] through various implementations and/or improvements.

In the year following the publication of RM1, Fekete *et al.*[30] introduced multiple protocol parameters named semiglobal semiempirical self-consistently scaled quantum mechanical (S4QM). The authors used a global adjustment for frequencies, embodying molecular descriptors corresponding to various types of vibratory modes. Through comparisons with the data published by Scott and Radom,[31] they concluded that the new methods (RM1[19] and PM6[32]) are better compared to their predecessors. In addition, the implementation of the S4QM protocol further reduced observed errors.

In 2008, Forti *et al.*[33] published the parameterization of the Miertus-Scrocco-Tomasi (MST)/RM1 continuous solvation model for neutral solutes in solvents, such as water, octanol, chloroform, carbon tetrachloride and for ions in aqueous solutions. The test set applied to the parameterization of the MST/RM1 method had free energies of solvation of 84 different systems that were not considered in the parameterization process. According to the authors:[33] "the root-mean square deviation (rmsd) between theoretical and experimental solvation-free energies are very close to the uncertainties obtained for the *ab initio* versions of the method".

The following year, Prof Yu and co-workers[34] presented a modification of the RM1 model to calculate the binding energy of hydrogen bonding. This model called RM1$_{BH}$ was formulated by adding, to the core-core repulsion terms, Gaussian functions in the RM1 model. Parameterization was then performed to reproduce the binding energies of hydrogen bonding, both experimental and obtained from high-level calculations (B3LYP/6-31G**/BSSE (basis set superposition error) and MP2/6-31G**/BSSE). In the process, the authors considered 35 base-pair dimers, 18 amino acid residue dimers, 14 dimers between a base and an amino acid residue, and 20 other dimers. In the validation process they concluded that, among the semiempirical methods, RM1$_{BH}$ presented the smallest overall average error when they compared the calculated values with the values obtained either experimentally or from MP2 calculations.

In 2010, Herman[35] used the mixed model RM1/AM1 by using RM1 parameters for H and C atoms, together with AM1 parameters for Si to demonstrate a controlled manipulation of silylene molecules at the subnanometer scale. This work provided an incentive to extend the parameterization of RM1 to the remaining elements of the periodic table. However, it is not an easy task to proceed with the parameterization of so many atoms while retaining the high accuracy already achieved for the first 10 parameterized atoms. Recently, we have completed the parameterization for the 15 lanthanide trivalent ions.[36-40]

Aiming at increasing the accuracy of semiempirical methods for the study of biomolecules in aqueous medium, Anisimov and Cavasotto[41] sought to optimize the atomic radii and surface tension coefficients associated to the continuum solvent conductor-like screening model COSMO. Moreover, the authors introduced a multiple atom-type for hydrogen, nitrogen and oxygen (see Table 1). For the elements C, F, P, S, Cl, Br, and I this procedure was not necessary.

Table 1. Different atom-types for hydrogen, nitrogen and oxygen considered in the parameterization of COSMO by Anisimov and Cavasotto[41]

Atom	Hydrogen	Nitrogen	Oxygen
Type 1	polar	nitro-group	hydroxyl
Type 2	nonpolar	cyano-group	deprotonated hydroxyl
Type 3	–	amine	carbonyl
Type 4	–	protonated	ether
Type 5	–	generic	noncarbon connected sp2
Type 6	–	–	protonated oxygen
Type 7	–	–	generic

The model was parameterized for AM1, PM3, PM5 and RM1 to reproduce the free energy of hydration. These parametrizations were tested for a set of 507 neutral and 99 ionic molecules resulting in AUE for neutral molecules of 0.64, 0.66, 0.73, and 0.71 kcal mol^{-1} for AM1, PM3, PM5, and RM1 models, respectively. There is no doubt that these binding free energies in biomolecular systems are of relevance. According to the authors, the set of parameters will contribute considerably to an increase in accuracy associated with these calculations. They attributed the good results to the introduction of multiple atomic-type scheme in the COSMO model.

In 2012, Forti *et al.*[42] proposed a multilevel scheme to perform a conformational analysis of molecules. This scheme is based on the predominant-state approximation, which divides the conformational space into different conformational wells.[42] The procedure applies the semiempirical RM1 version of the MST continuum solvation model for sampling the conformational minima and subsequently performs a Becke, three-parameter, Lee-Yang-Parr (B3LYP, gas phase) or MST-B3LYP (solution) geometry optimization, followed by single point MP2 calculations using Dunning's augmented basis sets for calibrating their relative stability.[42] A strategy applied by the authors to calculate the free energy of a conformational well in the gas phase is given by equation 1:[42]

$$G_i^{MULTI} = E_i^{MP2} + ZPE_i^{B3LYP} + G_i^{RM1,local} \qquad (1)$$

where E_i^{MP2} is the energy of the minimum determined at the MP2/aug-cc-pVDZ (or MP2/aug-cc-pVTZ) level, the term ZPE_i^{B3LYP} is the zero-point energy correction at the B3LYP/6-31G(d) model chemistry and the term $G_i^{RM1,local}$ is the local free energy contribution of well "i" calculated via RM1 sampling.[42]

For the calculation of the free energy of a conformational well in solution, they applied equation 2:[42]

$$G_i^{MULTI} = E_i^{MP2} + ZPE_i^{IEF-MST//B3LYP} + \Delta G_{hyd,i}^{IEF-MST} + G_i^{MST-RM1,local} \qquad (2)$$

where the term E_i^{MP2} is the same as in equation 1; $ZPE_i^{IEF-MST//B3LYP}$ is the zero-point energy correction at the integral equation formalism (IEF)-MST/B3LYP/6-31G(d) level, $\Delta G_{hyd,i}^{IEF-MST}$ is the hydration free energy derived from IEF-MST calculations, and $G_i^{MST-RM1,local}$ is the local free energy contribution of well "i" calculated via MST-RM1 sampling. According to the authors, this multilevel scheme proved to be successful, mirroring the change introduced by solvation in the conformational preferences of the complexes of interest.

Also in 2012, Řezáč and Hobza[43] implemented the D3H4 dispersion and hydrogen bond correction in AM1, PM3, OM3, PM6, RM1, and density functional based tight binding (DFTB) methods. This correction uses the D3 formalism proposed by Grimme[44] whereas the hydrogen-bonding corrections were designed and can be used for geometry optimization and molecular-dynamics simulations without any limitations. The S66x8 data set was used in the parameterization of correction D3H4 for each of the previously mentioned methods. Results indicated that DFTB-D3H4, PM6-D3H4, and RM1-D3H4 showed root mean square deviations (RMSDs) of 0.62, 0.66, and 0.90 kcal mol^{-1}, respectively. Because they presented errors lower than 1 kcal mol^{-1}, these methods can be considered of high accuracy.

Our research group[45] parameterized the Sparkle model for RM1 for the calculation of lanthanide complexes, which became known as Sparkle/RM1. The Sparkle model

consists in representing the trivalent lanthanide ion by a Coulombic charge of +3e superimposed to a repulsive exponential potential of the form exp(–αr) to resemble the size of the ion.[46] The Sparkle/RM1 was parameterized following the same procedure adopted in the development of its predecessors: Sparkle/AM1,[47-55] Sparkle/PM3[56-62] and Sparkle/PM6.[63] Considering all fifteen trivalent lanthanide ions, the Sparkle validation set is composed of 604 different complexes displaying a wide variety of ligands. The Sparkle/RM1 average unsigned mean error (UME) for the distances between the lanthanide ion and its coordinating atoms is 0.065 Å for all lanthanides, ranging from a minimum of 0.056 Å for Pm[III] to 0.074 Å for Ce[III], making Sparkle/RM1 "a well-tempered method across the lanthanide series".[45] Thus, the Sparkle/RM1 geometries can therefore be used as a starting geometry to compute other properties by any other methods, *ab initio* included. More recently, our group[36-40] performed a parameterization of the RM1 model also for the fifteen trivalent lanthanide ions, this time considering a semiempirical basis set of 5d, 6s, and 6p orbitals. The RM1 UME for all lanthanides, now range from a minimum of 0.04 Å for Dy[III],[39] Ho[III][39] and Er[III][39] to 0.08 Å for Ce[III],[39] Yb[III][37] and Lu[III] trivalent ions.[37]

Recently, Vázquez *et al.*[64] reported a strategy for "3D molecular overlays that exploits the partitioning of molecular hydrophobicity into atomic contributions in conjunction with information about the distribution of hydrogen-bond (HB)". This method was implemented in the PharmScreen software, and the authors added the derivation of the fractional hydrophobic contributions that included a quantum mechanical version of the MST continuum model.[64] The authors commented that the choice of implementing their strategy in RM1 was due to this model's low computational demand: "The hydrophobic descriptors were obtained by using the MST solvation model parameterized for the semiempirical Hamiltonian RM1. Choice of this level of theory was motivated by its low computational cost compared to *ab initio* methods".[64] The authors compared the performances of MST/RM1 and MST/B3LYP to evaluate the effects of the method to calculate the hydrophobic contributions, having obtained similar results. In conclusion, the authors mentioned: "Therefore, these findings support the suitability of the semiempirical RM1 Hamiltonian, which offers a much better balance between overlay accuracy and computational expensiveness".[64]

4. Organic Chemistry

First, let us start with the applications of RM1 in organic chemistry research, mainly to: (*i*) structural, and spectroscopic properties;[65-97] (*ii*) energy, and electronic properties;[81,85,98-122] and (*iii*) reaction pathways.[109,123-127]

4.1. Structural and spectroscopic properties

Several articles reported usage of RM1 to optimize geometries of organic compounds.[65-97] This procedure allows the researcher to interpret structural properties, such as bond lengths, bond angles and conformations as a whole. An important application of these computational studies is the possibility of assessing the effects on the structures due to modifications on the lead molecules.

Structures of several organic molecules obtained by X-ray crystallography[65,78,82,84,91] have been compared with RM1 predicted geometries, these include thiazolylhydrazone,[84] 1-cyanoacetyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles,[82] 2,5-dimethyl-3,4-dihydro-2*H*-pyran-2-carboxylic acid,[78] 4-butyloxyphenyl 4'-decyloxybenzoate,[65] and 2,2-bis(4-cyanatophenyl) propane.[91]

As Havlík *et al.*[88] describes for some compounds that are not easy to obtain in the form of a single crystal, computational methods, such as RM1, constitute a very important tool. RM1 can also be used instead of higher level *ab initio* calculations because of the low computational cost and competitive accuracy, such as in the case of Callipeltin A.[76] In this sense, Richter *et al.*[76] reported: "The semiempirical method RM1 can be safely used to obtain the optimized geometries of large molecules prior [to] coupling constants calculations. This result represents an immense saving of time, since the geometry optimization is effectuated in a little fraction of the time required by an ab initio or DFT method".

Of course, the low computational demand of RM1 facilitates its application in studies of very large organic systems, such as supramolecular compounds, as was reported in 2014 by Mattarella *et al.*:[128] "Due to its large size, the RM1 semiempirical Hamiltonian method was used to theoretically investigate the structural aspects of compound **18**, in particular, to investigate the potential for aggregation into cage-like supramolecular arrangements".

RM1 was also employed by researchers to calculate spectroscopic properties of organic molecules.[83,85] For example, coupling constants of ^{1}H nuclear magnetic resonance (NMR) spectra of the type $^3J_{HH}$ of the hydrogen nuclei chemical shifts were predicted using RM1. To obtain realistic results of ^{1}H chemical shifts from gauge-independent atomic orbital (GIAO)[129] calculations, it is very important to arrive at a high-quality structure, because GIAO is very sensitive to variations in the molecule geometry. Indeed, inaccurate geometries might lead to unrealistic

values of calculated ^1H chemical shifts. Richter *et al.*[76] also reported ^1H NMR data by using the semiempirical method PM6, as well as by employing the DFT methods (mPW1PW91/6-31G(d,p), B3LYP/6-31G(d,p) and PBEPBE/6-31G(d,p)). According to the authors: "For RM1, on the other hand, the results become even better than the DFT method. Therefore, the use of semiempirical methods shows to be a serious alternative to obtain the optimized geometries for coupling constants calculations, instead to be viewed as just a manner to determine preliminary geometries for the robust QM calculations".[76]

The high structural quality was also the reason for Hu *et al.*[77] to employ RM1 as the theoretical method of choice in their investigation of quantitative structure property relationships (QSPR). In their study, RM1 was used to describe models for predicting reaction rate constants for the chemical reactions of reductive debromination of polybrominated diphenyl ethers by using zero-valent iron. Hu *et al.*[77] remarked: "In this study, we utilized a new generation semiempirical RM1 method to obtain more accurate molecular parameters instead of using AM1 method which has been chosen by the previous researchers [6,7,13], since RM1 maintains the mathematical structure and qualities of AM1 while it significantly improves its quantitative accuracy [14]".

Spectroscopic data were investigated by using RM1 geometries optimized, such as data of the vibrational infrared and visible absorption spectroscopies.[85]

In 2010, our research group[83] reported a strategy to study a set of fluorene derivatives that are capable of absorbing two-photons. The strategy used was to first employ RM1 to optimize the geometries of the organic compounds considered, and then to take these structures to calculate the spectroscopic properties of the molecules by a sum over states approach to INDO/S results. This work confirmed the usefulness of RM1 in predicting two-photon absorption cross sections of these organic molecules.

Another use of RM1 semiempirical method by organic chemists is in the prediction of structural aspects of the transition states of molecules.[75,92] Hypotheses related to conceivable transition states are very common and important to elucidate reaction pathways. However, it is not easy to find evidence of the formation of transition states during a chemical reaction. Therefore, quantum chemical computational studies are very important to obtain such information. Structural properties of the possible transition state molecules formed during organic syntheses were calculated by using RM1[75,92] for organic syntheses that led to the formation of the following products: a set of ring-expanded calystegine B2;[75] N-protected species;[75] and [2]rotaxane.[92]

Syntheses of organic compounds can also result in several conformer possibilities. Indeed, the presence of structural conformers is very common in extraction procedures of natural products.[130-132] Therefore, to interpret data characterizations, such as data obtained by spectroscopy, and/or diffraction techniques, the optimized geometries of the target compounds can be useful. In this sense, RM1 semiempirical method was employed to evaluate various conformer possibilities of organic compounds that are formed during chemical reactions.[66-69,73,80,86,87,90,95,96] The energetic properties, such as enthalpy of formation, are very important in the conformer studies, as will be shown in the next section.

4.2. Electronic and energetic properties

RM1 semiempirical method was parameterized to calculate dipole moments and enthalpies of formation, with errors smaller than those for AM1 and PM3.[19] In terms of electronic properties, there are several articles that reported the usage of RM1 to calculate the dipole moments of organic species.[71,100,104,107,133] These articles reported dipole moment data for the following compounds: 4-hydroxy-2,5-dimethylphenyl-benzophenone;[71] structural conformers of the *trans*-1-acetyl-4,5-di-*tert*-butyl-2-imidazolidinone;[104] 1-(2-quinolyl)-2-naphthol, which is an intra-intermolecular photoacid-photobase molecule;[133] cinnamoyl pyrones;[107] 2,6-dibromo-4-[(*E*)-2-(1-methylquinolinium-4-yl)ethenyl]-phenolate and 2,6-dibromo-4-[(*E*)-2-(1-methylacridinium-4-yl)ethenyl)]phenolate.[100]

Dipole moment values can be useful for a chemist in the sense that they can be considered additional characterization data, of importance for the interpretation of other properties, such as solubility in either organic or in aqueous solvents.

Energetic properties of organic compounds can be calculated in both forms: isolated, and in solvent medium. The solvent effects on the RM1 energetic properties of organic compounds[77,100,101,105-108,122,123,125-127,133,134] have been calculated, for example, by using the COSMO polarizable continuum model.[135]

Another important aspect of RM1 is the easiness to perform the calculations. Indeed, Mathieu[117] reported in the computational details of his article: "Typical errors associated with RM1 formation enthalpies are about 20 kJ mol^{-1} [32] while experimental uncertainties may cause much larger errors (>100 kJ/mol). Therefore, no significant improvement is expected from the use of more accurate procedures. Larger theoretical uncertainties might possibly arise from the use of the RM1 orbitals to obtain the reactivity descriptors. Therefore, we have also

investigated in unpublished work the use of enthalpies and orbital energies derived from PBE0/6-31+G(d,p)//AM1 calculations combined with simple atom equivalent schemes [34]. It turned out that this higher theoretical level does not provide any significant improvement with respect to RM1-based procedures. Because RM1 calculations are much easier to carry out routinely in an industrial context, only the results obtained on this basis are presented in the sequel". In this article, Didier Mathieu reported the significance of the predicted enthalpy values associated in the decomposition of a set of nitroaromatic compounds. A conclusion of this investigation was that the use of energy theoretical values provides a valuable criterion to characterize thermal hazards.[117]

Energetic properties of organic compounds[98,100,107-109,112,113,116,118-122] are very important to find the most favorable structure. As previously noted, RM1 semiempirical method was employed to evaluate conformer possibilities of organic compounds, such as: arylazo phosphate dimer;[87] (1*R*,2*R*,6*S*)-3-methyl-6-(1-methylethenyl)cyclohex-3-ene-1,2-diol;[86] isomeric carbocations 9,9-dimethyl-10-*R*- and 9-*R*-9,10-dimethylphenanthrenyl, as well as of 3-*R*-2,3-diphenylbutan-2-yl and 1-*R*-2-methyl-1,2-diphenylpropan-1-yl cations;[80] 2,5-dihydropyridazine-4-carboxylate and 1,4-dihydropyridazine-3,5-dicarboxylate derivatives;[73] aurones synthesized by intramolecular cyclization of monobrominated (+)-usninic acid;[72] substituted cryptophane derivatives;[69] nitrogen-containing derivatives of (18α,19β)-19-hydroxy-2,3-secooleanane-2,3,28-trioic acid 28,19-lactone;[68] aryl and alkyl chlorophosphates;[67] spirocyclic nitroxides of 2,5-dihydroimidazole compounds;[66] lyoniresinol stereoisomers;[95] and 4- and 5-mono- and 4,5-disubstituted 3,3-diphenyl-3*H*-pyrazoles.[95]

An interesting strategy to study conformational flexibility of small molecules, of importance in drug design, was reported by Forti *et al.*[42] The reported strategy consisted in combining low-level methods such as RM1, to calculate the conformational minima and high-level techniques to calibrate their relative stabilities. The reason for the choice of RM1 as the low level method is stated as: "This choice is motivated by the fact that the RM1 method retains the formalism of AM1, PM3, and PM5 Hamiltonians but has been reparametrized using data of 1736 compounds relevant in organic and biochemical areas, leading to an improved accuracy compared to the former semiempirical methods. More importantly, this choice allows us to take advantage of the recent implementation of the MST continuum model in the RM1 framework for the calculation of solvation free energies…".[42] The authors concluded that RM1 as the

low-level method to predict conformational flexibility of small molecules is useful: "For instance, though the RM1 Hamiltonian was chosen as a LL (low-level) method, the conformational sampling could benefit from the use of classical force fields, which would reduce substantially the computational burden needed for identification of conformational wells for very flexible molecules".[42]

Further, Juárez-Jiménez *et al.*[96] extended this computational strategy to the prediction of the conformational possibilities of a series of phenylethylamines and streptomycin in aqueous solution. Their strategy was based on two types of computational methods used in a simultaneous manner. These methods were Metropolis Monte Carlo (MC) technique and RM1.[96] The reason for the choice of RM1 is reported by the authors: "First, this choice avoids the need to carry out the explicit parametrization of any (bio)organic ligand, as the RM1 method was developed using data of 1736 compounds relevant in organic and biochemical areas, thus avoiding the substantial effort and intrinsic limitations assumed in the force-field parametrization of drug-like compounds. Second, solvent effects can be accounted for consistently due to the implementation of the MST continuum in the RM1 framework".[96] Indeed, Juárez-Jiménez *et al.*[96] reported: "Nevertheless, because the multilevel results obtained from both MC(IEFMST/RM1) and MD(gaff) samplings are very consistent, the availability of generalized force fields for (bio)organic compounds appears promising for exploring the LL (low-level) sampling of drug-like compounds with classical simulations".

RM1 has also been employed by organic chemists to study energy aspects of the species formed during their syntheses. For example, Siwek *et al.*[136] evaluated an alternative synthetic route for compounds of the type 4-substituted-1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazoles that are potential candidates as bioactive substances. In this study, the authors tested RM1, and concluded: "In addition, we have shown that the new semiempirical method RM1 is capable of efficiently providing energetic and geometrical information about this class of compounds". They also tested other semiempirical methods and reported: "Although AM1 and PM3 erroneously predict higher stability of the thiol tautomer, RM1 yields this energetics correctly, with very good agreement with the results obtained at the DFT level. A comparison of the results obtained for thio- with oxo-compounds indicates that the RM1 method is an improvement over the older parameterizations".[136]

An investigation reported by de Araujo *et al.*[101] was performed in a systematic manner, by employing AM1,[16] PM3,[17] PM6,[32] and RM1[19] semiempirical methods to

calculate both structure, and energetic properties of inclusion reactions of pyrimethamine in the α-cyclodextrin (α-CD) cavity. In the characterization procedures of the organic compound α-cyclodextrin, de Araujo *et al.*[101] commented: "On the other hand, an α-CD structure very close to that determined from X-ray crystallography was optimized with RM1 method (Fig. 6(c and d)). In this structure some OH groups pointed toward the cavity while others were directed outside the cavity. Thus only the RM1 structure seems to be in agreement with the structure characterized by ROESY in aqueous solution, because in this case the hydroxyl groups can form hydrogen bonds with water molecules". Of course, the correct structure of the compound of interest is a decisive factor in studies on the nature of chemical reactions in a given solvent medium, such as water.

In addition, the RM1 method has also been employed by organic chemists to calculate the energy of the lowest unoccupied molecular orbital (LUMO), and of the highest unoccupied molecular orbital (HOMO), that are associated with the reactivity of organic compounds.[70,77,100,104-106,117,125] Organic compounds, that had their orbital energies (LUMO, and HOMO) calculated by RM1, include: 3-arylideneflavanone;[70] *E,Z* isomers of chromanone;[70] 3-arylflavones;[70] polymethine cyanine dyes in solutions of β-cyclodextrin;[106] *trans*-1-acetyl-4,5-di-*tert*-butyl-2-imidazolidinone;[104] a set of (*E*)-4-aryl-4-oxo-2-butenoic acids;[105] a set of nitroaromatic compounds;[117] species involved in a revised mechanism of Boyland-Sims oxidation;[125] 2,6-dibromo-4-[(*E*)-2-(1-methylquinolinium-4-yl)ethenyl]-phenolate;[100] and 2,6-dibromo-4-[(*E*)-2-(1-methylacridinium-4-yl)ethenyl)]phenolate.[100]

In this sense, a QSPR study reported by Hu *et al.*[77] employed the RM1 method to calculate geometry optimizations, energy, and electronic properties of a set of fourteen polybrominated diphenyl ether congeners, as such 2-mono-BDE (BDE-1), and 3-mono-BDE (BDE-2). The descriptors calculated by RM1 were used in statistical analyses based on artificial neural network models. Hu *et al.*[77] stated their reason for the choice of RM1: "In this study, we utilized a new generation semiempirical RM1 method to obtain more accurate molecular parameters instead of using AM1 method which has been chosen by the previous researchers [6,7,13], since RM1 maintains the mathematical structure and qualities of AM1 while it significantly improves its quantitative accuracy[14]".

The importance of the quality of the descriptor values described by Hu *et al.*[77] resulted in models for predicting reaction rate constants for reductive reactions of debromination of polybrominated diphenyl ethers by zero-valent iron. The authors conclude by statistical analysis of

RM1 data that the energies of the compounds, energy of the LUMO included, are important variables in their artificial neural network model.

Energetic properties of species formed during chemical reactions are widely employed by organic chemists to build energy surfaces.[110,111,114,115,137] By building energy surfaces, for example with structural, and thermodynamic data of species formed during the reaction, it is possible to carry out studies on the nature of the reaction pathways. The energy surfaces can result in the identification of the species most likely to occur from a thermodynamic perspective. Articles that reported the use of RM1 method for the prediction of energetic properties of conformer species of organic compounds, and to build an energy surface appeared.[110,111,114,115,137] In these studies, the RM1 method was used to predict the energetic properties of the transition states and intermediate systems, with their respective probabilities of formation for the following cases: conformational equilibria of six enantiomeric pairs of chiral α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol (TADDOL-s);[137] possible polymers formed during the electropolymerization of 3-hydroxyphenylacetic acid;[110] elucidation of factors that govern the selectivity of the sequence of reactions to synthesize homoallyl-homocrotylamine compounds;[111] chirality of methyl-tris(2,6-diisopropylphenoxy)silylsulfide;[115] and possible conformational structures of the polymers formed during the electropolymerization of 3-hydroxyphenylacetic acid.[110]

In surface energy studies, it is frequent to come up with transition states that are characterized by structures of either maximum energy or that can be characterized as saddle points in the potential energy surface, as described by Herman *et al.*[115] These authors justified their choice by RM1 in transition state investigations, as can be read: "The characterization of even a simple reaction potential surface may result in location of more than one transition state structure, and is likely to require many more individual calculations than are necessary to obtain equilibrium geometries for either reactant or product. For this reason, the semi-empirical RM1 method of estimation of transition state energy has been chosen…".[115]

Propositions of transition states and intermediate and transient compounds are very important in studies of photochemical reactions that can be initialized, for example, by electronic excitation of precursors due to external effects, such as light irradiation, which lead to photon absorption processes. This phenomenon results in excited species leading to the formation of electron isomers as is the case of transition states. Of course, the new species, present different structural, energetic, and vibrational properties from those of the corresponding ground state

species. In this sense, intramolecular proton transfer reactions in the excited state were studied by using the RM1 model.[133,138,139] This class of photophysical reactions occurs due to a proton transfer by the presence of intramolecular hydrogen bonds. Three cases that employed the RM1 model to investigate structural, and energetic properties of ground and excited states of organic compounds were: (*i*) in 3-methylsalicyclic acid and 3-methoxysalicyclic acid;[138] (*ii*) in 2-(benzimidazol-2-yl) derivative;[139] and (*iii*) in reactions between the naphthol and quinoline rings leading to 1-(2-quinolyl)-2-naphthol, which is a compound susceptible to proton transfer reactions in water and in organic solvents when electronically excited.[133]

From investigations of structural and energetic properties of compounds involved in a given chemical reaction, it is possible to postulate reaction pathways, such as those of the photochemical reactions with proton transfer by hydrogen bonds in a transition state species. The next section will describe usage of the RM1 method to describe structural and energetic aspects of organic species involved in reaction pathways.

4.3. Reaction pathways

Syntheses of organic compounds are much studied by reaction pathway perspectives. Usually, a given system can be synthesized by different routes, via different reaction pathways. The conjectured mechanism needs to be supported by experimental, and/or theoretical evidence, such as characterization data, chemical, and physical properties of the species formed during the chemical reaction under investigation.

The RM1 method was used to investigate the reaction pathways for the following cases: racemization processes of transition states in syntheses of diazabenz[*e*] aceanthrylene-based heterocycles;[102] the process of opening of the cyclopropane ring in carbocations derived from 9-cyclopropyl-10,10-dimethyl-9,10-dihydrophenanthren-9-ol in acid medium, that occur first by protonation of the cyclopropyl group, and then by a structural rearrangement of cyclopropyl–carbinyl;[109] oxidative polymerization processes of the compounds benzocaine,[126] and ethacridine;[123] oxidative reactions that obey the Boyland-Sims oxidation mechanism of the organic compounds aniline, several ring-substituted, such as 2-methylaniline, and 3-methylaniline, and *N*-substituted anilines, such as diphenylamine, and *N*,*N*-dimethylaniline;[125] a mechanism of the conformational rearrangement of the *N*-10-dodecyl-acridine orange (dye acridine range);[124] the rationalization of the factors that affect the formation of flavonols by reactions that follow the Algar-Flynn-Oyamada mechanism;[127] and the chemical fixation

of CO_2 with propylene oxide catalyzed by ammonium and guanidinium salts.[140] In these studies, RM1 was used for the description of reaction pathways, solely due to its perceived accuracy; comparisons with experimental or other theoretical calculations are yet to be performed.

5. Physical Chemistry

We verified that the main properties evaluated in physical chemistry research are the energetic properties of the studied systems, such as the enthalpies of formation and of reaction. These physical chemistry studies, generally, interface with other chemistry areas, such as organic and medicinal chemistry.

Energy quantities of the species harmane β-carboliniums derivatives, that are involved in the inhibition of cholinesterases were calculated by RM1 method.[141] In this article, Torres *et al.*[141] stated: "All calculations were carried out with the RM1 method, which was shown to have a better performance than earlier hamiltonians for the determination of ΔH_f (Rocha *et al.*, 2006); we also observed that the RM1-calculated geometries of sp2 N-containing groups (such as the side chains of histidine, tryptophan and arginine residues) are more planar than those obtained with the older hamiltonians".

Serdiuk *et al.*[142] reported the usage of quantum chemical methods, such as RM1 and M062X/cc-pVDZ to investigate structural and electronic aspects of 2'-hydroxychalcone derivatives. They mentioned: "The ratio of the long-wavelength and short-wavelength band area, equal to the oscillator strengths ratio of the corresponding transitions (f_1/f_2), does not correlate with the σ-para Hammett constants of the substituents. However, the f_1/f_2 values show linear dependence on the total charges of the substituents in the ground state, calculated by the semiempirical method RM1 ($r^2 = 0.987$). A worse correlation is obtained using the DFT method ($r^2 = 0.734$), but it generally reflects the tendency of the f_1/f_2 value increase with the increase of electron-releasing ability of substituent".[142]

RM1 energy quantities were also calculated in studies on the stability of structures of the sulfadiazine/hydroxypropyl-β-cyclodextrin host-guest;[143] on the investigation of the role of intermediate systems formed during oxidation of the SO_2 in sulfuric acid-water nucleation;[144] on inclusion reactions of the complex trimethoprim/2-hydroxypropyl-β-cyclodextrin;[145] and on electrodes processing by using cucurbit[6]uril, that are capable of detecting 3,4-methylenedioxymethamphetamine.[146]

Recently, Gibbs energies have also been calculated by the RM1 method, as well as by the improved methods RM1-DH2, and RM1-D3H4 that include dispersion

energy corrections, as can be seen in the work reported by Júnior *et al.*[147] Based on computational and quantitative structure-property relationships (QSPR), the authors concluded that the ability of donating electrons by the hydrogen bond acceptor is the most important property associated to the spontaneity of hydrogen bond formation, at least for the set of phthalimide derivatives considered.

Because of the large importance of the HOMO (E_H), and LUMO (E_L) orbital energy values, Morse *et al.*[148] reported comparisons between semiempirical methods (RM1 and PM3) and DFT methods. In this investigation, the authors chose as case study, a set of compounds of the type boronsubphthalocyanine: "We have compared the PM3 method with the newer RM1 method (albeit a mixed method due to the lack of RM1 parameters for boron) and the density functional theory method B3LYP and found that while the B3LYP method gave closer absolute estimates the semiempirical methods (PM3 and RM1) produced more accurate correlations between experimental and computed E_H and E_L data (eqs 1-6)".[148]

RM1 activation and reaction energies were reported by Barnes and Hase[149] that studied the fragmentation and reactivity by collisions of protonated diglycine with modified surfaces of perfluorinated alkylthiolate-self-assembled. In that study, the authors used a combination of programs VENUS[150] and MOPAC7.0[18] (a general public license program freely available) to perform molecular dynamics simulations. For each semiempirical method, 320 trajectories were calculated for a range of collision energies (E_i) from 5 to 110 eV with θ_i equal to 0° and 45°. The authors obtained theoretical results in excellent agreement with previous computational and experimental work, with average energy transfer at normal incidences falling within 2% of their experimental results. Barnes and Hase[149] remarked: "These comparisons, and those given above for concerted fragmentation of glyn-H$^+$, reaction of gly$_2$-H$^+$ with the CF$_3$COCl model of the COCl-SAM, and the model systems of gly$_2$-H$^+$ + COCl-SAM concerted reaction, indicate that RM1 provides at the very least, and maybe substantially better, qualitative energies for reactions of gly$_2$-H$^+$ in collisions with the SAM surfaces". Indeed, they also commented:[149] "In addition, though the ion/surface electrostatic interaction is described correctly by RM1, dispersion interactions are approximated".

By a physicochemical perspective, an interesting work was reported by Zhou *et al.*,[151] that questioned the need of the use of quantum mechanics (QM) methods for predicting binding free energies. RM1 method was employed to calculate energy quantities of a set of compounds that are capable to inhibiting West Nile virus NS3 serine protease (WNV PR), as well as the aspartic protease of the human immunodeficiency virus (HIV-1 PR) and the human cyclin-dependent kinase 2 (CDK2). The authors concluded: "Therefore, the comparison of LIECE and QMLIECE indicates that the use of QM is necessary when complexes with different inhibitors have significantly diverse charge-charge interactions, i.e., a large variability of polarized charges of protein atoms upon binding different inhibitors".[151]

RM1 was employed by Macaluso *et al.*[152] in order to investigate energetic and structural aspects of the shattering fragmentation due to the dissociation induced by collision of the doubly protonated tripeptide threonine-isoleucine-lysine ion (TIK(H$^+$)$_2$).

Recently, Homayoon *et al.*[153] performed comparisons between the unimolecular fragmentation of the doubly protonated tripeptides threonine-isoleucine-lysine TIK(H$^+$)$_2$ and threonine-leucine-lysine TLK(H$^+$)$_2$. The authors used RM1 to calculate structural and energetic properties of both TIK(H$^+$)$_2$ and TLK(H$^+$)$_2$ systems. They commented:[153] "In addition, the use of RM1 for the current study allows a direct comparison with the previous simulation results. The use of density functional theory (DFT) or an *ab initio* electronic structure method for the direct dynamics simulations is not computationally practical for the simulations reported here".

Finally, RM1 was also used in graduate chemical education, in the investigation of enthalpy of reactions.[154] In this investigation, Martins and Lima[154] presented several possible reactions to synthesize CO_2, and the graduate students were exposed to the quantum chemical calculations of their energetic properties to motivate learning of this topic.

6. Inorganic Chemistry

Due to the fact that RM1 has not been parameterized for transition metals, only few articles have used RM1 in the context of inorganic chemistry.[155-159] RM1 was mostly restricted to the calculation of properties of the ligands that are interacting with metals[158] and to the calculation of the properties of the inorganic species that participate in organic reactions.[140]

Examples of the usage of RM1 in inorganic chemistry include a study of the CO_2 absorption by protic and aprotic ionic liquids,[157] as well as the prediction of HOMO, and LUMO energies of ligands coordinated to trivalent dysprosium and geometry optimization of a set of ligands coordinated to trivalent europium, ytterbium and holmium.[156]

The Sparkle model, that allows calculation of trivalent lanthanide complexes by semiempirical methods has been

parameterized for RM1.[45-63] By using this model, structural, energetic and electronic properties of large lanthanide systems can be calculated with high quality and a much lower computational demand, when compared to those obtained with DFT and *ab initio* methods.

Inorganic chemistry studies also reported the usage of RM1 as the first step in higher accuracy geometry optimization calculations.[158,159] This strategy can result in a much more adequate starting geometry to more accurate calculations that will employ DFT or *ab initio* methods. For example, Kavakka *et al.*[158] reported a zinc complex, which is a selective nicotine receptor. In this study, the geometry of the propionic acid side chain and of the pyrrolidine moiety of the nicotine were calculated by using the RM1 method. The same strategy was used by Loukhovitski *et al.*,[159] that reported structural possibilities of Al_nN_m clusters (n and m can be 0 to 5).

7. Analytical Chemistry

RM1 method has been employed in analytical chemistry in the context of QSPR to obtain correlations between predicted properties, and experimental properties, such as the pK_a.

Seybold[160] carried out analysis of the values of pK_a for a set of the aliphatic amines by using descriptors predicted by RM1, and B3LYP/6-31G(d) methods. In this work, the author observed: "These results suggest that, at least for this specific congeneric series, the gas-phase RM1 calculations provide an accurate account of the electronic/inductive features affecting the pK_as". The author also observed: "Perhaps surprisingly, the semiempirical RM1 method [20] produced somewhat better results for this set of compounds than the more elaborate density functional theory B3LYP/6-31G* method. This may be because the RM1 method, which represents an extension of the original AM1 approach [23], is more compatible with the SM5.4A solvent model, which is also based on the AM1 approach".[160]

Kreye and Seybold[161] also studied the correlations between properties, such as bond lengths, and atomic charge values, that can be regarded as quantum chemical indices and the pK_a of a set of phenol derivatives. Further, Seybold and Kreye[162] reported the use of the RM1 method to investigate correlations between chemical descriptors and a set of alcohols, phenols and azole compounds, in the gas phase, in dimethyl sulfoxide (DMSO) and in aqueous solutions. The authors mentioned: "The semiempirical RM1 method generally acquitted itself well for the alcohols and phenols. In fact, the RM1 model for the aqueous pK_a was among the best obtained, and was essentially as accurate as the more demanding B3LYP/6-31+G**/SM8 calculations. For the azoles, this method did not yield strong fits for the gas-phase acidities, but performed well for the pK_as in DMSO and water".[162]

Furthermore, Ugur *et al.*[163] reported the use of RM1 to predict atomic charge descriptors that were correlated with pK_a values of a set of compound alcohols and thiols, and employed this strategy to predict the values of pK_as for a set of amino acids.

Silva *et al.*[164] employed the RM1 method to optimize the geometries of the plasticizers di-2-ethylhexylsebacate, di-2-ethylhexylphthalate and 2-nitro-phenyl-octylether, as well as of the poly(vinylchloride) sensing phase. In particular, the plasticizer di-2-ethylhexylsebacate increases the ability of a poly(vinylchloride) sensing phase of detecting contaminants in water samples. All RM1 geometries were used to calculate the molecular volume of the systems (plasticizers, and poly(vinylchloride)).

Finally, RM1 was employed by Souza *et al.*[165] in order to evaluate the potential applicability of a set of polymeric matrices to the determination of organic contaminants in water. The computational strategy employed by the authors was to evaluate the impact of the polymer matrix sensing phases, such as polyvinyl chloride, polydimethylsiloxane, and polyisobutylene, and polyurethane as solvents, on the Gibbs energy of solvation of the organic contaminants toluene, benzene, chlorobenzene and ethylbenzene.[165] They concluded that the limit of detection of contaminants for each polymeric matrix correlated well with the RM1 property of Gibbs energy of solvation.

8. Medicinal Chemistry

Several articles employed the RM1 method in medicinal chemistry research.[70,84,166-223] In general, usage of the RM1 method in such research includes: (*i*) geometry optimizations, and (*ii*) calculations of energy, and electronic properties of compounds that exhibited biological activities; as well as (*iii*) in studies based on the quantitative structure-activity relationships (QSAR), and quantitative structure-toxicity relationships (QSTR).

Now let us explore the main uses of RM1 in medicinal chemistry.

8.1. Geometry optimizations of molecules that exhibit medicinal properties

RM1 method was employed in an investigation of the antimicrobial properties of compounds of the type 4-aryl-3-(2-methyl-furan-3-yl)-Δ^2-1,2,4-triazoline-5-thione.[168] In particular, this class of organic systems is well-known

by researchers of medicinal chemistry due to its ability of interaction with the central nervous system, as well as to their strong antinociceptive, and anti-inflammatory natural ability.[168] In this article, Siwek *et al.*[168] reported the use of RM1 for geometry optimizations of four compounds of this type, motivating them to comment in their abstract: "New RM1 parameterization has been shown to perform very well for this class of compounds".

Other medicinal chemistry studies employed the RM1 method to optimize the geometries of the following compounds of biological interest: a potent thiazolylhydrazone-based antitrypanosomal;[84] alkaloids obtained from *Hippeastrum morelianum* Lem. (Amaryllidaceae);[173] *C*-glucosidic ellagitannins, prepared by a biomimetic synthesis of compound 5-*O*-desgalloylepipunicacortein A;[187] (5*Z*)-5-[(5-bromo-1*H*-indol-3-yl)methylene]-3-(4-chlorobenzyl)-thiazolidine-2,4-dione, which is effective as pan peroxisome proliferator-activated receptor agonist and cyclooxygenase inhibitor;[189] 1,7-bis(aminoalkyl)diazachrysene derivatives, that are capable of inhibiting three unrelated pathogens: the botulinum neurotoxin serotype A light chain; *Plasmodium falciparum* malaria and Ebola filovirus;[190] derivatives of thiazolidinones with anti-*Trypanosoma cruzi* activity;[192] derivatives of the *E,Z*-isomers of 3-arylidene substituted flavanone, chromanone and 3-aryl substituted flavone, that exhibited biological activities for the treatment of the following types of cancer: cell lines (HL-60, NALM-6, WM-115) and normal cell line (HUVEC);[70] 2-pyridyl thiazoles, that are anti-*Trypanosoma cruzi* agents;[193] surfactants of the type bispyridinium diexadecyl cationic gemini, which are nonviral gene-deliveries;[196] phthalimides with antiproliferative and immunomodulatory activities;[202] *Aedes aegypti* larvicidal based on thiosemicarbazones;[209] inhibitors of chikungunya virus (CHIKV; genus *Alphavirus*) protease;[210] peroxisome proliferator-activated receptor gamma (PPARγ), which is capable of regulating pathways involved in the pathogenesis of obesity and atherosclerosis;[215] a series of 4-amino-7-chloroquinoline (4,7-ACQ) compounds, that exhibited higher antimalarial activities;[216] usnic acid enamines that enhance the cytotoxic effect of camptothecin, and, therefore, are inhibitors of the tyrosyl-DNA phosphodiesterase;[218] cyclic urea and carbamate derivatives that are α-glucosidase inhibitors;[166] 4-aminoquinolines as quorum sensing inhibitors in *Serratia marcescens* and *Pseudomonas aeruginosa*;[222] and a set of 77 *Leishmania donovani* inhibitors of *N*-myristoyltransferase.[224]

Optimized geometries calculated by RM1 were also used as strategy to obtain initial structure for the target systems, to subsequently employ DFT and/or *ab initio*

methods.[169,207,219,221] RM1 was also employed to be compared with these computational methods.[178,214] As such, Hall *et al.*[183] mentioned: "These computations confirmed the simple rule assignment for the other 22 structures, as the rule based assignment agreed with the calculated proton affinity in all cases. It is of note that, except for *N*-methyl-L-histidine and 4-aminohippuric acid, the semiempirical method RM1 gave the same protonation site indication as the DF 6-31G* computations". This article, reported models for nontargeted metabolomics based on indices of MS Ecom$_{50}$ (the energy in electron volts required to fragment 50% of a selected precursor ion), and indices of retention.

Generally, by performing geometry optimizations, it is also possible to calculate energetic and electronic properties of a target compound. In this sense, studies of the stable structures can form a strategy to rationalize important aspects of medicinal compounds, as will be shown in the next section.

8.2. Energetic and electronic properties of molecules that exhibit medicinal properties

Energetic properties of several compounds that exhibit medicinal properties, such as enthalpy of formation ($\Delta_f H$), were calculated by employing the RM1 method.[203] Ilardo *et al.*[203] studied energetic properties of a set of 20 amino acids of the standard genetic code, and remarked: "RM1 is therefore much more precise than the previously used AM1 and PM3 methods and has the same level of accuracy as PM6. As has been shown using a large set of molecules, the RM1 method is able to predict geometries and heats of formation consistent with DFT results and experimental observations.[36] The speed of MOPAC2009 and improved accuracy of RM1 are particularly valuable for generating electronic descriptors for structure-activity and structure-property relationship analyses".

Several articles reported usage of RM1 to optimize the geometry of the target medicinal compounds, as well as their energetic properties.[174,179,185,186,188,191,195,199,208] These articles studied the following systems of medicinal chemistry interest: a neolignan skeleton from *Chimarrhis turbinata*;[174] a prototype of G-quartet-based G-quadruplex ligand (porphyrin-templated synthetic G-quartet);[185] 2-iminothiazolidin-4-one systems, that are anti-*Trypanosoma cruzi*;[186] organic compounds that are insect repellents of *Anopheles gambiae*;[188] compounds of the types 4-aryl/alkyl-1-(piperidin-4-yl)-carbonylthiosemicarbazides and 4-benzoylthiosemicarbazides, that are inhibitors of topoisomerase I/II;[191] organic compounds obtained from *Dioscorea bulbifera*, that are inhibitors of α-amylase and

α-glucosidase, and, therefore can be used in the treatment of type II diabetes mellitus;[195] and in the rationalization of the effect of protonation site in the lysine containing peptide.[208]

By using semiempirical, *ab initio* and DFT methods, Kamble *et al.*[200] studied the conformational preferences of modified nucleoside 5-taurinomethyluridine. In this study, the authors reported comparisons between structural and energetic properties, that were calculated by the methods RM1, HF SCF/6-31G(d,p) and DFT B3LYP/6-31G(d,p),[200] and commented: "The HF and DFT optimization results revealed that 50-taurinomethyl side chain retained similar kind of geometry as observed in the RM1 preferred stable conformation".[200]

Conformational analyses by employing RM1 method were also reported for the case of the stable preferences of modified nucleoside N^2-methylguanosine, as well as N^2-dimethylguanosine. The computational results indicate that the preferential conformer occurs at the 26th position in the transfer ribonucleic acid (tRNA).[175]

A strategy employed by medicinal chemistry research to obtain energy data of organic compounds that exhibited medicinal activities also included the use of RM1 as the first step of their computational calculations, when, subsequently, DFT and/or *ab initio* calculations were performed. It is possible to cite the following studies: the conformations of the hypermodified nucleic acid base wybutine, which is predicted to occur at the 37th position in anticodon loop of tRNA^{Phe};[176] the antifungal activities of the derivatives of 4-arylthiosemicarbazides, that can be used against *Candida* species;[181] conformational analyses of the hypermodified nucleic acid base, mS^{2}hn^{6}Ade, which is in the 3'-adjacent (37th) position in the anticodon loop of the hyperthermophilic tRNAs;[182] conformational studies of the potassium salts of the *N*-acylhydrazinecarbodithioates, that have antifungal activity;[194] Raman studies to obtain qualitative water content of the skin dermis of healthy young, healthy elderly and diabetic elderly women;[204] and drugs based on complexes of sodium montmorillonite (Na-MMT) and amine-containing drugs (rivastigmine, doxazosin, 5-fluorouracil, chlorhexidine, dapsone, nystatin) that were found to successfully intercalate Na-MMT.[205]

In the context of the energetic properties, values of HOMO and LUMO energies were calculated by Tang *et al.*[223] using the RM1 method. From calculated energy values of HOMO and LUMO, the authors obtained the electrostatic potential of the systems involved in the modification of C-*seco* taxoids through ring tethering and substituent replacement. This procedure led to agents that are capable of acting against tumor drug resistance mediated by βIII-tubulin and P-glycoprotein overexpressions.

On the other hand, partial atomic charges have been calculated by using RM1, as reported by Guimarães *et al.*[201] in their design of inhibitors of thymidylate kinase from the variola virus, that are capable of being selective drugs against smallpox. In this sense, de Almeida *et al.*[211] calculated partial atomic charges by using the RM1 method in their docking and molecular dynamics study of a set of peripheral site ligand-oximes capable of reactivating the sarin-inhibited human acetylcholinesterase. Partial atomic charges have also been calculated by Ferreira Neto *et al.*[220] in their investigation of a guanylhydrazone derivative, which is a potential acetylcholinesterase inhibitor for Alzheimer's disease.

Energy, and electronic properties, as well as structural properties calculated by computational methods, especially RM1, are valuable strategies for a researcher to obtain descriptor data (that are associated to a target property), to perform statistical studies, such as structure-activity relationships (SAR), QSAR, and QSTR.

8.3. QSAR, SAR and QSTR studies

QSAR analysis of a set of *n*-nitroso-2,6-diarylpiperidin-4-one semicarbazones derivatives as antibacterial and antifungal agents was reported by Hemalatha *et al.*,[167] that commented: "The geometry optimization was done using MOPAC 2007 [21]. The optimization was done at AM1, PM3 and RM1 level for a set of compounds and it was found that RM1 [22] gave better results and significant thermochemistry values. Moreover, this method used the optimization of the molecule in a solvent like atmosphere, referred as COSMO [23] (Conductor Like Screening Model)".

Recently, pentacyclic triterpenoid compounds obtained from *Prismatomeris tetrandra*, a Malaysian plant, presented hyaluronidase inhibitory activity.[213] In this study, a QSAR study was performed, where the RM1 method was employed to calculate the lowest energy conformations of the compounds considered. The following statement is made in this investigation: "The RM1 method was selected for our calculations because the average errors in the prediction of enthalpies of formation, dipole moments, ionization potentials, and inter atomic distances, using the RM1 methods were found to be less than the average errors given by AM1, PM3 and PM5 methods".[213]

2D QSAR analyzes with three descriptors of the binding affinity of progestins to the receptor of human cytosol.[170] In this study, the RM1 method was used in the optimization of the geometries of a set of twenty-three progestins, and to calculate the HOMO and LUMO energies and Mulliken atomic charges. These properties were then employed as QSAR descriptors.

Funar-Timofei *et al.*[171] reported an investigation of the QSTR by considering benzodiazepine drugs that are employed as anticonvulsants, hypnotics, tranquillizers, and anxiolytics. In this work, the RM1 method was employed to optimize the geometries and to calculate the energy values for a set of benzodiazepine compounds. Several descriptors, such as constitutional, functional group counts, and topological descriptors were evaluated from all RM1 optimized geometries.

Finally, the RM1 method was employed to optimize the geometries of the systems for the following studies: QSAR for the prediction of anticancer activity of aliphatic nitrosoureas,[177] and seconucleoside nitrosourea analogs;[217] and SAR for the biological evaluation of the trimethoxy-chalcone derivatives as inhibitors of the *Leishmania braziliensis* growth.[180]

9. Biological Chemistry

RM1 was designed to be useful to drug research as well as to biochemistry and biological chemistry. Indeed, many articles report its use in these contexts.[34,225-244] For example, Aldulaijan and Platts[244] studied the peptide binding to the histocompatibility II receptors. Statistical results indicated a correlation between the half maximal inhibitory concentration (IC_{50}) and RM1-D interaction energy. The authors observed: "It was found that the semi-empirical RM1 approach with additional correction for dispersion effects gives the best reproduction of *ab initio* data, with a mean unsigned error of a little more than 1 kcal/mol over almost 50 interactions after optimization of the global scaling factor. Performance is similar for several other parameterizations of semi-empirical theory, with RM1 chosen for its slightly better results".[244]

The energetics of the intermolecular interactions of peptides to major histocompatibility complex (MHC) class II receptors was evaluated by Aldulaijan and Platts[245] by means of classical force fields and semiempirical methods. As molecular mechanics (MM) force fields these authors used OPLS-AA (all-atom optimized potentials for liquid simulations), AMBER94 (assisted model building with energy refinement), and MM/GBVI (generalized Born volume integration) and, as semiempirical methods, RM1, AM1, PM3, PM6, RM1-D, AM1-D, PM3-D, PM6-D, and RM1-BH. Available IC_{50} data was used to get some correlations between calculated binding energies to the experimental data. Starting geometries of most of the peptide-receptor complexes were taken from the X-ray structures retrieved from protein data bank (PDB), with hydrogen atoms in all structures inserted according to typical protonation states. All hydrogen atom positions

only were then optimized by using the AMBER94 force field, by previously freezing the heavy atom positions. Calculations on the resulting fixed geometries (single point energy) by means of molecular mechanics and quantum mechanics were carried out at different dielectric constants to simulate vacuum, water and other external media. For QM calculations, the authors used the MOZYME[246] linear scaling technique developed by James Stewart and implemented on the MOPAC program. In addition, some medicinal chemistry tools were used to analyze the theoretical results. Correlation analysis indicated that MM/GBVI was the best method to fit the experimental data; with the correlation between IC_{50} and RM1-D interaction energies being satisfactory. In addition, RM1 and its variants that take into account non-covalent interactions, $RM1_{BH}$ and RM1-D, were used to estimate the interaction energies between a peptide and the active site of the MHC class II receptor.[245] The mean unsigned error (MUE) relative to MP2/6-31G(0.25d), considering all 49 amino acid interactions identified in their investigation for RM1 was 2.17 kcal mol^{-1}, whereas the corresponding values for RM1-D and $RM1_{BH}$ were 2.13 and 2.27 kcal mol^{-1}, respectively. The best semiempirical method was RM1-D(0.7), with MUE equal to 1.36, with the s_6 parameter of the dispersion correction function optimized to 0.7.[245]

LUMO energies were calculated by El-labbad *et al.*,[241] that used both DFT B3LYP/6-31+G* and RM1 methods. They stated: "We also observed that the LUMO energies calculated using the faster RM1 semi-empirical method achieves similar performance."[241] In this study, El-labbad *et al.*[241] reported a peptidomimetic that acted as an irreversible inhibitor of the CHIKV NsP2 protease.

Feng *et al.*[34] studied the usefulness of a set of semiempirical methods to calculate the binding energy of hydrogen bonds for biological compounds and mentioned: "It was demonstrated that $RM1_{BH}$ model outperforms the PM3 and RM1 models in the calculations of the binding energies of biological hydrogen-bonded systems by very close agreement with the values of both high-level calculations and experiments. These results provide insight into the ideas, methods, and views of semiempirical modifications to investigate the weak interactions of biological systems".[34]

RM1 was used to help the matrix assisted laser desorption/ionization (MALDI) mass spectrometry analyses of hexapeptide ALA-ASP-LEU-LYS-PRO-THR, a bioactive peptide widely used in the pharmaceutical industry for skin cosmetics.[230] Then, RM1 calculations were carried out mainly to predict bond orders of selected chemical bonds. This information allowed the authors to interpret the fragmentation pattern in mass spectrometry.

Feng *et al.*[34] used RM1$_{BH}$ to model biological molecular systems interacting through hydrogen bonds. Gaussian functions positioned at the hydrogen-bond distance at the N and O atoms were added to the core-core repulsion term, while the remaining RM1 parameters were kept unchanged. The parameterization set was built containing dimers and multimers between amino acid and base-pairs. The optimal parameters were found by minimizing a response function that compared interaction energies from experiment and high-level calculations with the RM1$_{BH}$ ones. Predictions of interaction energies of molecules from a test set showed that this new RM1 parameterization outperformed the original RM1 and PM3, being comparable to experimental data as well as to B3LYP/6-31G**/BSSE and MP2/6-31G**/BSSE results.

In general, RM1 has been employed in biological chemistry research to optimize the geometries of the target systems, as well as to predict their energies and electronic quantities before the docking calculations. In this sense, RM1 has been widely used as the quantum chemical method to refine molecular docking poses, carry out preliminary conformational searches, calculate atomic partial charges and determine ground state geometries of a set of ligands to further perform molecular docking, high throughput screening calculations or SAR studies. Studies of this kind included: the ability of the tariquidar and elacridar to inhibit the multidrug resistance transporter P-glycoprotein;[231] prediction of the partial atomic charges of the thymidylate kinase obtained from variola virus;[232] drug action mechanisms of a set of chloroquine compounds that present antiplasmodial activity against chloroquine-resistant parasites;[233] glycosidase inhibitors, and immunosuppressive agents that are based on γ-hydroxyethyl piperidine iminosugar and *N*-alkylated derivatives;[234] the use of gamma radiation to degrade the systems phenylethylamine and tyramine;[235] a ternary complex formation in the catalysis of the *Trypanosoma cruzi trans*-sialidase, which is an important protein for the therapy of Chagas disease by chemotherapy;[236] geometry optimizations and partial atomic charge quantities of the species involved in the inhibition of nerve agents by oxime BI-6 and acetylcholinesterase;[237] evaluation of the ability of the 1,3,4-thiadiazole and *s*-triazole derivatives as antimicrobial agents;[238] conformational aspects of the modified nucleosides k^{2}C (hypermodified nucleoside lysidine) and t^{6}A (hypermodified nucleoside N^6-(*N*-threonylcarbonyl) adenosine) that are present in the anticodon loop of the tRNA^{Ile};[239] structural properties of the system *M. tuberculosis* enoyl-acyl carrier protein (ACP) reductase-NADH (protonated nicotinamide dinucleotide), as well as its interaction with the diphenyl ether inhibitors;[240] the

identification of the inhibitor of the angiotensin converting enzyme;[242] optimization of the geometries of both a set of 1,4-naphthoquinone derivatives that are capable of inhibiting the P2X7 receptor, which is an ATP-gated ion-channel,[247] as well as of the AMCA-peptide-TAMRA system, where AMCA and TAMRA stand, respectively, for 7-amino-4-methyl-3-coumarinylacetic acid and 5-carboxytetramethylrhodamine;[248] partial atomic charge calculations of oximes, such as HI6 and 2-PAM that are nucleophiles capable of reactivating the inhibited human enzyme acetylcholinesterase;[249] structural calculations of peroxywybutosine present in the 37th position in the anticodon loop of tRNA^{Phe} when both RM1 and multiple molecular dynamics methods were employed;[250] QM/MM calculations on the mechanism of carboxylation of ribulose-1,5-biphosphate, where RM1 was used in QM part;[251] and geometry optimizations of a set of eight 3-phenylcoumarin derivatives with 6,7- or 5,7-dihydroxyl groups, either free or acetylated, bound to the benzopyrone moiety, in order to study modulation of effect or functions of human neutrophils.[252]

10. Molecular Dynamics

In chemistry, as well as in its interfaces with biology and materials science, molecular dynamics (MD) represents an important strategy to investigate target systems, such as the proteins.

An interesting dynamics investigation was carried out by Gonçalves *et al.*,[253] that explored reactivation routes of the organophosphorus compounds capable of inhibiting human acetylcholinesterase. This class of organic compounds presents potential as antidotes against poisoning by chemical warfare agents. In this work, RM1 was selected to calculate structural and energetic properties of the species involved in the mechanism of reactivation by pralidoxime of human acetylcolinesterase inhibited by tabun, a synthetic organophosphorus compound. They carried out hundreds of picoseconds of QM/MM MD. The authors were able to find a possible transition state that connects reagents and products for the reaction of the HuAChE reactivation by pralidoxima, indicating this substance as a possible antidote against poisoning by organophosphorus nerve agents. Their choice of RM1 was justified as follows: "Results in the plot of SI, Figure S7, show that with the RM1 method, the system stabilizes more quickly in this hybrid MD simulation. For this reason, RM1 was chosen to simulate the reactivation of HuAChE/GA by 2-PAM in this work".[253] Gonçalves *et al.*[253] also observed: "Another questionable issue of this work is the use of semi-empirical methods to the calculations of TSs

(transition states) and IRCs (intrinsic reaction coordinates). This methodology, however, has already been discussed in literature in our most recent paper[6] in which we showed that the same TS can be obtained using the semi-empirical methods RM1 and PM6 and the most robust method DFT/B3LYP 6-31G(d,p)".

Gregg *et al.*[254] studied the fragmentation of molecular ions through their collisional activation with a surface, focusing on the proton motion and on the mechanism of the initial fragmentation event. In this later paper, the author also used RM1 as the quantum chemical method as well as the same data set obtained in their prior work.[229] RM1 yielded good qualitative agreement with the DFT and CCSD(T) (coupled-cluster singles doubles and non-iterative triples correction) calculations, being superior to PM7, PM6, PM6-D and AM1 semiempirical methods. Gregg *et al.*[254] remarked in their study of the elucidation of the proton transfer role in surface-induced dissociations within mass spectrometry: "RM1 yields good qualitative agreement with the higher-level calculations and is significantly better than the other semiempirical methods considered. Given the large amount of energy deposited into the internal degrees of freedom of the peptide by the collision, the 2–4 kcal/mol differences are acceptable".

In a similar study, Ridgway *et al.*[255] carried out molecular dynamic simulations in order to understand the relationship between intermediate reactions and products for the reaction of benzene and alicyclic monoterpene sabinene with ozone. To simulate these reactions, the authors combined elements of bimolecular collision theory and RM1 calculations, through an approach named as the stepped forced molecular dynamics (SFMD) method, to generate more than 900 collisions between ozone and targeted organic species. Their calculations produced a distribution of reaction products from what it was possible to carry out their categorization in terms of the types of transformations that occurred, such as: ring opening, hydrogen abstraction, electrophilic substitution/elimination, and so on. As a remarkable result, the authors observed that some molecular species were predicted because of the collision trajectories, a finding that was experimentally confirmed by means of vapor-phase photocatalytic ozonation reactions.

In a short communication, Anisimov *et al.*[256] studied the quantum mechanical dynamics of charge transfer in ubiquitin in aqueous solution. For this investigation the authors carried out 20 ps of full quantum mechanics NVT (constant number of particles, constant-temperature, and constant-volume canonical ensemble) molecular dynamics (using 1 fs of time step) of ubiquitin in a water droplet (a molecular system consisting of 1231 protein atoms and

3656 water molecules totalizing 12199 atoms), using four semiempirical methods, including RM1. They used LocalSCF program[257] to perform QM molecular dynamics simulation on that system. Results from that investigation indicated an unphysical tendency of both AM1 and RM1, within LocalSCF, to dissociate the O–H bond of water during the simulations.

On the other hand, Świderek *et al.*,[258] in their benchmarking comparisons of QM/MM methods to study the thymidylate synthase catalyzed hydride transfer, commented: "In addition, RM1 is the method that provides the highest stabilization of the product complex (-10.7 kcal mol^{-1})".

Pol-Fachin *et al.*[259] carried out a series of molecular dynamics simulations on three *N*-acylhydrazone derivatives, substances with potential cardioinotropic and vasodilatory activities. The main propose of their investigation was to map an ensemble of conformations of these molecules in aqueous solutions. First, a systematic and exploratory semiempirical conformational study (using RM1) was performed to gain insight into the flexibility of these systems. Then, each conformation found was submitted to large MD simulations to describe their conformational behavior in aqueous solution. This investigation pointed out how each functional group present in this type of compound impacts on their biological activities.

Traditional force fields use fixed atomic charges to compute electrostatic interactions between atoms. In the literature, many strategies to derive atomic charges for increasing performance of both force fields and molecular simulations to investigate many physical and chemical phenomena were reported, especially condensed-phase and enzymatic chemical reactions. In this sense, Vilseck *et al.*[260] studied new scaling factors for atomic charges (CM1R and CM3R) derived from RM1 in conjunction with CM1[261] and CM3[262] charge models. The optimal values (1.11 and 1.14 for the CM1R and CM3R methods, respectively) were found by minimizing errors in absolute free energies of hydration, ΔG_{hyd}.[260] These values were calculated by performing molecular annihilations of 40 selected small neutral organic molecules using a Monte Carlo/free energy perturbation (MC/FEP) protocol. Regarding the molecules considered in the parameterization set, the comparison between the predicted and experimental ΔG_{hyd}, in terms of unsigned average errors, were 2.05 and 1.89 kcal mol^{-1} for the CM1R and CM3R methods, respectively. In addition, the authors carried out a test of significance of the scaling factors for the atomic charges derived in their work. So, the $NH_3 + CH_3Cl \rightarrow CH_3NH_3^+ + Cl^-$ reaction in water was computed by using an RM1/TIP4P-Ew/CM3R procedure. The results indicated that RM1 predicts $\Delta_r G$ (Gibbs

energy of reaction) and geometries in agreement with other computational methods, albeit underestimating $\Delta G^{\ddagger}$ (Gibbs energy of activation). The authors also observed that the RM1 errors for energetic properties of ionic species were large.

Nilov *et al.*[263] investigated the formation of the enzyme-substrate complex of formate dehydrogenase by applying classical, steered and hybrid QM/MM dynamic simulations. In their study, QM was defined as the region containing the formate molecule and nicotinamide-ribose fragment of NAD+ molecule, whereas the MM region contained the rest of the coenzyme, the protein, and the solvent. For the QM region, the authors applied AM1, PM3 and RM1 semiempirical methods. Their results indicated similar performance for all semiempirical methods in reproducing the stable hydrogen bonds between the substrate and important residues in the active site.

Chen *et al.*[264] compared the performance of several semiempirical methods, including RM1, as well as DFT, in the investigation of hydrogen bonds and polar interactions of two inhibitors of the enzyme trypsin. Results showed that PM6 was the best semiempirical method to describe the interactions between the ligands and trypsin.[264] In addition, the authors predicted $\Delta_{bind}G$ (Gibbs energy of binding) of the two ligands on trypsin by using QM/MM GBSA (generalized Born and surface-area solvation) methodology. The results revealed that all computational methods gave similar results for such property.

In a similar benchmarking work, Świderek *et al.*[258] examined the performance of several semiempirical methods to study the hydride-transfer step catalyzed by the thymidylate synthase enzyme. The authors selected AM1, PM3, pairwise distance directed Gaussian (PDDG)/PM3, RM1 and three re-parameterizations of AM1 that include specific reaction parameters for modeling FDH (formate dehydrogenase) and DHFR (dihydrofolate reductase) hydride transfer catalyzed reactions as semiempirical methods. In addition, the authors also used the M06-2X hybrid density functional to establish some comparisons with the semiempirical methods. In this study, they calculated proton and tritium transfers in four different temperatures, evaluating their kinetic parameters, including kinetic isotope effects (KIEs). A special highlight was given to the RM1 method that was able to reproduce the experimental results in excellent agreement. The authors commented: "Dynamics and quantum-tunneling effects are revealed to have little effect on the reaction rate, but are significant in determining the KIEs and their temperature dependence. A good agreement with experiments is found, especially when computed for RM1/MM simulations".[258]

Delgado *et al.*[265] also studied hydride transfer reactions in biological systems by using semiempirical quantum chemical methods. In their study, the modeled system was the enzyme morphinone reductase that, specifically, catalyzes a hydride transfer from the C4 atom of NADH to the N5 atom of a bound FMN cofactor (flavin mononucleotide). They used a combination of QM/MM simulations and experimental measurements of the rate constants, energy barriers and KIEs for that biomolecular system and reaction. The authors chose RM1 for describing the QM region of the enzyme's active site based on its good results for other enzyme catalyzed hydride transfer reactions. Results revealed excellent agreement with those experimentally measured properties, especially for rate constants and KIEs.

Binding energy estimations of four endo peptidyl epoxide ligands interacting with papain, a cysteine protease enzyme, were carried out in the paper of Perlman *et al.*[226] The authors ran short NPT (constant number of particles, constant-pressure, constant-temperature ensemble) molecular dynamics simulations to produce equilibrated structures for the four papain-inhibitor complexes. Using the time-averaged structures of such complexes, molecular clusters were extracted producing sub-structures of the entire enzyme-inhibitor complexes that contain the inhibitors and the active-site residues of the enzyme. Then, these clusters were optimized in molecular mechanics force field, at gas phase. The final structures were used to calculate binding energy by means of RM1. Results showed that only one *cis* epoxide and one *trans* epoxide bind to the enzyme, revealing a highly stereoselective interaction in formation of the papain-inhibitor complex.

Ahmed *et al.*[266] performed docking and binding free energy calculations (by using MM-PB(GB)SA methods) to discover the exact binding and inhibitory profiles of a class of compounds containing lactone and thiolactone groups. RM1 was used to find the ground state geometries of the ligands. To assign the atomic charges for the RM1 ground state geometries of the ligands, the authors used HF/cc-pVTZ through partial atomic electrostatic potential charges (ESP) calculations. Results indicated that inhibitor-protein complexes having inhibitors with a lactone-based moiety were more stable than the thiolactone-based ones.

Using plenty of medicinal chemistry tools, including homology modeling, ensemble docking, rescoring using MM-PB(GB)SA and QM-GBSA, and QSAR, Slynko *et al.*[267] tested a series of potential drugs that could act on protein kinase C related kinase 1, PRK1, commonly pointed out as an important target for prostate cancer therapy. In this study, RM1 was used as the quantum chemistry model to predict $\Delta_{bind}G$ by means of the QM-GBSA approach. After dozens of calculations, the authors obtained theoretical predictions of pIC_{50} that

correlated with the experimental ones, displaying a squared correlation coefficient R^2 of 0.78 for the fitting of all inhibitors considered.

Some studies used the RM1 semiempirical method to obtain ground state geometries, or compute atomic charges of biomolecules, as well as inhibitor-protein complexes, as in the articles by de Souza *et al.*[249] and of Gushchina *et al.*[268] In these two studies, the authors pointed out that the RM1 method helped them increase the understanding of their modeled molecular systems.

Effect of mutations on the barrier height of the first step of the amide hydrolysis reaction, that is catalyzed by *Candida antarctica* lipase B, was addressed by Hediger *et al.*[228] First, the authors presented a computational strategy that combined both the automatic generation of mutant structures and the preparation of the semiempirical calculations in order to calculate kinetic parameters, such as k_{cat} (the turnover number of the enzyme), transition state geometries, intrinsic reaction coordinates, and so on. To reduce the computational efforts, the authors decided to build models of active site pocket with different sizes and evaluate the impact on structural and energetics properties of that reaction. That investigation focused on PM6 and RM1, in comparison with DFT QM/MM calculations. The authors estimated that the processing of a hundred mutants using semiempirical methods took only a few weeks in a 10-processor computer when their approach was adopted.

An investigative study was accomplished by Sonawane and co-workers[178,269] to find the conformational details of k^2C and t^6A in the anticodon loop of tRNA^{Ile} by means of quantum chemistry methods. First, RM1 calculations were carried out to optimize the gas-phase ground state geometries of previously generated conformers. A complete description of geometrical parameters was presented in Sonawane and Tewari[178] article through tables, graphics and analyses. In addition, molecular dynamics simulations on the anticodon stem loop model of tRNA containing modified nucleosides k^2C and t^6A were carried out. Classical and conventional protocols of MD simulation were applied to simulate these molecular structures on aqueous media. The authors concluded that structural details predicted by using RM1 were in agreement with the corresponding ones calculated with MD simulations.

The next two studies employed RM1 in full quantum molecular dynamics simulations.

Homayoon *et al.*[270] studied the thermal dissociation of the doubly protonated tripeptide threonine-isoleucine-lysine ion, labeled as $TIK(H^+)_2$, in four different temperatures, ranging between 1250 and 2500 K. The authors determined how many fragmentation pathways exist in each temperature they considered and observed that the number of different fragmentation pathways increases with increasing temperature.[270] Several kinetic parameters were calculated using RM1 and AM1 semiempirical methods as quantum chemical models. In special, the authors pointed out that the activation energy values determined from the simulated Arrhenius plots displayed good agreement with the predicted reaction barriers when RM1 was used in the simulations.

Raeker and Hartke[271] carried a joint experimental and theoretical study focusing on salicylic acid and its capability for intramolecular proton transfer in the excited-state. The potential energy surface (PES) for such reaction was scanned along the proton transfer coordinates in one and two dimensions. They carried out what they called full-dimensional photodynamics using the floating-occupation configuration-interaction (FOCI) treatment with single and paired double excitations. To define the quantum chemical method used in the calculations, the authors first carried out an exploratory investigation (varying some parameters, i.e., CI excitation level, size of the active orbital space, and so on) as a way to reproduce the main transitions in comparison to high-level methods. The RM1 method in combination with a 12,12 active space and a CIS+pD excitation level (all single and paired double excitations) showed excellent agreement with the results of the energy transitions on selected points of the PES from the CASPT2/ANO-L (complete active space second-order perturbation theory with large atomic natural orbital basis sets) level of theory. Then, considering such setup, the authors evaluated the time-evolution of relevant degrees of freedom (DOF), quantum yields and isomer populations through two hundred surface-hopping trajectories. Results revealed that RM1 scans and trajectories exhibited the same quality as those obtained by DFT.

Mones *et al.*[272] presented an article describing their implementation of the adaptive buffered force (AdBF) quantum-mechanics/molecular-mechanics (QM/MM) method on CP2K and AMBER suits of programs where they used various semiempirical methods, including RM1.

RM1 was also employed in other QM/MM studies, that included: method EH-MOVB (effective Hamiltonian mixed molecular orbital and valence bond) for the chemical and enzymatic reactions;[273] the structural position of the hypermodified nucleic acid base hydroxywybutine, which is the 37th position in the anticodon loop of yeast tRNA^{Phe};[274] interactions between colchicinoids and a recombinant human αI/βI-tubulin heterodimer;[275] the antifungal activities of the coumarin derivatives;[276] reactivation steps of the human acetylcholinesterase tabun-inhibited by pralidoxime;[277] and a set of reactions, that occurred in ionic liquids medium.[278]

11. Materials Science

Because of the heavy computational demand required to study solid systems, quantum chemical calculations of their properties require larger resources. Although RM1 has been initially developed with an eye to organic, biochemistry and drug research, it is also being intensively used in materials science.[279-295] For example, Duong *et al.*[291] studied the molecular organization in 2D and 3D co-crystallizations of compounds of the type pyridyl-substituted diaminotriazines. The authors noted: "This method is expected to yield models of 2D organization that are qualitatively reliable. However, the method requires only modest computational resources, unlike high-level density-functional approaches in which long-range dispersive interactions are taken into account, such as those we and others have reported earlier".[291]

Venkatraman *et al.*[197] carried out a QSPR study for modeling Grätzel solar cell dyes, when the vibrational frequency-based eigenvalue (EVA) method was investigated by employing the descriptors obtained from RM1 calculations. In this work Venkatraman *et al.*[197] mentioned: "Even though vibrational modes calculated using density functional theory methods are known to be more accurate,[118] for the current dataset EVA descriptors based on semiempirical AM1 and RM1 approximations have yielded good predictive models while being computationally less demanding and can be potentially extended to more heterogeneous datasets".

The applicability of RM1 to materials science also included: structural properties, and dipole moments of Langmuir-Blodgett films;[293,294] an evaluation of the imidazole derivatives inhibition of mild steel corrosion in 1 M HCl;[292] geometry optimizations of the self-assembly of diblock copolymers MePEG-*b*-PAAm into micellar structures;[290] processing of 3-dimensional carbon nanostructures;[289] prediction of the enthalpy of formation of the species involved in the self-assembly from oxidation steps to obtain from nanorods to microspheres;[288] structural and vibrational properties of polycyclic aromatic hydrocarbons to carry out nanovehicles equipped with triptycene wheels;[287] energetic properties of a set of 16 molecules that span the most significant families of explosive compounds;[286] an investigation of mesophase behavior of binary mixtures of bent-core and calamitic compounds;[285] tip-based nanofabrication of diamondoid structures;[284] conformational possibilities of a set of 1,1,2-trichloroethane in faujasite (FAU)-type zeolites;[283] nanocrystal clusters that were carried out by biomineralization synthesis;[282] structural properties of a set of coordination polymer phases carried out by the extraction of trivalent lanthanide ions by

the bis(2-ethylhexyl)phosphoric acid;[281] the oxidation of the surface of graphene layers;[280] a study of the electronic properties of carbon nanotubes that were complexed with a DNA nucleotide;[295] computational strategies to simulate electronic polarization effects;[296,297] binding and relative energies of the $(H_2O)_{16}$ and $(H_2O)_{17}$ clusters;[298] and conformational structures of *trans*-1,2-dichlorocyclohexane adsorbed in zeolites.[299]

12. Comparison Studies

The performance of RM1 has been exhaustively explored and examined by means of several benchmarking studies, which evaluated its success for the calculation of several molecular properties. In some of these studies, the authors made comparisons among several semiempirical, as well as high-level methods.[91,245,258,260,296-343] In addition, the authors performed these comparisons both on small sets of molecules of particular classes of compounds, as well as on larger sets of molecules. These comparisons range from applications of computational chemistry for molecules and systems, up to hybrid calculations of molecular dynamics.

Examples of the usage of RM1 together with other quantum chemical methods include: calculations of the enthalpy of formation of tensile cyclic molecules in condensed phase by employing electrostatic potentials and QSPR;[307] calculations of the linear free energy studies of the rates of reductive defluorination of a set of perfluorinated alkyl compounds;[301] a conformational investigation of the oxime compounds toxogonine, trimedoxime bromide (TMB-4) and obidoxime (HI-6);[341] energy and structural properties of the acid-catalyzed aromatic epoxide ring openings;[344] a benchmark computational study of the proton transfer reaction cysteine-histidine in protein environment;[325] a QM/MM evaluation of the chemical glycobiology;[318] a study of the chemical reactivity in a virtual environment;[317] a benchmark investigation of the geometries of the ground-state of p-type semiconducting molecules that exhibit different polarities;[316] evaluation of the electrostatic potentials on the docking precision of cyclin-dependent kinase 2 protein;[315] and a benchmark study in order to investigate aspects of the reaction to protonate glycine by an ion-molecule collision.[345]

RM1 was also used in many studies to predict physicochemical and optical properties, such as activity coefficients,[346] reaction energies,[310,343] energy profiles of reactions,[317,329] and cysteine-histidine proton transfer reactions in different environments.[91,309,316,318,323,344] In most of these studies, RM1 was used to obtain the ground state geometries and other molecular properties, either in gas phase, or in solution (using any solvation model). In the

following studies, RM1 displayed good performance: (*i*) in reproducing circular dichroism (CD) spectra for (M)-hexahelicene and in giving experimentally consistent results for reduced rotational strengths of cyclohexanones,[324] (*ii*) in being consistent with experimental data for aqueous pK_a of 48 sulfhydrol compounds (thiols) by using SM5.4 and SM8 solvent models[322] and (*iii*) in giving low overal mean absolute error (MAE) for Δ_rH (enthalpy of reaction) of 34 isomerization reactions of 4.2 kcal mol^{-1} and Δ_fH of 1356 molecules, radicals, ions, and complexes (MAE of 5.0 kcal mol^{-1}).[343] Nonetheless, some studies also pointed out certain RM1 failures, such as: (*i*) inability to describe the interaction of small organic molecules with graphene;[321] (*ii*) wrong prediction of planar configurations for both the ground and singlet states for *trans*-stilbene;[330] (*iii*) overestimation of *cis-trans* isomerization energy and ionization potential of both *cis-* and *trans*-stilbene;[330] and (*iv*) larger errors in describing cysteine-histidine proton transfer at aqueous media with the COSMO implicit solvent model.[325]

Comparative studies between RM1 and force fields methods were performed by Seabra *et al.*,[303] that sought to answer the question: "Are current semiempirical methods better than force fields?". This investigation was carried out with a thermodynamic perspective, and took into consideration MNDO, AM1, PM3, RM1, PDDG/MNDO, PDDG/PM3, and self-consistent charge (SCC)-DFTB. These methods were employed as the QM part of a hybrid QM/MM scheme for the calculation of thermodynamic properties of a set of biological molecules. The thermodynamic quantities were compared with the corresponding values obtained using the Amber ff99SB force field method. As such, they used a system composed of the alanine dipeptide in a box with 929 water molecules in order to assess the performance of semiempirical methods in yielding consistent results for conformational distributions of the peptides at 300 K, free energy profiles and dipolar coupling constants, $^3J(H_N, H\alpha)$, and others more. Alanine dipeptide was described quantum-mechanically, whereas the solvent was modeled by means of the TIP3P water force field. In addition, replica exchange molecular dynamics were used to ensure adequate sampling of the conformational distribution of the peptides in aqueous solution. The remarkable conclusion from their study is better stated: "In contrast with the computational chemist's intuitive idea that the more expensive a method the better its accuracy, the ff99SB force field results were more accurate than most of the semiempirical methods, with the exception of RM1". The authors said: "Comparison with the latest generation of classical force fields shows that results provided by the semiempirical Hamiltonians

are not especially closer to experiment than the classical ones. Indeed, results from the classical ff99SB force field are generally in better agreement with experiment than most of the quantum methods. The exception was the RM1 parametrization, which was the only method to show consistently better results, although it still did not fully agree with experimental numbers. This improved performance likely originates from the explicit inclusion of biological molecules in its training set".[303]

In 2007, the PM6 semiempirical molecular orbital method was presented in an article by Stewart.[32] In his article, James J. P. Stewart mentioned that, prior to PM6, "A statistical analysis showed that RM1 was more accurate than any of the other NDDO methods, and therefore was the method of choice for modeling organic compounds".[32] PM6 is based on the NDDO formalism with the following modifications to PM3: (*i*) d orbitals for metals and hypervalent atoms (such as Cl, S, or P); (*ii*) a different error function was minimized to reproduce heats of formation; (*iii*) reference data were based on experimental results and high-level calculations; (*iv*) expression for core-core interactions was modified according to specific bonds; (*v*) core-core repulsion expression uses diatomic parameters and a simple function based on the first term of the Lennard-Jones potential; and (*vi*) parameterization was carried out for 70 atoms in the periodic table. The PM6 performance was presented by means of average unsigned error between calculated and reference data for heat of formation, dipole moments, geometric parameters and ionization potential. In that paper, semiempirical and *ab initio* methods were also used to evaluate the PM6 performance. For a set of 1,373 compounds involving the same elements of RM1 (H, C, N, O, F, P, S, Cl, and Br), the PM6 error in the enthalpy of formation was 4.4 kcal mol^{-1}. For the methods RM1, B3LYP/6-31G*, PM5, PM3, HF/6-31G* and AM1 the enthalpy of formation errors were 5.0, 5.2, 5.7, 6.3, 7.4 and 10.0 kcal mol^{-1}, respectively. RM1 therefore proved to lead to more accurate results than, not only the other earlier semiempirical methods, but also both HF/6-31G* and B3LYP/6-31G*.

Calculation time is also an important criterion in the choice of a computational method. In this regard, Zheng *et al.*[308] carried out comparisons between various quantum chemical methods to describe barrier heights for heavy-atom transfer, nucleophilic substitution, and unimolecular and association reactions as benchmarks. In this study, the authors considered 205 theoretical methods. Their results indicated that RM1 underestimates barrier heights (BHs) for heavy-atom transfer (HAT) quantities, as well as overestimates the properties associated to BHs of nucleophilic substitution (NS) and unimolecular

and association (UA) reactions when compared with the more robust method MP2/6-31+G(d,p). However, the calculation time is much faster when compared to the MP2/6-31+G(d,p) one, as they stated: "The five NDDO semiempirical methods tested, AM1, PM3, PM6, RM1, and PDDG/PM3, all underestimate the BHs of HAT reactions and significantly overestimate the BHs of NS and UA reactions. But they are faster than MP2/6-31+G(d,p) by about 5 orders of magnitude for phosphinomethanol gradients and by even more for a larger system".[308] In general, the results for the semiempirical ones were practically the same.

Calculation time was also considered in the study reported by Piliszek *et al.*,[335] that carried out artificial neural network (ANN) predictions of the partition coefficients of a set of 399 congeners of polychlorinated azoxybenzenes. They observed that: "In light of these data, the semi-empirical RM1 calculations in MOPAC software and followed by ANN were a much less time consuming and less expensive compared to the DFT B3LYP method".[335]

RM1 has been widely used as the quantum chemistry method to provide descriptors to be later used in the formulation of QSPR/QSAR models, or in procedures based on artificial neural networks. Puzyn *et al.*[306] demonstrated an important applicability of semiempirical methods. It was shown in this work that by applying RM1 and PM6 descriptors, it is possible to obtain QSPR models of a quality similar to those based on B3LYP descriptors. Puzyn *et al.*[306] performed the QSPR study, by carrying out comparisons among semiempirical (RM1 and PM6), DFT (B3LYP/6-31G(d), B3LYP/6-311G(d,p), and B3LYP/6-311++G(d,p)) methods. The main goal of this work was to calculate descriptors by using all these methods and compare their model predictions of environmentally relevant physicochemical data for persistent organic pollutants with experimental results via statistical analysis. The descriptors considered were mean polarizability, dipole moment, highest negative Mulliken partial charge on atoms, HOMO, and LUMO energy. Puzyn *et al.*[306] remarked: "Therefore, if similar predictive ability characterizes both types of the QSPR models for congeners, those developed with the 1D or 2D descriptors and those based on the descriptors from the RM1 and PM6 calculations, then is it necessary to apply the quantum-mechanical descriptors at all?". They answered their question as follows: "The calculations for 1,8-dichloronaphthalene at the B3LYP/6-311++G(d,p) level took about 1.5 h on two processors (geometry optimization and frequency analysis), whereas the same tasks by PM6 and RM1 methods required only 2.5 and 1.2 min, respectively, on a single processor. Therefore, if one works with a very large set of congeners and if some

minimal differences between them are negligible, one can expect a relatively good QSPR model when PM6 and RM1 descriptors are used".[306]

Accordingly, RM1 was used, with good performance, in the studies that built QSPR/QSAR equations to calculate: vitamin C and trolox equivalent antioxidant capacities by using predictions of bond dissociation enthalpy of OH groups present in flavonoid compounds;[338] and mutagenic potency of nitrated monocyclic and polycyclic aromatic hydrocarbons in the TA100 strain of *Salmonella typhimurium*.[319]

Sattelmeyer *et al.*[343] carried out a comparison of SCC-DFTB and NDDO-based semiempirical methods for a set of organic compounds and stated: "PDDG/PM3 gives the lowest overall MAE (5.0 kcal/mol), and it is not out-performed for any subset, whereas RM1 does represent a significant improvement over AM1 and PM3".

Piliszek *et al.*[327] studied the aqueous solubility of the herbicidal toxic impurities, and predicted data of 399 chlorinated *trans*-azoxybenzene congeners by carrying out RM1 and DFT B3LYP/6-311++G** quantum chemical calculations. After the QSPR analysis, they concluded: "Both computational models used were characterized by good predictive abilities and small errors, while calculations by RM1 method were highly competitive compared to a much more time-consuming and expensive method by DFT".

Likewise, another QSPR study reported by Piliszek *et al.*[328] was the prediction of subcooled vapor pressures of 399 polychlorinated *trans*-azoxybenzenes. In this work they observed: "The quantitative structure-property relationship (QSPR), an approach which is based on geometry optimalization and quantum-chemical structural descriptors in RM1 and DFT methods and artificial neural networks (ANNs), an approach that predicts abilities that give similar results of estimated log PL and the accuracy of the methods was also similar. The RM1 method was less time consuming and less costly compared to calculations by the DFT method".[328]

A benchmark investigation involving RM1 and DFT methods was also performed in the estimation of the aqueous pK_as of a set of thiols.[322] In this work, Hunter and Seybold[322] concluded: "Perhaps surprisingly, the semiempirical RM1 computational method provided comparable results to the SPARC and ACD benchmark calculations in estimating the pK_as for the complete set. Before application of the SM8 solvent model, the more demanding DFT B3LYP/6-31+G* calculations not only did not offer any advantage over the RM1 calculations but also gave poorer results".

Comparisons of the ability of a set of semiempirical methods to optimize the geometries of the pyridylindolizine

derivatives, which contain phenyl and phenacyl groups, were carried out by Cojocaru *et al.*[323] They stated that, although AM1 was still the best method for describing bond angles, "The best semi-empirical model for prediction of bond lengths is RM1 with 4.529% ARE followed by PM3 with 4.680% ARE.", where ARE stands for average relative errors.

A study that also focused on non-linear optics properties was performed by de Andrade *et al.*[314] This time, the studied molecular systems were small oligomers of *trans*-polyacetylene. Semiempirical methods, DFT and Hartree-Fock model chemistries were used to calculate the second hyperpolarizability (γ) for these molecular systems. The authors noted that RM1 was able to reproduce γ experimental results with good performance. Statistical parameters for the comparison of RM1 predictions for γ with the experimental results produced $R^2 = 0.995$ and $\gamma_{EXP} = 1.158\gamma_{RM1} - 1.33$. In addition, they pointed out that diffuse and polarizability functions in the basis set for Hartree-Fock calculations provided better results in comparison to experimental data. They stated: "It was concluded that RM1 methodology better agrees with γ experimental results for TPA oligomers". Another recent benchmark investigation was carried out by Fizer *et al.*[346] that evaluated different charges in order to predict partitioning coefficient through the hydrophilic/lipophilic index. The authors concluded that: "The performance order of suitable semiempirical methods is the same as for the semiempirical Mulliken charges: PM7 > RM1 > PM6-D3H4 $\geq$ PM6 > PM3".[346]

On the other hand, Miriyala and Řezáč[347] carried out a comparative study in order to evaluate a set of 13 semiempirical and eight density functional methods to describe the interaction energies associated with the repulsive contacts in organic molecules. The authors evaluated 160 complexes that were generated by combining 12 monomers (CO, H_2, N_2, acetylene, ammonia, benzene, ethylene, formaldehyde, methane, methanol, pyridine and water).[347] The authors mentioned that: "The RM1 (which is a reparameterization of AM1) provides the smallest systematic error (MSE close to zero) but the overall accuracy is still low because of the remaining random error".[347]

RM1 was also applied to QM/MM modeling, coupled to either molecular dynamics or Monte Carlo simulations, as reported below.

Chen *et al.*[313] proposed a multiple time-step integrator based on a dual Hamiltonian and a hybrid method combining molecular dynamics and Monte Carlo simulation methods. That approach was proposed as a strategy to speed up the sampling of molecular systems in the canonical ensemble.

As such, DFT and RM1 were chosen as the two theoretical approaches that were used to study water cluster systems in terms of their known molecular behavior. The authors pointed out that RM1, used as the computationally less expensive Hamiltonian, showed expected behavior for MD and MC trajectories of these systems while keeping excellent computational performance.

RM1 was applied to the QM/MM modeling of L-lactic dehydrogenase complexed to oxamate anion from rabbit muscle.[300] The authors calculated binding isotope effects of selected atoms of oxamate in the active site of both LDH's chains A and B *vs.* oxamate in aqueous solution. Interactions of oxamate anion in the active site of monomers of lactic dehydrogenase (LDH) were also modeled. RM1 was the best method in reproducing some experimental interatomic distances involving atoms on the active site of LDH's chain A. For interatomic distances in LDH's chain B, OPLS-AA was the best one. The authors considered the RM1 calculated binding isotope effects as being satisfactory.

Marcos *et al.*[305] examined the performance of some quantum chemistry methods for the prediction of geometry and energy details of pentacoordinated phosphorus containing molecules in the presence of an external electric field. They considered DFT functionals and several semiempirical methods, including variants of AM1, such as, AM1*,[348] AM1/Arantes[349] and AM1/d-PhoT,[350] that are actually reparameterizations of AM1, specific for a certain property or class of molecules. From their results, the authors noted that the semiempirical methods that best described these systems and their reactivities were those that have d orbitals in their formulation, such as PM6 and AM1/d-PhoT. The authors further detected that RM1 and the re-parametrization AM1/Arantes were reasonably good, which they considered as being clear improvements over AM1, PM3 or MNDO-d: "With regard to model **1**, if we now consider the field dependence of d_2 (Fig. S2), we see that in general d functions are needed to describe the slope of the distance variation and that methods without it tend to underestimate this field dependence (RM1 being the only clear exception)".[305] In contrast, AM1* was not as good as they expected.

The performance of semiempirical methods to predict non-linear optical polarizabilities of five of donor-π-acceptor azo chromophores were studied in the Avcı's work.[333] First, the author determined the ground state geometries of such molecules by using AM1, MNDO, MNDO-d, PM3, RM1 and PM6 methods. After that, he applied finite field (FF), time-dependent Hartree-Fock (TDHF) and sum-over-states (SOS) approaches to calculate static and frequency-dependent non-linear

optical polarizabilities. For the first two approaches, he used MOPAC and for SOS he used Hyperchem 8.03 and ZINDO/S-CIS method to calculate the excited states of these molecules. In his study, the author also noted that the performance of MNDO and MNDO-d methods for first- and second-hyperpolarizabilities were low, especially for the first hyperpolarizabilities, whereas RM1 performance was considered good. A similar investigation had been previously carried out by the same author,[337] applying semiempirical methods for the calculation of nonlinear optical properties of donor-acceptor chromophores containing α-cyan. The performance of the AM1, MNDO, MNDO-d, PM3, RM1 and PM6 methods were evaluated with the RM1 performance classified as good.

A limitation of the RM1 usage is related to the values of the ionization potentials (IPs).[302] Another limitation, reported by Mathieu and Pipeau,[340] is the low accuracy of heats of formation of ionic species. This limitation was also detected by Lee *et al.*[336] in their study of the rationalization of the protonation states of the catalytic residues in the β-ketoacyl ACP synthase I (KasA) of the *Mycobacterium tuberculosis*. This investigation involved an arsenal of theoretical strategies in order to elucidate the protonation states of the catalytic residues in *Mycobacterium tuberculosis* β-ketoacyl ACP synthase I enzyme, *mt*KasA.[336] RM1 was used for QM/MM MD simulations with umbrella sampling to compute the potential of mean force (PMF) for the proton transfer reaction. From their results, the authors pointed out that RM1 showed good estimations for the difference in energy between the zwitterionic form and the neutral form in comparison to estimation performed by using DFT methods. However, RM1 overestimates the stability of the intermediate state that involves hydronium ions, being pointed out as an artifact by the authors.

Mikulskis *et al.*[331] carried out comparisons between the methods AM1, RM1 and PM6. In this study, they considered a combination of these semiempirical methods with molecular-mechanics with generalized Born and surface-area solvation in order to evaluate a conductor-like screening model with the MM/GBSA for ligand-binding affinity calculations.[331] The performance of that developed approach was evaluated by studying three different proteins (avidin, factor Xa and ferritin) with some ligands each. RM1 was the best method when applied to ferritin protein-ligand complexes. Likewise, Elioff *et al.*[312] studied the accuracy of the RM1 and PM7 to calculate the enthalpy of formation of a set of 45 nitrogen compounds. They commented that both RM1 and PM7 were less accurate than the other approaches employed to calculate the enthalpy of formation of the studied compounds.

Camilo *et al.*[330] carried out comparisons between RM1 and PM6 to describe structural and energetic properties of the forms of the *trans*-stilbene, that were the ground and (excited) singlet, triplet and ionic states (positive and negative polarons and bipolarons). They concluded that for the stilbene-like molecules, RM1 and PM6 data are similar to the corresponding AM1 and PM3 values.

Lee *et al.*[212] studied the pathways of the fragmentation of protonated testosterone by employing molecular dynamics simulations. In this work they evaluated the RM1 values of the energetic properties of the systems, as well as values calculated by other methods in comparison to DFT B3LYP. They observed that PM3, PM6 and RM1 underestimated both proton affinity and the energy difference between the two isomers studied when compared with the corresponding B3LYP values.

Electronic properties and structural aspects of signaling biomolecules were benchmarked by means of quantum chemistry methods in the Ferro and Bredow's study.[351] So, a test set comprised of some organic molecules including indole-, naphthalene-, phenol-, benzoic-, phenoxy- and auxin-derivatives was used to have their molecular properties predicted and compared for performance. HOMO/LUMO energies were calculated and compared to the corresponding experimental ionization potential (IP) and electron affinity (EA) values. The authors detected that KMLYP, MSINDO, and PM3 methods showed good performance for the whole set of molecules. They pointed out that, surprisingly, the new NDDO methods RM1, PM6, and MNDO-d did not provide accurate results for such properties, with statistically significant average deviations for electron affinities of, respectively, 0.36, 0.71, and 0.59 eV. Results for IPs showed that all NDDO-type semiempirical methods overestimated the IPs with a mean deviation of 0.71 eV.

An extended assessment work was performed by Zheng *et al.*[342] aiming at the prediction of chemical reaction barrier heights (CRBH) of a database set with 24 barrier heights, named DBH24/08, by means of 348 model chemistries. The authors detected that, obviously, the high-demand methods (having complexity N^5 or more) are the most accurate in predicting CRBHs. For instance, the best method was CCSD(T)(full)/aug-cc-pCV(T+d)Z (having N^7 complexity), that showed a MUE of 0.46 kcal mol^{-1}. The performance of semiempirical methods for calculation of CRBHs was also evaluated. From their results, MUE for RM1 predictions was 17.75 kcal mol^{-1}. The best semiempirical method was PM3, showing a MUE of 12.67 kcal mol^{-1}.

Assessment of semiempirical methods in describing halogen bonding was the focus of the investigation carried out by Ibrahim.[334] In his study, the performances of MNDO,

MNDO-d, AM1, RM1, PM3 and PM6 were tested for the prediction of: (*i*) geometries and binding energy calculations of halogen-containing molecules complexed with Lewis bases; (*ii*) thermochemistry of solvation of halobenzenes, considering both explicit and implicit generalized Born solvents; and (*iii*) proper descriptions of ligand-receptor complex systems in QM/MM molecular dynamics. RM1 led to reasonable descriptions of the molecular systems considered, descriptions at least equivalent to the ones obtained from more sophisticated quantum chemistry methods. However, calculated solvation free energies for halobenzenes relative to benzene, $\Delta_{solv}G$ (Gibbs energy of solvation) indicate that RM1 and PM3 methods do not evaluate the correct charge descriptions for such molecular systems. Nevertheless, RM1 was still the best method for calculations involving iodine systems: "For iodo complexes, the RM1 method gives better results than the AM1 method, whose halogen bond lengths are long".[334]

Ionic liquids had their enthalpies of formation assessed by means of several quantum chemistry methods in the article by Mathieu and Pipeau.[340] They formed a database composed of neutral molecules containing CNOF atoms, as well as its cationic and anionic forms. In order to compare the predictive power of the models for ions, the authors used as main criterion the root-mean-square deviation (RMSD) between calculated and experimental enthalpies of formation. RM1 was the least satisfactory semiempirical method for the prediction of enthalpies of formation for all molecules, displaying an RMSD of 26.2 kcal mol^{-1}, twice higher than AM1. As a result, the authors reported that RM1 does not correctly describe that property for ions. Another recent work on the prediction of enthalpies of formation detected that RM1 led to structures with multiple bonds within unusual rings, such as 1,5-cyclooctadiene or crowded structures such as tri-*tert*-butylmethane.[352] They further detected that RM1 systematically underestimates the enthalpy of formation of highly fluorinated compounds such as 1,1,1,3,3,3-hexafluoropropane.

In order to assess the performance of Hartree-Fock calculations with different basis sets and NDDO semiempirical methods to predict molecular polarizabilities, a study was presented by Fiedler *et al.*[296] In that study, the authors calculated the polarizabilities of 38 simple molecules and compared their results with the experimental values in terms of the mean unsigned percentage error (MUPE). They verified that all semiempirical methods underestimated molecular polarizabilities. MUPE for RM1 was 42, almost the same value for AM1 and much better than PM6, with a MUPE of 56. They detected that RM1 and AM1 were better than minimal basis set calculations, such as STO-3G, STO-3G(d) and 3-(21,3,3)

G. They also noted that adding diffuse p functions on hydrogen atoms rather than adding d basis functions on non-hydrogenic atoms is the key to better reproduce the electric dipole polarizabilities. Hartree-Fock with the basis set aug-cc-pVDZ was the best combination to reproduce the molecular polarizabilities of all considered molecules.

Experimental and theoretical studies for the inclusion complex of trimethoprim in randomly methylated beta-cyclodextrin was carried out by Kubota *et al.*[332] For the experimental section, the authors performed thermochemistry TG (thermogravimetry), DTG (differential TG) and DTA (differential thermal analysis) and spectroscopic infrared (IR) and ^{1}H NMR studies. For the theoretical part, the authors tried to predict the enthalpy of inclusion of trimethoprim into the methylated beta-cyclodextrin host by means of semiempirical methods AM1, PM3, PM6, RM1 and PM3-D. From the analysis of obtained theoretical results, they noticed that PM3-D presented the most consistent results when compared to the experimental ones.

Water nanoparticles were the focus of the theoretical study by Leverentz *et al.*[298] Theoretical methods (DFT, semiempirical and their modifications by considering dispersion corrections) were used to calculate binding and relative energies of $(H_2O)_{16}$ and $(H_2O)_{17}$. They selected five conformers of $(H_2O)_{16}$ and two conformers of $(H_2O)_{17}$ to calculate their relative energies using geometries obtained from MP2/aug-cc-pVTZ calculations at gas phase. The binding energies were calculated by using the following expression: $E_{bind} = 16E_{H_2O}^X - E_Y^X$, where $E_{H_2O}^X$ is the single-point energy of the monomer at method X and E_Y^X is the single-point energy of nanoparticle $(H_2O)_{16}$ at method X. Mean unsigned errors (MUE) were calculated comparing obtained results to CCSD(T)/aug-cc-pVTZ. Semiempirical methods with dispersion corrections presented much better performance than common semiempirical methods, like RM1, AM1 and MNDO. PM3-D had an excellent performance for binding energies of water 16-mers and water 17-mers in terms of MUE, which was of 3.2 kcal mol^{-1} for both. MUE values were also calculated for the relative energies of all conformers of the two considered nanoparticles. For this property, PM6 method presented the best performance for $(H_2O)_{16}$ (with MUE equal to 0.4 kcal mol^{-1}). The authors confirmed that dispersion corrections are important for the prediction of binding energies of non-covalent complexes.

Wang *et al.*[320] proposed new semiempirical parameterizations (AM1-W and AM1PG-W) based on AM1, specific for proton transfer reactions in water clusters. These two new methods included a pairwise Gaussian function to the core repulsion function, similar to MNDO/HB

and PDDG methods, which the authors reported to be better for the description of water clusters. They reported the new parameters for H and O atoms. From their results it can be noted that, for molecules from the test set composed by a selection of tetramer, pentamer, and hexamer structures, overall errors (that considered hydrogen-bonding energies, reaction energies, activation energies, and proton transfer energy profiles) were, in kcal mol^{-1}: 13.4 for AM1, 4.6 for RM1, 32.5 for PM3, 1.9 for AM1-W, and 2.0 AM1PG-W.

Finally, charge models derived from different semiempirical and *ab initio* methods were tested in the scope of molecular docking calculations.[315] The authors used cyclin dependent kinase 2 protein (CDK2) as biomolecular system to evaluate the performance of all tested methods with respect to their abilities to provide good molecular docking poses for CDK2 inhibitors as well as ΔG_{bind}. All theoretical methods presented poor correlation between binding and experimental free energies, lower than 0.5 for R^2. RM1 and AM1 were the best ones, while Hartree-Fock with 6-31G* was the worst.

13. General Advices, Advantages and Drawbacks of RM1

The applicability of RM1 by researchers in organic chemistry was mainly based on the predictions of structural and spectroscopic properties, as well as of energy, and electronic properties of the compounds involved in organic reactions. Usages of RM1 by organic researchers to investigate thermodynamic and structural quantities of species, present in reaction pathways as well as in energy surfaces, were also verified. These species included reaction intermediates and transition states.

Structural properties, such as bond lengths and bond angles predicted by RM1 were extensively compared with experimental values obtained by X-ray crystallography. Likewise, spectroscopic data such as those related to infrared, ^{1}H NMR, and UV-visible absorption, that were investigated by using RM1 geometries, were compared with experimental values. Structural properties and energy quantities were employed to decide which conformer could be more stable from sets of several possibilities.

Physical chemistry researches used RM1 results to study the energetic properties of the systems of interest, such as the enthalpies and Gibbs energies, both of formation and of reaction. Such studies interfaced profoundly with other areas, such as organic and medicinal chemistry.

Because of the small set of atoms parameterized in RM1, which so far does not contain any transition metals, few articles reported inorganic chemistry studies employing RM1, as usage of this method has been restricted to the calculation of properties of the ligands that were interacting with the metals.

From an analytical chemistry perspective, researchers employed RM1 to carry out quantitative structure-property relationship studies (QSPR) to obtain correlations between predicted and experimental values of properties, such as pK_a.

Several articles reported medicinal chemistry research employing RM1. In general, the usage of RM1 by researchers of this interface of chemistry included geometry optimizations and calculations of energetic and electronic properties of compounds that exhibited biological activities, including toxicities, in a QSAR framework.

Biological chemistry employed RM1 to optimize the geometries of the target systems, as well as to predict their energies and electronic quantities in molecular dynamics and docking calculations.

Because of the large computational demand required to investigate solid systems by other techniques, RM1 has been employed to calculate structural and electronic properties of materials, including Langmuir-Blodgett films.

Articles carried out comparisons between RM1 and other types of computational chemical methods, such as force field, DFT, *ab initio* and other semiempirical methods. These comparisons ranged from calculations of interest to organic chemistry to molecular dynamics calculations.

Inaccuracies of computed properties by RM1, that may present a difficulty, lie mainly in predicting ionization potentials;[302] heats of formation of ionic species;[340] overestimation of intermediate states involving hydronium ions;[336] enthalpies of formation of some nitrogen compounds;[312] calculated HOMO/LUMO energies to compare with experimental ionization potential (IP) and electron affinity (EA) values for some organic molecules such as indole-, naphthalene-, phenol-, benzoic-, phenoxy- and auxin-derivatives.[351] Finally, RM1 chemical reaction barrier heights displayed a mean unsigned error of 17.75 kcal mol^{-1},[342] a figure that could be much bettered in future improvements of the model.

In general, RM1 displayed substantial value in the prediction of structural, energetic and electronic properties of the various systems reported, coupled with a very light demand of computational resources.

14. Conclusions

Since its release, RM1 experienced almost immediate availability in several quantum chemistry software packages, such as MOPAC,[18] Hyperchem[23] and Spartan,[20] and also widespread usage, being even cited in books like Levine's Quantum Chemistry,[353] and Physical Chemistry.[354]

Recently, RM1 was also cited on chapter two written by Greer and Kwon[355] of the book Applied Theoretical Organic Chemistry.[356] This widespread availability motivated several research groups to publish improvements to the method, such as the multiple protocol parameters named semiglobal semiempirical self-consistently scaled quantum mechanical (S4QM),[27] for the adjustment of harmonic vibrational frequencies; the continuous model for neutral solutes in water, octanol, chloroform, carbon tetrachloride and for ions in water, MST/RM1;[33] a modification of RM1 to calculate the binding energy of hydrogen bonding, $RM1_{BH}$;[34] optimization for RM1 of some atomic parameters associated to the continuum solvent COSMO model;[41] implementation of D3H4 dispersion and hydrogen bond correction in RM1 by Řezáč and Hobza;[43] parameterization of the Sparkle model within RM1 for the calculation of lanthanide complexes;[45] and, finally, parameterization of RM1 itself for the lanthanide trications.[36-40]

All improvements greatly expanded the scope of RM1 leading to a wide range of applications to organic chemistry, physical chemistry, analytical chemistry and inorganic chemistry, as well as to their interfaces with medicine, biology and materials science.

The feedback we have been receiving from users has been quite encouraging and has provided us with enthusiasm to extend RM1 to more elements. Of course, we know that there are problems with RM1, but because it is widely used, these problems are recognized (many of them have been pointed out in this review) and that if users are aware of them, they can be avoided, and users can carry out their work with increased confidence.

Finally, semiempirical methods have been continuously pushing the frontier of the number of atoms of molecular and supramolecular systems whose properties of interest require a wave function. As the speed of computers continuously improve, increasingly complex structures become within the realm of possibilities of semiempirical methods. Of course, first principles methodologies will also keep expanding their applicability, but semiempirical methods will always be ahead of the quantum chemistry motorcade of methods. Is there any limit? Well the human cell has 100 trillion atoms.

Acknowledgments

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