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Short Report

Molecular Structure of Heterocycles: 6. Solvent Effects on the ^{17}O NMR Chemical Shifts of 5-Trichloromethylisoxazoles

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Com o objetivo de elucidar e quantificar os efeitos do solvente sobre os deslocamentos químicos de ^{17}O de três 5-triclorometilisoxazóis [(**1a**) não-, (**1b**) 3-metil- e (**1c**) 4-metil-substituído] foi realizada uma análise de regressão multilinear, utilizando os parâmetros solvatocrômicos de Kamlet-Abboud-Taft (KAT). Os deslocamentos químicos do átomo de oxigênio do anel, O1, dos compostos **1a-c** mostraram dependências (em ppm) em função da polaridade-polarizabilidade do solvente de -4.8π*, -3.2π*, -8.9π*, em função da acidez do solvente (HBD) de 0.9α, -0.2α, -2.7α e em função da basicidade do solvente (HBA) de -0.4β, 1.9β, 0.9β, respectivamente. Os dados de carga líquida de O1 e de momento de dipolo, obtidos por cálculos de orbitais moleculares (AM1), são comparados com os parâmetros de efeitos do solvente determinados para os compostos **1a-c**.

A multilinear-regression analysis using the Kamlet-Abboud-Taft (KAT) solvatochromic parameters in order to elucidate and quantify the solvent effects on the ^{17}O chemical shifts of three 5-trichloromethylisoxazoles [(**1a**) non-, (**1b**) 3-methyl- and (**1c**) 4-methyl-substituted] is reported. The chemical shifts of ring oxygen atom, O1, of compounds **1a-c** show dependencies (in ppm) on the solvent polarity-polarizability of -4.8π*, -3.2π*, -8.9π*, on the solvent hydrogen-bond-donor (HBD) acidities 0.9α, -0.2α, -2.7α and the solvent hydrogen-bond-acceptor (HBA) basicities -0.4β, 1.9β, 0.9β, respectively. The data of net charges of O1 and dipole moment, obtained from MO calculations (AM1), are compared with the solvent effect parameters obtained for compounds **1a-c**.

Keywords: ^{17}O NMR, solvent effects, isoxazoles, MO calculations

Introduction

Several papers have been devoted to the empirical and theoretical studies of solvent effect on the ^{17}O chemical shifts in different organic compounds[1,2]. Special attention has been devoted to the study of solvent effects in amides, where the ^{15}N and ^{17}O nuclei are observed[2]. Recently we applied a multilinear-regression analysis using the Kamlet-Abboud-Taft (KAT)[3] solvatochromic parameters in order to elucidate and quantify the solvent effects on the ^{17}O chemical shifts of 1,1,1-trichloro-4-methoxy-3-alken-2-ones[4] and 5-hydroxy-4,5-dihydroisoxazoles[5a]. According to the KAT formalism, the observed chemical shift of compound X at infinite dilution in solvent Y, δ^X_Y, would be given by the relationship[3] shown in Equation 1.

$$\delta^X_Y = \delta^X_{CH} + s^X (\pi^*_Y + d^X \delta_Y) + a^X\alpha_Y + b^X\beta_Y \qquad (1)$$

The solvent effects are described by the solvent parameters δ^X_{CH}, π^*_Y, δ_Y, α_Y and β_Y. The π^*_Y scale is an index of solvent dipolarity/polarizability, which measures the ability of the solvent to stabilize a charge or a dipole due to its dielectric effect. The α_Y scale of solvent hydrogen-bond-donor (HBD) acidities describes the ability of the solvent to donate a proton in a solvent-to-solute hydrogen bond. The β_Y scale of hydrogen-bond-acceptor (HBA) basicities measures the ability of the solvent to accept a proton (*i.e.*, to donate an electron pair) in a solute-to-solvent hydrogen bond. The δ_Y parameter is a polarizability correction term for polychlorinated ($\delta_Y = 0.5$) and aromatic ($\delta_Y = 1.0$) solvents. The coefficients s^X, a^X and b^X in Equation 1 define the sensitivity of δ^X_Y to solvent dipolarity/polarizability, acidity and basicity, respectively. The product of coefficients s^Xd^X defines the sensitivity of δ^X_Y for the

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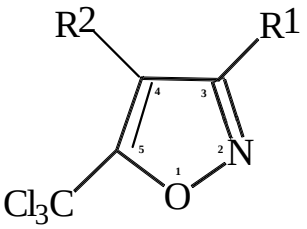
polarizability correction term. The term δ^{X}_{CH} is the chemical shift of substrate X measured in cyclohexane since this reference solvent does not form hydrogen bond ($\alpha_{CH} = \beta_{CH} = 0$) and was selected to define the origin of π^*_Y scale ($\pi^*_{CH} = 0$). The term $s^X(\pi^*_Y + d^X\delta_Y)$ accounts for the difference between the contribution to δ^X_Y in solvent Y and in cyclohexane from the solute-solvent interactions other than hydrogen bonding. The terms $a^X\alpha_Y$ and $b^X\beta_Y$ represent the contributions from hydrogen bonds of substrate X with solvents HBD and HBA, respectively.

As a part of our research program we have studied the synthesis[6-9], structure[5] and the multi-nuclear NMR chemical shifts[10] of 5-, 6- and 7-membered heterocycles. The aim of this work is to elucidate and quantify the solvent effects on the ^{17}O chemical shifts of 5-trichloromethyl-isoxazoles **1a-c** using the Kamlet-Abboud-Taft (KAT) solvatochromic parameters[3] (Scheme).



1a-c

	R2	R1
1a	H	H
1b	H	Me
1c	Me	H

Scheme

Experimental

Compounds

The synthesis of compounds **1a-c** was developed in our laboratories[6a].

NMR spectroscopy

The ^{17}O NMR spectra were recorded on a Bruker DPX 400 at 54.25 MHz. The sample temperature was set at 323 ± 1 K. The instrumental settings were as follows: spectral widths 38 KHz (705 ppm), 8K data points, pulse width 12 μs (90°), acquisition time 54 ms, preacquisitions delay 10 ms, 16000-90000 scans, LB of 100 Hz, sample spinning 20 Hz. The spectra were recorded with a RIDE (RIng Down Eliminate) sequence[13] for suppression of acoustic ringing. The general reproducibility of chemical shift data is estimated to be better than ± 1.0 ppm (± 0.2 within the same series). The half-height widths were in the range 150-800 Hz.

All spectra were acquired in a 10mm tube, at natural abundance, in acetone, methanol, acetonitrile, dimethyl-sulfoxide, toluene, chloroform and dichloromethane as solvents. The concentration of the samples used in these experiments was 0.5, 1.0, 2.0, 3.0, 4.0 and 6.0 mol L^{-1}, and the signals were referenced to external H_2O (in a capillary coaxial tube).

Semiempirical MO calculations

The MO calculations were carried out by the Austin Model 1 (AM1) semiempirical method[11], implemented in the HyperChem 6.03 package (1999)[12]. Geometries were completely optimized without fixing any parameter, thus bringing all geometric variables to their equilibrium values. The energy minimization protocol employs the Polak-Ribiere algorithm, a conjugated gradient method[11,12]. Convergence to a local minimum is achieved when the energy gradient is < 0.01 kcal mol^{-1}. The calculations were performed on a PC Pentium IV 1.4 GHz computer equipped with a printer.

Results and Discussion

The ^{17}O chemical shifts of 5-trichloromethylisoxazoles **1a-c** in various solvents are listed in Table 1. These values were determined by extrapolation to infinite dilution from spectral data obtained in several concentrations (0.5 to 6 mol L^{-1}) relative to external water, at 323 K (see experimental). The Kamlet-Abboud-Taft (KAT) solvatochromic parameters (π^*_Y, α_Y, β_Y and δ_Y) used in the present work are also given in Table 1. Considering the ^{17}O NMR chemical shifts of the oxygen atom of the heterocyclic ring (O1) of compounds **1a-c** and according to the KAT formalism, we can re-write Equation 1 as Equation 2 (where X = O1).

$$\delta^{O1}_Y = \delta^{O1}_{CH} + s^{O1}(\pi^*_Y + d^{O1}\delta_Y) + a^{O1}\alpha_Y + b^{O1}\beta_Y \quad (2)$$

Table 2 presents the least-squares-fitted solute (**1a-c**) estimates using Equation 2. The chemical shifts of ring oxygen atom, O1, of compounds **1a-1c** show dependencies (in ppm) on the solvent polarity-polarizability of -4.8π*, -3.2π*, -8.9π*, on the solvent hydrogen-bond-donor (HBD) acidities 0.9α, -0.2α, -2.7α and on the solvent hydrogen-bond-acceptor (HBA) basicities -0.4β, 1.9β, 0.9β, respectively.

Preliminary comparison shows that the response values of the oxygen chemical shifts to the solvent-solute dipolarity-polarizability (s^{O1}) are of shielding effect for O1. The response to the solvent HBD acidities (a^{O1}) is of deshielding for O1 of **1a** and shielding for **1b** and **1c**.

Table 1. ^{17}O NMR chemical shifts of compounds **1a-c** at infinite dilution[a] and solvent parameters[b] used in Equation 2.

Solvent	Compound			Solvent Parameters			
Y	**1a**	**1b**	**1c**				
	O1	O1	O1	π*	α	β	δ
$Me_2C=O$	340.42	332.60	346.00	0.62	0.08	0.48	0.0
MeOH	340.96	332.56	343.15	0.60	0.93	0.62	0.0
MeCN	339.85	331.77	343.84	0.66	0.19	0.31	0.0
Me_2SO	338.08	331.79	342.41	1.00	0.00	0.76	0.0
PhMe	342.03	335.39	348.06	0.49	0.00	0.11	1.0
$CHCl_3$	340.90	333.10	345.17	0.69	0.44	0.00	0.5
CH_2Cl_2	340.85	332.56	343.61	0.73	0.30	0.00	0.5

[a]See experimental; [b]From references 2,3.

Table 2. Least-square-fitted solute **1a-c** parameters for Equation 2.

Compd.	$\delta^{O1}CH$	s^{O1}	sd^{O1}	d^{O1}	a^{O1}	b^{O1}	r
1a	343.32	-4.850	1.209	-0.249	0.896	-0.456	0.989
1b	333.47	-3.190	3.305	-1.036	-0.192	1.978	0.991
1c	350.67	-8.946	1.843	-0.206	-2.724	0.890	0.949

The influence of the solvent hydrogen-bond-acceptor (HBA) basicities (b^{O1}) is of shielding effect for **1a** and deshielding for **1b** and **1c**.

The contributions (in ppm) to the ^{17}O chemical shifts of O1 for compounds **1a-c** from the terms of Equation 2 are listed in Table 3. The contribution of solvent-solute dipolarity-polarizability ($s^{O1}\pi^*$) shows a shielding effect for chemical shift of O1 groups (**1a-c**) in all solvents, in the following order: dimethylsulfoxide > dichloromethane > chloroform > acetonitrile > acetone > methanol > toluene. The contribution of solvent HBD acidities ($a^{O1}\alpha$) shows a negligible (< 1.0 ppm) deshielding (**1a**) or deshielding (**1b** and **1c**) effect on the chemical shift of O1, except for methanol and chloroform in compound **1c**. The contribution response to the solvent HBA basicities ($b^{O1}\beta$) show a negligible (< 1.0 ppm) shielding (**1a**) or deshielding (**1b** and **1c**) effect for chemical shift of O1 oxygen atom, except for methanol and dimthyl-sulfoxide in compound **1b**.

Considering that the terms s^{O1}, a^{O1} and b^{O1} are a measurement of the sensitivity of the studied compound to the solvent dipolarity/polarizability (π^*_Y), the solvent hydrogen-bond-donor acidities (α_Y) and the solvent hydrogen-bond-acceptor basicities (β_Y), respectively, the differences between these parameters for compounds **1a-c** must reflect the differences in some intramolecular properties of these molecules. In order to better understand the differences of the sensitivity of each compound to the solvent effects the MO calculations were performed. Selected data of the most stable molecular structure of compounds **1a-c** were determined by energy minimization calculations using the AM1 semiempirical method[11,12] are listed in Table 4.

Table 3. Contributions (in ppm) to the ^{17}O chemical shift of O1 of compounds **1a-c** from terms of Equation 2.

Compound (X)	**1a**		
Solvent (Y)	$s^{O1}\pi^*$	$a^{O1}\alpha$	$b^{O1}\beta$
$Me_2C=O$	-3.007	0.072	-0.219
MeOH	-2.910	0.833	-0.283
MeCN	-3.201	0.170	-0.141
Me_2SO	-4.850	0.000	-0.347
PhMe	-2.377	0.000	-0.050
$CHCl_3$	-3.347	0.394	0.000
CH_2Cl_2	-3.541	0.269	0.000
Compound (X)	**1b**		
Solvent (Y)	$s^{O1}\pi^*$	$a^{O1}\alpha$	$b^{O1}\beta$
$Me_2C=O$	-1.978	-0.015	0.949
MeOH	-1.914	-0.179	1.226
MeCN	-2.105	-0.036	0.613
Me_2SO	-3.190	0.000	1.503
PhMe	-1.563	0.000	0.218
$CHCl_3$	-2.201	-0.084	0.000
CH_2Cl_2	-2.329	-0.058	0.000
Compound (X)	**1c**		
Solvent (Y)	$s^{O1}\pi^*$	$a^{O1}\alpha$	$b^{O1}\beta$
$Me_2C=O$	-5.547	-0.218	0.427
MeOH	-5.368	-2.533	0.552
MeCN	-5.904	-0.518	0.276
Me_2SO	-8.946	-0.000	0.676
PhMe	-4.384	-0.000	0.098
$CHCl_3$	-6.173	-1.199	0.000
CH_2Cl_2	-6.531	-0.817	0.000

Although the solvent effect was obtained only for three compounds, and therefore we can not make a statistical treatment, when these data were compared with molecular data obtained by MO calculations, it was possible to observe some reasonable trends.

The solvent-solute dipolarity-polarizability (s^{O1}) does not show any trend when compared with the dipole moments of compounds **1a-c** (Table 4). The other parameters show a tendency to decrease (a^{O1}) and increase (b^{O1}) with dipole moments of compounds **1a-c**. All absolute values of solvent parameters (s^{O1}, a^{O1}, b^{O1}) for O1 decrease with the decrease of the net charge in this atom (Table 4).

Conclusion

This work show the validaty to use the Kamlet-Abboud-Taft (KAT) model for complete evaluation of the solvent effects on the ^{17}O chemical shifts of compounds **1a-c**. From a multi-linear-regression analysis using the Kamlet-Abboud-Taft (KAT) solvatochromic parameters (π^*_Y, α_Y, β_Y and δ_Y) and the observed ^{17}O chemical shifts of compounds **1a-c**, at infinite dilution, it was possible to determine the terms s^{O1}, a^{O1} and b^{O1}. These terms are a measurement of the sensitivity of the studied compounds to the solvent dipolarity/polarizability, the solvent hydrogen-bond-donor acidities and the solvent hydrogen-bond-acceptor basicities, respectively.

Table 4. Selected structural data*a* obtained by AM1 calculations for compounds **1a-c**.

Data	Compounds **1a**	**1b**	**1c**
Oxygen Net Charge	-0.0304	-0.0302	-0.0338
Dipole (sum, debyes)	2.624	2.982	3.140
Bindind Energy (kcal.mol-1)	-1016.96	-1300.20	-1299.66
Bond Length (Å)			
O1-N2	1.3131	1.3120	1.3119
N2-C3	1.3430	1.3507	1.3401
C3-C4	1.4596	1.4655	1.4663
C4-C5	1.3820	1.3797	1.3855
C5-O1	1.4218	1.4212	1.4253
C3-H3	1.0915	-	1.0913
C4-H4	1.0860	1.0858	-
C3-CH3	-	1.4734	-
C4-CH3	-	-	1.4606
C5-C6	1.4748	1.4747	1.4755
Bond Angle (degrees)			
O1N2C3	109.57	109.60	109.53
N2C3C4	109.07	108.54	109.28
C3C4C5	104.07	104.34	103.82
C4C5O1	107.71	107.71	107.54
C5O1N2	109.58	109.81	109.84
N2C3H3	123.65	-	123.95
C5C4H4	129.31	129.46	-
N2C3CH3	-	126.91	-
C5C4CH3	-	-	131.44
C5C6Cl	109.32	109.34	110.60
O1C5C6	117.41	117.39	115.70
Dihedral Angle (degrees)			
O1C5C4H4	180.00	179.96	-
O1N2C3H3	180.00	-	180.00
O1C5C4CH3	-	-	179.96
O1N2C3CH3	-	179.75	-
O1C5C6Cl	180.00	179.68	179.16
H4C4C3CH3	-	0.28	-
H3C3C4CH3	-	-	0.02
H3C3C4H4	0.00	-	-

[a]See experimental.

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