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The role of stereoelectronic interactions in the conformational isomerism of some phosphorus-containing model compounds

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The rotational isomerism of model phosphorus-containing compounds was evaluated by using theoretical methodologies. The *trans* rotamer of chloromethylphosphonic acid dichloride (1) was found to be the prevailing form in the gas phase and in non-polar solvents, with an inverse behaviour from chloroform solution. Although the use of direct spin–spin coupling constants (SSCCs) do not apply for the quantitative determination of conformers in 1, due to the small dependence of *J* with conformation, the observed measurements and calculated individual couplings suggest that the *gauche* conformer is progressively stabilized with increasing the solvent polarity. In addition, theoretical calculations at the CBS-Q level for the corresponding phosphine of 1 (compound 2) showed the *gauche* rotamer as the prevailing one in the isolated state. Natural Bond Orbital (NBO) analysis indicated that steric and electrostatic effects rule the rotational isomerism of 1, while the anomeric effect $n_P \rightarrow \sigma^*_{CCl}$ also plays an important role on the conformational equilibrium of 2. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: conformational analysis; solvation theory; phosphorus-containing compounds; classical effects; anomeric effect

INTRODUCTION

Phosphorus-containing compounds are interesting models to be studied due to many features. In the NMR point of view, ^{31}P has a natural abundance of 100% and spin ½, being suitable for analysis,[1] whereas in the biochemical field, these compounds play an important role in metabolism, for instance as ATP.[2] However, few efforts have been done to understand which interactions govern the conformational equilibrium of this class of compounds, being solely classical effects often invoked to explain their conformational preferences. Moreover, coupling constants involving ^{31}P have not been used in conformational analysis, although average couplings between conformers in a given solvent can be easily provided. In this way, if one estimates intrinsic couplings, conformer populations may be obtained through the equation given below:

$$\begin{aligned} J_{\text{obs}} &= n_A J_A + n_B J_B \\ n_A + n_B &= 1 \end{aligned} \tag{1}$$

where J_{obs} is the observed coupling, n_A and n_B are the molar fractions of conformer A and B, respectively and J_A and J_B are the individual couplings of such conformers.

The solvation theory developed by Abraham and Bretschneider,[3] which has been successfully focussed in several conformational studies,[4–10] allows the determination of conformer populations in different solvents and, consequently, the achievement of intrinsic couplings. Individual couplings may also be obtained through theoretical calculations, by summing the Fermi contact (FC), spin dipolar (SD), paramagnetic spin orbital (PSO) and diamagnetic spin orbital (DSO) terms, where the former (FC) is the main term describing ^1J couplings.[11]

An important class of phosphorus-containing compounds is the phosphonates, whose potential as mimetic and hydrolytically stable phosphates in bioorganic chemistry is known for a long time.[12] The introduction of electronegative atoms in the methylene group, such as chlorine, makes the acidity of phosphonates as the corresponding phosphates, which are one of the most important constituents of living systems.[12,13] The target compound of our conformational analysis is the chloromethylphosphonic acid dichloride **1** (Fig. 1), which is a phosphonate analogue. It will be theoretically and experimentally (NMR) compared with its corresponding phosphine **2** (highly hydrolysable), in order to evaluate the governing interactions of this other important class of organophosphorus compounds.

The solvation theory applied here is fully described in Reference 2, and the used methodology, which is based on the dependence of adequate coupling constants with the solvent dielectric constant and further analysis through MODELS and BESTFIT programmes,[3] can also be found in several papers of ours.[4–10]

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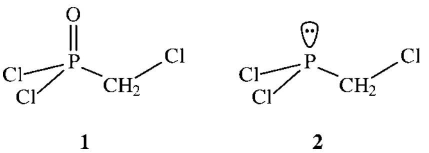

Figure 1. Chloromethylphosphonic acid dichloride (**1**) and its corresponding phosphine (**2**)

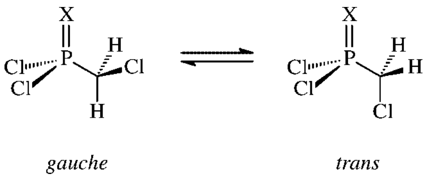

Figure 2. Rotational equilibrium for **1** ($X = O$) and **2** ($X =$ lone pair)

EXPERIMENTAL

NMR experiments

Compound **1** was commercially obtained from Aldrich. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-500 spectrometer operating at 499.88 and 125.70 MHz, respectively. Spectra were taken for *ca*. 20 mg cm^{-3} solutions with a probe temperature of 295 K. Benzene-d_6 was used as the deuterium lock for the CCl_4 solution and all spectra were referenced to TMS. Typical conditions for proton spectra were: spectral width 4000 Hz with 32 K data points and zero filled to 128 K, giving a digital resolution of 0.06 Hz. For carbon-13 spectra, the conditions were: spectral width 30 000 Hz with 128 K data points and zero filled to 512 K, giving a digital resolution of 0.1 Hz.

Theoretical calculations

Rotamers of compounds **1** and **2** were predicted by building a Potential Energy Surface (PES) using the Gaussian 03 programme,[14] through rotating the O═P—C—Cl and lone pair—P—C—Cl dihedral angles at the B3LYP/6-311 + g(d,p) level. Each minimum was then optimized using the improved CBS-Q method,[15] and the NBO[16] calculations, including deletion of all Rydberg and antibonding interactions, were carried out at the B3LYP/aug-cc-pVTZ level. Further calculations, including solvent effects, were performed by utilizing the Onsager model at the B3LYP/6-311 + g(d,p) level. Calculated coupling constants ($^1J_{PC}$, $^2J_{PH}$ and $^1J_{CH}$) for both conformers of **1** were obtained by summing the FC, SD, PSO and DSO terms. Calculations of all four terms of spin–spin coupling constants (SSCCs) were carried out using the B3LYP functional, and the B3LYP/aug-cc-pVTZ-J basis set for H, C and O,[17] aug-cc-pVTZ for Cl and a 18s14p10d basis set for phosphorus.[18]

RESULTS AND DISCUSSION

Two stable conformers were found for compounds **1** and **2,** *trans* and *gauche* (Fig. 2), with *trans* as the prevailing rotamer in the gas phase for **1**, and *gauche* the most abundant one for **2**, as illustrated in PES (Fig. 3). Each minimum of PES was optimized using the CBS-Q method, giving the energy values of Table 1. This shows that the entropic contribution to the Gibbs energy in the rotational isomerism is small and thus the ΔE^V obtained through the solvation theory can be compared with the calculated ΔG for **1**. The energy difference found differs in some extent with a previous value obtained through electron diffraction data more than three decades ago, which indicates that two conformers are present in approximately equal amounts in the vapour phase.[19]

The resulting molecular geometries for both rotamers of **1** were used in the solvation calculations with the MODELS programme,[3] in order to obtain the reaction field parameters

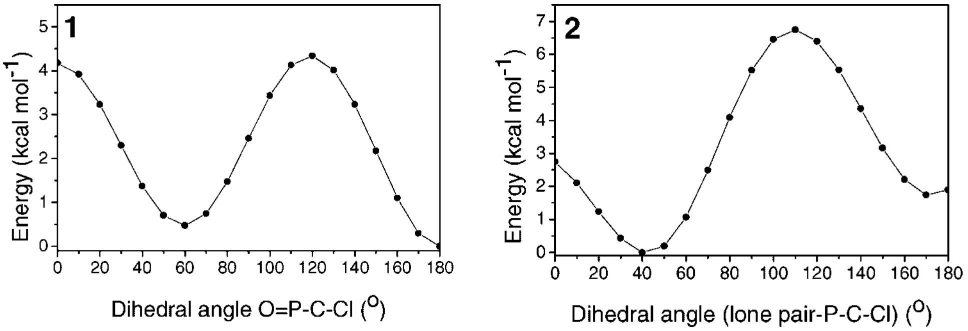

Figure 3. Potential energy surfaces for **1** and **2**, obtained at the B3LYP/6-311 + g(d,p) level

Table 1. Results from theoretical calculations (CBS-Q) for compounds **1** and **2**

Compound	Rotamer	μ (D)	G (hartrees)	ΔG (kcal mol^{-1})	$T\Delta S$ (kcal mol^{-1})
1	*gauche*	3.91	−1834.66335	0.67	0.13
	trans	2.43	−1834.66442	0	0
2	*gauche*	1.39	−1759.47303	0	0
	trans	2.27	−1759.47094	1.31	0.09

Table 2. Reaction field parameters for compound **1**[a]

Rotamer	k	h	l	n_D	V_M	μ
gauche	2.4691	1.8170	0.5221	1.4352	94.507	2.534
trans	1.4227	3.0523	0.5221	1.4352	94.507	1.923

[a] k, μ^2/a^3 [μ, dipole moment (in D); a, solute radius]; h, q^2/a^5 (q, quadrupole moment); l, $2(n_D^2 - 1)/(n_D + 2)$; n_D, refractive index; V_M, molar volume.

(Table 2), which are terms related to dipole and quadrupole moments, refraction index and molar volume. These, together with the experimental couplings of Table 3, were used to achieve the conformer energies and intrinsic couplings, through the BESTFIT programme.[3]

The measured $^2J_{PH}$ and $^1J_{CH}$ couplings follow a regular trend with changing the solvent dielectric constant (ε), while $^1J_{PC}$ does not. Thus, $^2J_{PH}$ and $^1J_{CH}$ were used to estimate the rotational energies of Table 3. According to the solvation theory approach, the *trans* population of **1** varies from 61% in vapour phase, which coincides with the calculated ΔG^V value, to 47% in CD_3CN, due to the larger dipole moment of the *gauche* rotamer, which is more stabilized when increasing the solvent polarity. The BESTFIT[3] intrinsic couplings for **1** were $^1J_{CH(gauche)}$ 173.6 Hz, $^1J_{CH(trans)}$ 136.6 Hz, $^2J_{PH(gauche)}$ 1.4 and $^2J_{PH(trans)}$ 10.6 Hz. Whilst the $^2J_{PH}$ magnitudes are in agreement with the reported coupling constants for similar compounds,[20] the intrinsic $^1J_{CH}$ couplings obtained seem to be not realistic, that is such values must be overestimated, because of the small dependence of the observed coupling constants with the media; a larger dependence was expected according to the significant difference between the dipole moments of *gauche* and *trans* conformers. As a result, the intrinsic $^1J_{CH}$ couplings for *gauche* and *trans* should be much smaller than predicted by MODELS/BESTFIT. If coupling constants change just by few amounts when varying solvent polarities, as observed (up to 2 Hz), estimation with BESTFIT is expected to not work well, as any extrapolation. In order to solve this problem, direct SSCCs calculations were carried out for both conformers to provide more accurate values for intrinsic couplings.

According to the non-relativistic Ramsey's formulation, isotropic SSCCs are contributed by four terms, namely, FC, SD, PSO and DSO as shown in Eqn (2):

$$J = {}^{FC}J + {}^{SD}J + {}^{PSO}J + {}^{DSO}J \qquad (2)$$

where the FC term is the main contributing parameter for ^1J spin–spin couplings. The sum of the above terms resulted in the following individual couplings: $^1J_{CH(gauche)}$ of 166.7 Hz, $^1J_{CH(trans)}$ of 166.1 Hz, $^2J_{PH(gauche)}$ of 3.1 Hz, $^2J_{PH(trans)}$ of 3.2 Hz, $^1J_{CP(gauche)}$ of 98.2 Hz and $^1J_{CP(trans)}$ of 99.0 Hz. These values disagree from the BESTFIT results and confirm that individual couplings are closely similar. Thus, they may not be used to accurately account for the conformational energies of **1**.

Although the lack of applicability of NMR in precisely predicting the conformational preferences of **1** in solution, $^1J_{CH}$ and $^2J_{PH}$ coupling constants exhibit a small but regular trend by varying solvents; the *gauche* population should increase by increasing the solvent dielectric constant, as a result of minimization of dipolar repulsion by solvent polarity. Such behaviour was evaluated through using the Onsager approach to compute conformer energies in solution. Optimization calculations for **1** at the B3LYP/6-311 + g(d,p) level showed energy results comparable to CBS-Q level for the compound in the gas phase; thus solvation calculations using the DFT method can be used to account for the solvent effects on the conformational equilibrium of compound **1**. The computed solvent effects obtained at the B3LYP/6-311 + g(d,p) level (Table 4) suggest that

Table 3. Experimental and (fitted) coupling constants (Hz), chemical shifts (ppm), energies (kcal mol^{-1}) and *gauche* mole fractions for compound **1**, obtained through MODELS/BESTFIT

Solvent	ε	$\lvert ^2J_{PH} \rvert$	$^1J_{CH}$	$^1J_{PC}$	δ_H	δ_C	ΔE_{g-t}	n_{gauche}
Vapour	1.00						0.67	0.39
CCl_4	2.24	6.6 (6.6)	153.6 (153.0)	117.3	3.91	45.12	0.55	0.43
$CDCl_3$	4.81	6.2 (6.3)	153.8 (154.2)	117.6	4.18	45.86	0.49	0.46
CD_2Cl_2	9.01	6.1 (6.0)	154.3 (155.0)	116.9	4.21	46.08	0.43	0.49
Pyridine	12.40	5.8 (6.0)	155.8 (155.4)	111.6	5.41	46.45	0.41	0.50
CD_3CN	37.50	6.0 (5.7)	156.3 (156.4)	115.1	4.46	46.26	0.34	0.53
Pure Liq.	11.30[a]	5.8 (6.0)	155.3 (155.3)	114.4	4.14	45.90	0.42	0.49

[a] Pure liquid dielectric constant was estimated by interpolation in a $^1J_{CH}$ *versus* ε plot.

Table 4. Solvent effects on the conformational energies (kcal mol^{-1}) of **1**, obtained at the B3LYP/6-311 + g(d,p) level and the Onsager model

Solvent	E_{rel} (*gauche*)	E_{rel} (*trans*)
Vapour	0.44	0
CCl_4	0.11	0
$CHCl_3$	0	0.10
CH_2Cl_2	0	0.21
Pyridine	0	0.24
CH_3CN	0	0.31

Table 5. Total hyperconjugative energies, relative Lewis-type energy and antiperiplanar orbital interactions, for compounds **1** and **2** (kcal mol^{-1})

	1		**2**	
Interaction	*gauche*	*trans*	*gauche*	*trans*
$E_{hyperconjugation}$	657.25	647.01	215.63	227.43
ΔE_{Lewis}	10.91	0	0	13.11
$LP_P \rightarrow \sigma^*_{C-Cl}$	—	—	—	5.42
$LP_P \rightarrow \sigma^*_{C-H}$	—	—	1.97	—
$LP_O \rightarrow \sigma^*_{C-Cl}$	—	1.09	—	—
$\sigma_{PO} \rightarrow \sigma^*_{C-Cl}$	—	0.75	—	—
$\sigma_{P-Cl} \rightarrow \sigma^*_{C-Cl}$	1.95	—	2.49	—
$\sigma_{P-Cl} \rightarrow \sigma^*_{C-H}$	1.05	0.96 (2×)	1.33	1.30 (2×)
$\sigma_{C-Cl} \rightarrow \sigma^*_{P-Cl}$	1.61	—	1.13	—
$\sigma_{C-H} \rightarrow \sigma^*_{P-Cl}$	2.79	—	1.72 + 0.66	2.24 (2×)
$\sigma_{C-Cl} \rightarrow \sigma^*_{PO}$	—	1.64		

the conformational changes of **1**, on going from the gas phase ($\varepsilon = 1.0$) to acetonitrile solution ($\varepsilon = 37.5$), is higher than predicted by MODELS/BESTFIT, probably because of the failures described above when using this latter methodology.

The conformational behaviour of the title compounds may be interpreted by using Natural Bond Orbital (NBO) analysis.[16] Lewis-type interactions are traditionally invoked to interpret the rotational equilibrium of model compounds. However, non-classical interactions have shown to contribute strongly, and in some cases decisively,[21] for the conformer stabilization. The calculated energy difference in **1** is 0.67 kcal mol^{-1} in the gas phase favouring the *trans* conformer, though stabilization due to electronic delocalization is much larger than this amount for the *gauche* conformer, which are summarized in Table 4. These results suggest that Lewis-type interactions play an important role for the conformational isomerism of **1**, essentially the electrostatic repulsion between the negatively charged oxygen (−0.845) and chlorine (−0.206) atoms.

This figure changes when the oxygen of compound **1** is replaced by a lone pair, to give compound **2**. For the isolated molecule, the *gauche* conformer of **2** is more stable than the *trans* conformer by a calculated amount of 1.3 kcal mol^{-1}, which is an excellent agreement with the value found elsewhere.[22] By comparing with **1**, this value is obviously a result of smaller electrostatic repulsion in **2**, which does not experience O. . .Cl repulsion. However, the neat result does not agree with the expected energy difference, if only the traditional Lewis-type energies are taken into account. Table 5 shows that conformer *trans* of **2** is largely stabilized by electronic delocalization (11.8 kcal mol^{-1}), whose major contribution is from $LP_P \rightarrow \sigma^*_{C—Cl}$ (*ca*. 5.4 kcal mol^{-1}), as illustrated in Fig. 4. Similar interaction has shown to be relevant in other compounds, though it was smaller than for the corresponding nitrogen systems.[23]

The anomeric effect has been extensively studied for oxygen-containing compounds, especially sugars.[24] The hyperconjugative effect of sulphur when replacing oxygen in such compounds is supposed to be smaller,[24] though its lone pair donation to antiperiplanar C—Cl* orbital has been demonstrated to be highly energetic.[25] The effect of a nitrogen atom is also comparable to the oxygen,[24] but the corresponding interaction in phosphines has been somewhat scarcely investigated, though an infrared determination of the conformational preferences of (methylthio)dichlorophosphine has been already reported.[26] Thus, this study also shows that the anomeric effect in α-substituted phosphines is an important rule for its conformational isomerism and that the traditional approach involving only steric/Coulombic repulsion in dealing with structural issues in chemistry is inadequate.

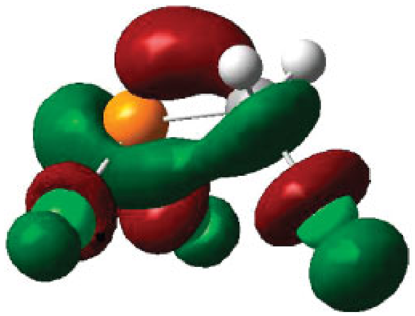

Figure 4. HOMO and LUMO orbitals for *trans* conformer of **2**, illustrating the LP_P and C–Cl* overlap (the anomeric effect). Antibonding P–Cl* orbital is also included

CONCLUSIONS

Our experimental and computational studies demonstrated that chloromethylphosphonic acid dichloride isomerizes between *gauche* and *trans* conformers, with the former slightly more populated in polar solvents. This behaviour has shown to be dictated predominantly due to classical steric and electrostatic interactions. However, replacement of oxygen in chloromethylphosphonic acid dichloride by a lone pair to give the corresponding phosphine changes greatly the conformational preferences. For this compound, theoretical calculations exhibit the *gauche* conformer as the most stable form in the isolated state, but hiperconjugation, especially the $LP_P \rightarrow \sigma^*_{C—F}$ interaction (the anomeric effect), was competitive with Lewis-type interactions, and then may not be ignored when addressing the conformational stability of similar compounds.

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