

## Solvent Effects on the Conformer Distribution of 2-Methoxypropanal and Chloroacetaldehyde. A Model Case for the Conformational Analysis in Solution of Chiral Aldehydes Including Polar Groups

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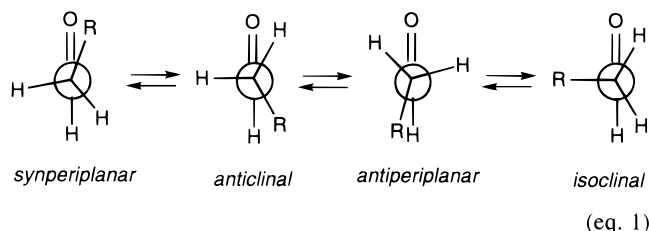
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A detailed conformational analysis of 2-methoxypropanal including solvent effects and electron correlation is reported. It is found that the conformer distribution is substantially different from that obtained *in vacuo*. In general, conformations in which the carbonyl and alkoxy dipoles are synperiplanar to each other are stabilized with respect to the gas phase. Donating groups such as methyl or hydrogen groups are preferably orthogonally disposed with respect to the carbonyl groups. A computational study on the conformational analysis of chloroacetaldehyde is also reported. It is found that the conformer distribution is reversed with respect to the gas phase. The differences in energy are in excellent agreement with the experimental values.

### Introduction

Carbonyl compounds possessing chiral  $\alpha$  carbon atoms are extremely important in organic chemistry.<sup>1</sup> In particular,  $\alpha$ -alkoxy aldehydes play a key role in organic synthesis through either addition reactions of carbon nucleophiles<sup>2</sup> or pericyclic reactions.<sup>3</sup> The stereochemical outcome of these processes has been frequently rationalized on the basis of the preferred conformations of the starting  $\alpha$ -alkoxy aldehyde.<sup>1,4</sup> Within this context, a detailed knowledge of the conformational analysis of this kind of compounds is essential. Several authors have reported valuable contributions in this field, both experimentally<sup>5</sup> and computationally.<sup>6</sup> Most of these studies correspond to the gas phase. The main conclusion of

these studies is that in  $\alpha$ -monosubstituted aldehydes donor substituents prefer to be synperiplanar with respect to the carbonyl group, whereas when electron-withdrawing substituents are present antiperiplanar conformations are preferred, the value of the dihedral angle  $\omega = \text{R}-\text{C}_\alpha-\text{CO}$  depending on the nature of the substituent (eq 1). When several groups are present, the



conformer distribution is more complex. Unfortunately, the number of experimental studies on these latter compounds is very scarce<sup>7</sup> and does not include aldehydes with donor and acceptor groups attached to the same  $\alpha$  carbon atom, in spite of the importance of these compounds in synthetic organic chemistry. In contrast, Frenking *et al.*<sup>8</sup> have reported very interesting computational studies including *ab initio* calculations on the different conformations of 2-chloropropanal<sup>8a</sup> and 2-methoxypropanal<sup>8b</sup> in the gas phase.

It is well-known that solvent effects may modify substantially the conformational equilibria of organic compounds.<sup>9</sup> Once again, the number of experimental studies on substituted aldehydes in solution is very scarce.<sup>10–12</sup> It is known, however, that when electron-withdrawing groups are present, the synperiplanar con-

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(1) See, for example: (a) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: Oxford, 1996. (b) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, 1993. (c) Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: Weinheim, 1987.

(2) (a) Huryn, D. M. In *Comprehensive Organic Synthesis*, Vol. 1; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Oxford, 1991; pp 49–75. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; pp 123–193.

(3) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.

(4) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 975–990.

(5) (a) Kilb, R. W.; Lin, C. C.; Wilson, E. B., Jr. *J. Chem. Phys.* **1957**, *26*, 1695. (b) Bartell, L. S.; Guillory, J. P.; Parks, A. T. *J. Phys. Chem.* **1965**, *69*, 3043. (c) Ronn, A. M.; Woods, R. C. *J. Chem. Phys.* **1966**, *45*, 3831. (d) Abe, M.; Kuchitsu, K.; Shimanouchi, T. *J. Mol. Struct.* **1969**, *4*, 245. (e) Pickett, H. M.; Scroggin, D. G. *J. Chem. Phys.* **1974**, *44*, 3954. (f) Dyngeseth, S.; Schei, H.; Hagen, K. *J. Mol. Struct.* **1983**, *102*, 45. (g) Thomas, L. P.; True, N. S.; Bohn, R. K. *J. Phys. Chem.* **1980**, *84*, 1785. (h) Durig, J. R.; Guirgis, G. A.; Little, T. S.; Stiefvater, O. L. *J. Chem. Phys.* **1989**, *91*, 738. (i) Sakurai, T.; Takeshita, K.; Fukushi, K.; Konaka, S. *J. Phys. Chem.* **1990**, *94*, 1793. (j) Durig, J. R.; Kenton, R.; Phan, H. V.; Little, T. S. *J. Mol. Struct.* **1991**, *247*, 237.

(6) (a) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035. (b) Bowen, J. P.; Pathiaseril, A.; Profeta, S., Jr.; Allinger, N. L. *J. Org. Chem.* **1987**, *52*, 5162. (c) Wiberg, K. B.; Murcko, M. A. *J. Comput. Chem.* **1988**, *9*, 488. (d) Durig, J. R.; Phan, H. V.; Little, T. S.; Van der Veken, B. J. *J. Mol. Struct. (THEOCHEM)* **1989**, *202*, 143. (e) Berry, R. J.; Waltmann, R. J.; Pakansky, J.; Hagler, A. T. *J. Phys. Chem.* **1995**, *99*, 10511. (f) Jonsdottir, S. O.; Rasmussen, K. *New. J. Chem.* **1995**, *19*, 1113. (g) DeTar, D. F. *J. Org. Chem.* **1995**, *60*, 7125. (h) Miyahara, I.; Inazu, T. *J. Mol. Struct. (THEOCHEM)* **1996**, *364*, 131.

(7) (a) Kao, P. N.; Turner, P. H. *J. Am. Chem. Soc.* **1979**, *101*, 4497. (b) Durig, J. R.; Badawi, H. M.; Little, T. S.; Guirgis, G. A.; Kalasinsky, V. F. *J. Mol. Struct.* **1984**, *125*, 211. (c) Durig, J. R.; Little, T. S. *Croat. Chem. Acta* **1988**, *61*, 529. (d) Durig, J. R.; Badawi, H. M. *Chem. Phys.* **1990**, *148*, 193. (e) Chouan, Y.; Takayuki, E.; Yamamoto, Y. *J. Am. Chem. Soc.* **1995**, *117*, 3167.

(8) (a) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 8991. (b) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3971.

(9) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH Publishers: Weinheim, 1990; pp 110–120 and references therein.

(10) Karabatsos, G. J.; Fenlio, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 1124.

formations are stabilized with respect to the *anti* conformers. This result has been corroborated in a recent paper including solvent effects at the computationally semiempirical level on monosubstituted aldehydes,<sup>13</sup> computed using the semiempirical Hamiltonian PM3.

Given the importance of homochiral aldehydes and, in particular, enantiopure  $\alpha$ -alkoxy aldehydes in organic synthesis, we report in this paper a detailed *ab initio* study on conformational analysis of  $\alpha$ -methoxypropanal including solvent effects. Since experimental data in solution are available for chloroacetaldehyde, we have checked the reliability of the methodology used by comparing those data with our predictions. The conclusions reported here will be useful for experimentalists interested in the chemistry of chiral carbonyl compounds including donor and acceptor groups attached to the same carbon atom.

### Computational Methods

All the results presented in this work have been obtained using the GAUSSIAN 94<sup>14</sup> series of programs, with the standard 6-31G\* basis set.<sup>15</sup> Electron correlation was partially taken into account by means of either Møller–Plesset theory up to second order<sup>16</sup> (MP2) or density functional theory<sup>17</sup> (DFT) using the hybrid functional usually denoted as B3LYP.<sup>18</sup> All the structures described in this work were fully optimized by analytical gradient techniques and characterized by frequency calculations.<sup>19</sup> Zero-point vibrational energies (ZPVEs) obtained at the HF/6-31G\* level were scaled<sup>20</sup> by 0.89. Bond orders<sup>21</sup> and atomic charges<sup>22</sup> were calculated with the natural bond orbital (NBO) method.<sup>23</sup> Donor–acceptor interactions

have also been computed by means of the NBO model, according to the following equation:

$$\Delta E_{\phi\phi^*}^{(2)} = -2 \frac{\langle \phi | \hat{F} | \phi^* \rangle^2}{\epsilon_{\phi^*} - \epsilon_{\phi}} \quad (2)$$

where  $\hat{F}$  is the Fock operator and  $\phi$  and  $\phi^*$  are two filled and unfilled NBOs having  $\epsilon_{\phi}$  and  $\epsilon_{\phi^*}$  energies, respectively.

Absolute hardnesses<sup>24</sup> ( $\eta$ ) have been computed at the HF/6-31G\* and B3LYP/6-31G\* levels by means of the following approximations:

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right) \approx \frac{I - A}{2} \approx \frac{\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}}{2} \quad (3)$$

where  $N$  is the number of electrons,  $I$  is the ionization potential, and  $A$  is the electron affinity. Given that hardness has been proposed as an indicative of favored processes according to the Maximum Hardness Principle<sup>25</sup> and that several authors have studied the variation of HOMO and LUMO energies for several conformers,<sup>8b,26</sup> we have also included the hardnesses of the computed structures in order to provide a single value which encompasses these data.

Solute–solvent interactions have been computed by means of several methods on the basis of the self-consistent reaction field (SCRF) approach.<sup>27</sup> In the simplest one, usually called the Onsager model,<sup>28</sup> the solute is modeled as a sphere and the solvation energy is approximated as

$$\Delta G_{\text{S}} \approx -\frac{1}{2} \left[ \frac{2(\epsilon - 1)}{2\epsilon + 1} \frac{\mu^2}{a_0^3} \right] \quad (4)$$

where  $\epsilon$  is the dielectric constant of the solvent,  $\mu$  is the dipole moment and  $a_0$  is the spherical cavity radius.<sup>29</sup> In this paper, we shall denote this method as L1A1, according to the notation proposed in a previous paper from our group.<sup>30</sup> A more elaborate treatment involves a multipole expansion of the electrostatic solute–solvent interaction up to the sixth order, and the solute shape is approximated as an ellipsoid with three independent axes. In this scheme, the solvation energy is evaluated as<sup>31</sup>

$$\Delta G_{\text{S}} \approx -\frac{1}{2} \sum_{l,l'=1}^6 \sum_{m,m'=-l,l'}^{+l,l'} M_l^m f_{l,l'}^{m,m'} M_{l'}^{m'} \quad (5)$$

where  $M_l^m$  represents the  $(l,m)$  component of the multipole expansion evaluated at the center of the cavity and  $f_{l,l'}^{m,m'}$  terms are called reaction field coefficients and only depend upon the geometry cavity and  $\epsilon$ . This model shall be denoted as L6A3 as previously proposed.<sup>30</sup> The L6A3 data have been obtained by means of a locally modified version of the GAUSSIAN code, in order to implement the SCRFAC link.<sup>32</sup> The two remaining SCRF methods used in this work are based on

(11) (a) Abraham, R. J.; Bretschneider, E. In *Internal Rotation in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: New York, 1974; p 481. (b) Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, *38*, 1485.

(12) (a) Allinger, J.; Allinger, N. L. *Tetrahedron* **1958**, *2*, 64. (b) Djerassi, C. *Optical Rotatory Dispersion*; McGraw-Hill: New York, 1960; pp 125–126.

(13) Varnali, T.; Aviyente, V.; Terryn, B.; Ruiz-López, M. F. *J. Mol. Struct. (THEOCHEM)* **1993**, *280*, 169.

(14) Gaussian 94, Revision B.2. M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Peterson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995.

(15) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; pp 65–88 and references therein.

(16) (a) Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1.

(17) (a) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford: New York, 1989. (b) Bartolotti, L. J.; Fluchick, K. In *Reviews in Computational Chemistry*, Vol. 7; Lipkowitz, K. B.; Boyd, D. B., Eds.; VCH Publishers: New York, 1996; pp 187–216.

(18) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1980**, *37*, 785. (d) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.

(19) McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(20) Pople, J. A.; Schleyer, B.; Krishnan, R.; DeFrees, D. J.; Binkley, J. S.; Frisch, H.; Whiteside, R.; Hout, R. F., Jr.; Hehre, W. J. *Int. J. Quantum Chem. Symp.* **1981**, *15*, 269.

(21) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.

(22) Wiberg, K. B.; Rabien, P. R. *J. Comput. Chem.* **1993**, *14*, 1504.

(23) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(24) (a) Parr, R. G.; Donnelly, R. A.; Levy, M.; Palke, W. E. *J. Chem. Phys.* **1978**, *68*, 3801. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (c) Mulliken, R. S. *J. Chem. Phys.* **1934**, *2*, 782.

(25) Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *113*, 1854.

(26) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017.

(27) (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Simkin, B. Ya.; Sheikhet, I. *Quantum Chemical and Statistical Theory of Solutions-A Computational Approach*; Ellis Horwood: London, 1995; pp 78–101. (c) Cramer, C. J.; Truhlar, D. G. In *Reviews in Computational Chemistry*, Vol. VI; Lipkowitz, K. B.; Boyd, D. B., Eds.; VCH Publishers: New York, 1995; pp 1–72.

(28) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486.

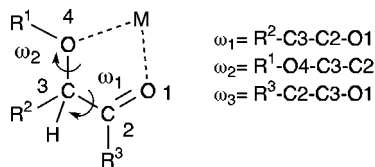
(29) (a) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 523. (b) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645.

(30) Morao, I.; Lecea, B.; Arrieta, A.; Cossio, F. P. *J. Am. Chem. Soc.* **1997**, *119*, 816.

(31) Rivail, J.-L.; Rinaldi, D.; Ruiz-Lopez, M. In *Theoretical and Computational Models for Organic Chemistry*; Formosinho, S. J., Csizmadia, I. G., Arnaut, L., Eds.; Kluwer Academic Publishers: Dordrecht, 1991; Vol. 339, pp 79–42.

(32) Rinaldi, D.; Pappalardo, R. R. *Quantum Chemistry Program Exchange*; Indiana University: Bloomington, IN, 1992; Program No. 622.

Chart 1



- 1:  $R^1=R^2=CH_3$ ;  $R^3=H$ ;  $M=None$   
 2:  $R^1=R^2=CH_3$ ;  $R^3=H$ ;  $M=Li^+$   
 3:  $R^1=Alkyl, Aryl, Acyl$ ;  $R^2=Alkyl, Aryl$ ;  $M=None$   
 $R^3=H, OH, Alkyl, Alkoxy, Amino$

the polarization continuum model<sup>33</sup> (PCM), in which the solvation energy is evaluated as

$$\Delta G_S \approx \frac{1}{2} \left[ - \sum_i^{\text{electrons}} \oint_S \frac{\sigma_p(r_S) dr_S}{|r_i - r_S|} + \sum_j^{\text{nuclei}} Z_j \oint_S \frac{\sigma_p(r_S) dr_S}{|r_j - r_S|} \right] \quad (6)$$

where  $\sigma_p$  is the superficial charge density and  $Z_j$  is the charge of the nucleus  $j$ . The solute cavity is defined as a static gas phase or a self-consistent isodensity surface, with an isosurface value of 0.001 au. These methods are denoted as IPCM and SCIPCM, respectively.<sup>34</sup>

The searches for conformations of compounds of type **3** (see Chart 1) were made with version 5.09 of the Cambridge Structural Data Base (CSD), by using the appropriate options available in the QUEST3D<sup>35</sup> program. All searches were restricted to organic molecules, including macro- but not microcyclic compounds, and were confined to error-free structures, according to the criteria of the CSD system. Statistics were performed with the VISTA package.<sup>35</sup>

## Results and Discussion

We first studied the possible conformers of 2-methoxypropanal (**1**) at both HF/6-31G\* and B3LYP/6-31G\* levels in the gas phase. The main dihedral angles  $\omega_1$  and  $\omega_2$  considered in the exploration of the potential energy hypersurface are those defined in Chart 1. The notation of the conformations in carbonyl compounds is not unified, and different names can be found in the literature.<sup>4,19</sup> In this work we shall use the terms proposed by Klyne and Prelog.<sup>1a,36</sup> Given that some atoms or groups can define dihedral angles of  $\pm 90^\circ$  with the carbonyl moiety, we shall use the term isoclinal for these positions.

We have found six conformers at both theoretical levels, a result similar to that reported by Frenking.<sup>8b</sup> The main geometrical features of the conformers **1A–F** are reported in Figures 1 and 2. As can be seen, the lowest energy conformer has the methyl group isoclinal with respect to the carbonyl, the corresponding  $\omega_1$  values being  $86.6^\circ$  and  $89.9^\circ$  at HF/6-31G\* and B3LYP/6-31G\* levels, respectively. The values of  $\omega_2$  are also close to  $90^\circ$  at both levels (see Figure 1). The carbonyl group in conformer **1A** is appreciably pyramidalized, as indicated by the  $\omega_3$  values. The conformer closest in energy to **1A**

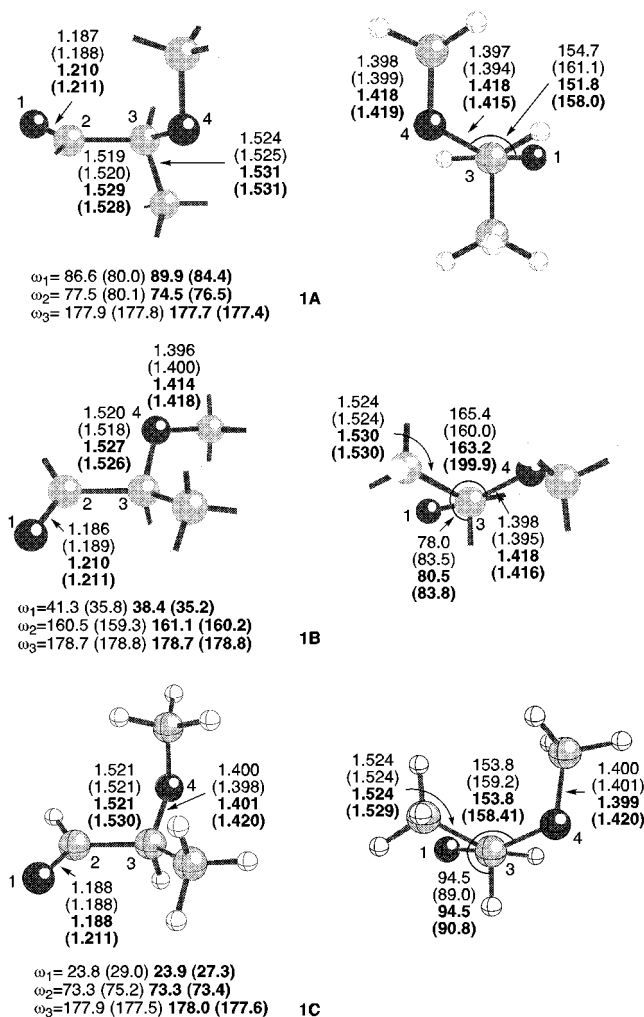
(33) (a) Tomasi, J.; Bonaccorsi, R.; Camini, R.; Olivares del Valle, F. J. *J. Mol. Struct. (THEOCHEM)* **1991**, *234*, 401. (b) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117. (c) Miertus, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239. (d) Camini, R.; Tomasi, J. *J. Comput. Chem.* **1995**, *16*, 1449.

(34) (a) Wiberg, K. B.; Castejon, H.; Keith, T. A. *J. Comput. Chem.* **1996**, *17*, 185. (b) Wiberg, K. B.; Keith, T. A.; Frisch, M. J.; Murcko, M. J. *Phys. Chem.* **1995**, *99*, 9072. (c) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261.

(35) *CSD User Manuals*; Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, U.K.

(36) Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521.

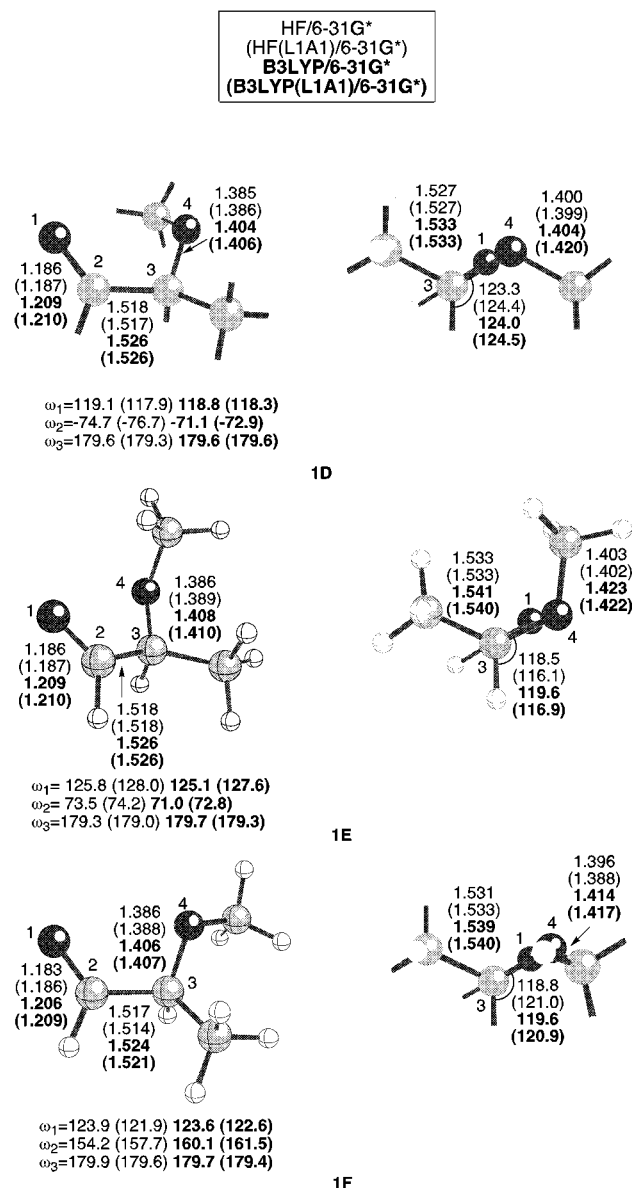
HF/6-31G\*  
 (HF(L1A1)/6-31G\*)  
 B3LYP/6-31G\*  
 (B3LYP(L1A1)/6-31G\*)



**Figure 1.** Ball-and-stick representation of the three methoxy antiperiplanar conformers **1A–C** of (*S*)-methoxypropanal, computed at several theoretical levels. In this and the following figures which incorporate ball-and-stick representations, unless otherwise noted, atoms are represented by increasing order of shadowing as follows: H, C, O. Distances and angles are given in Å and deg, respectively. Dihedral angles are given in absolute value.

is **1B**, in which the  $\alpha$ -hydrogen atom is now isoclinal to the carbonyl group, the corresponding dihedral angle being  $80.5^\circ$  at the B3LYP/6-31G\* level. This conformer is calculated to be only 0.19 kcal/mol higher in energy than **1A** at the same level (see Table 1). There is another conformer of **1** which has an isoclinal  $\alpha$ -hydrogen. This conformer, denoted as **1C** in Figure 1, is 1.73 kcal/mol higher in energy than **1A** at B3LYP/6-31G\* level.

The three remaining conformers **1D–F** have the methoxy group synperiplanar to the carbonyl, only differing in the  $\omega_2$  values (see Figure 2). Among these local minima, conformer **1D** is found to be the closest in energy to **1A**, with a relative energy of only 0.73 kcal/mol at the B3LYP/6-31G\* level. The two remaining conformers **1E** and **1F** have the two methyl groups synclinal and anticlinal each other, whereas in **1D** these groups are antiperiplanar. In addition, in **1F** the repulsion between



**Figure 2.** Ball-and-stick representation of the three methoxy synperiplanar conformers **1D–F** of (*S*)-methoxypropanal. See Figure 1 caption for additional details.

the lone pairs of the two oxygen atoms is the highest one. The contribution of these factors results in a relative stabilization of conformer **1D** and a destabilization for **1F**.

We have also computed the main two-electron interactions between the Lewis and non-Lewis localized NBOs of **1**. The resulting second-order perturbational energies (HF/6-31G\* level) for conformers **1A–F** are reported in Table 2. From our data it is readily seen that in **1A** the main interaction consists in a donation from the C–Me  $\sigma$  bond to the antibonding  $\pi$ -orbital of the carbonyl group. The efficiency of this interaction is maximized by the isoclinal methyl group. However, in conformers **1B** and **1C**, both with isoclinal hydrogen atoms, the second-order energies associated to the  $\sigma_{C-H} \rightarrow \pi_{C=O}^*$  interaction are considerably higher than the  $\sigma_{C-Me} \rightarrow \pi_{C=O}^*$  interaction energy in **1A**, 2.67 kcal/mol higher in the case of **1C**. This trend is kept in the methoxy-synperiplanar conformers **1D–F** (see Table 2). Since in these latter local minima both the  $\alpha$ -methyl groups and the  $\alpha$ -hydrogen atoms are anticlinal and therefore have similar dihedral angles with

**Table 1.** Relative Energies<sup>a</sup> (kcal/mol) of the Six Conformers (A–F) of  $\alpha$ -Methoxypropanal (**1**), Computed *in Vacuo* ( $\epsilon = 1.00$ ) and in Dichloromethane Solution ( $\epsilon = 9.08$ )

level	A	B	C	D	E	F
$\epsilon = 1.00$						
HF/6-31G* <sup>b</sup>	0.00	0.15	2.14	1.46	3.97	3.92
MP2/6-31G* <sup>b</sup>	0.00	0.26	1.72	0.90	3.30	3.52
B3LYP/6-31G* <sup>c</sup>	0.00	0.19	1.73	0.73	2.93	3.01
$\epsilon = 9.08$						
HF(L1A1)/6-31G* <sup>d</sup>	0.00	-0.55	2.22	1.06	3.41	2.58
MP2(L1A1)/6-31G* <sup>d</sup>	0.00	-0.41	1.79	0.58	2.77	2.28
B3LYP(L1A1)/6-31G* <sup>e</sup>	0.00	-0.46	1.72	1.08	2.50	1.79
HF(L6A3)/6-31G* <sup>d</sup>	0.00	1.62	2.57	0.98	3.74	2.38
MP2(L6A3)/6-31G* <sup>d</sup>	0.00	1.14	1.90	0.52	2.84	2.18
HF(IPCM)/6-31G* <sup>d</sup>	0.00	-0.22	1.35	0.93	2.54	1.53
MP2(IPCM)/6-31G* <sup>d</sup>	0.00	0.03	1.12	0.51	2.18	1.59
HF(SCIPCM)/6-31G* <sup>d</sup>	0.00	0.24	2.08	0.74	3.08	1.99
MP2(SCIPCM)/6-31G* <sup>d</sup>	0.00	0.23	1.64	0.35	2.47	1.86

<sup>a</sup> Zero-point vibrational energy corrections computed at the level of geometry optimization are included. <sup>b</sup> Energies computed on fully optimized HF/6-31G\* geometries. <sup>c</sup> Energies computed on fully optimized B3LYP/6-31G\* geometries. <sup>d</sup> Energies computed on fully optimized HF(L1A1)/6-31G\* geometries. <sup>e</sup> Energies computed on fully optimized B3LYP(L1A1)/6-31G\* geometries.

**Table 2.** Second-Order Perturbational Energies<sup>a</sup> (kcal/mol) Calculated on the NBO Basis for Conformers **1A–F**

interaction	A	B	C	D	E	F
$\epsilon = 1.00$						
$\sigma_{C-H} \rightarrow \pi_{C=O}^*$	1.55	6.10	7.03	5.85	6.84	6.20
$\sigma_{C-Me} \rightarrow \pi_{C=O}^*$	4.36	1.69	0.69	3.91	3.44	3.48
$\sigma_{C-O} \rightarrow \pi_{C=O}^*$	0.55	0.00	0.80	0.00	0.00	0.00
$\sigma_{C=O} \rightarrow \pi_{C-H}^*$	0.00	1.33	1.49	1.63	1.56	1.71
$\sigma_{C=O} \rightarrow \pi_{C-Me}^*$	1.68	0.70	0.00	1.61	1.69	1.66
$\sigma_{C=O} \rightarrow \pi_{C-O}^*$	1.15	0.77	1.67	0.00	0.00	0.00
$\epsilon = 9.08$						
$\sigma_{C-H} \rightarrow \pi_{C=O}^*$	2.23	6.47	7.26	5.79	7.28	6.24
$\sigma_{C-Me} \rightarrow \pi_{C=O}^*$	4.54	1.43	0.92	4.08	3.35	3.86
$\sigma_{C-O} \rightarrow \pi_{C=O}^*$	0.00	0.68	0.67	0.00	0.00	0.00
$\sigma_{C=O} \rightarrow \pi_{C-H}^*$	0.51	1.39	1.39	1.58	1.57	1.60
$\sigma_{C=O} \rightarrow \pi_{C-Me}^*$	1.59	0.54	0.00	1.60	1.60	1.62
$\sigma_{C=O} \rightarrow \pi_{C-O}^*$	0.69	1.00	1.34	0.00	0.00	0.00

<sup>a</sup> Energies computed at HF/6-31G\* and HF(L1A1)/6-31G\* levels for  $\epsilon = 1.00$  and  $\epsilon = 9.08$ , respectively.

respect to the carbonyl group, these results indicate that the C–H bond acts as a better donor than the C–Me bond. However, the energy differences due to the more efficient interaction from the C–H bonds are not large enough to place the conformers below **1A**, which has the more advantageous steric and electrostatic interactions.

From the data collected in Table 2, one may also conclude that the  $\pi_{C=O} \rightarrow \sigma_{C-R}^*$  interactions are much less important in magnitude than those already mentioned. In particular, the  $\pi_{C=O} \rightarrow \sigma_{C-O}^*$  interaction lies in the range 0.77–1.67 kcal/mol. The efficiency of this interaction is hampered by the unfavorable synperiplanar, anticlinal or almost antiperiplanar methoxy group in the six conformers. In summary, we can conclude that stabilizing stereoelectronic effects in the conformations of **1** are dominated by the  $\sigma_{C-R} \rightarrow \pi_{C=O}^*$  donations. We also conclude, on a quantitative basis, that the C–H bond is a better donor than the C–C bond in compound **1**.<sup>37</sup>

We have computed the hardnesses ( $\eta$ ) and the dipole moments of conformers **1A–F**. Since it is well-known

(37) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

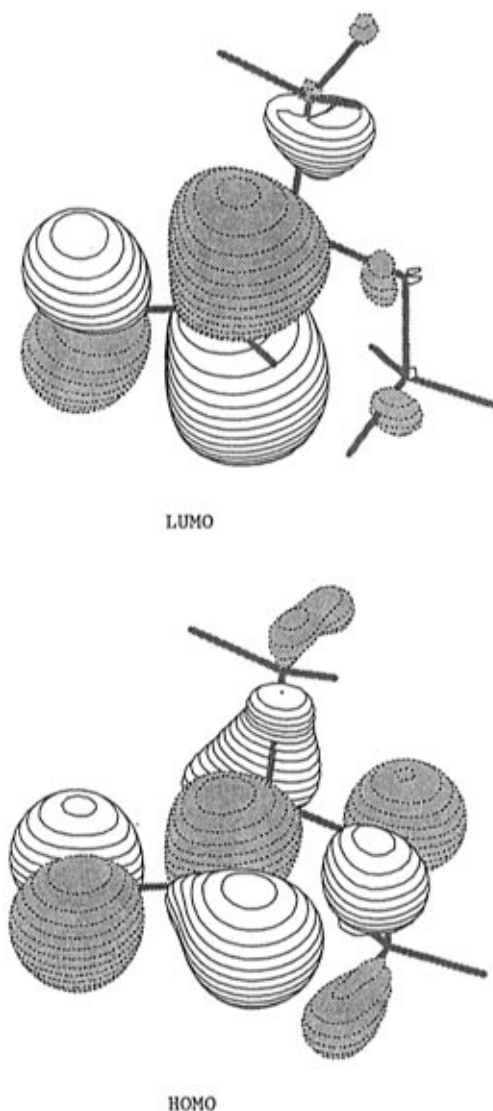
**Table 3.** Hardnesses ( $\eta$ , au), Relative Hardnesses ( $\Delta\eta$  kcal/mol, in parentheses), Dipole Moments ( $\mu$ , D), and Carbonyl Bond Orders ( $B_{C=O}$ ) of Conformers 1A–F

conformer	$\eta$ ( $\Delta\eta$ )		$\mu$		$B_{C=O}$	
	$\epsilon = 1.00$	$\epsilon = 9.08$	$\epsilon = 1.00$	$\epsilon = 9.08$	$\epsilon = 1.00$	$\epsilon = 9.08$
<b>A</b>	0.10644 (0.00)	0.10581 (0.00)	0.71	0.84	1.884	1.878
<b>B</b>	0.11300 (+4.12)	0.11250 (+4.20)	1.14	1.34	1.882	1.872
<b>C</b>	0.10620 (−0.15)	0.10543 (−0.24)	0.64	0.81	1.878	1.872
<b>D</b>	0.10700 (+0.35)	0.10712 (+0.82)	1.00	1.14	1.880	1.873
<b>E</b>	0.10646 (+0.01)	0.10668 (+0.16)	1.05	1.23	1.878	1.870
<b>F</b>	0.11385 (+4.65)	0.11358 (+4.88)	1.46	1.67	1.897	1.882

<sup>a</sup> All magnitudes have been computed on B3LYP/6-31G\* and B3LYP(L1A1)/6-31G\* geometries.

that HF methods tend to overestimate the dipole moments of organic compounds,<sup>38</sup> we have computed these magnitudes at the B3LYP/6-31G\* level. These data are reported in Table 3. Our results indicate that, in the case of **1**, in general the more stable the conformer is, the lower its dipole and its hardness in the gas phase. Thus, the methoxy synperiplanar conformers **1D–F** have dipole moments equal or higher than those in **1D**. Although these polar conformers are destabilized in the gas phase, it is expected that they will be relatively stabilized in solution (*vide infra*). On the other hand, there is no correlation between the hardness and the stability of conformers **1A–F**, within the limits of the approximations expressed in eq 3. The HOMO of **1** is dominated by an anti-phase interaction between the C<sub>2</sub>–C<sub>3</sub>–H moiety and a p-lone pair of the carbonyl oxygen O1, as is exemplified in Figure 3 for the HOMO of **1A**. The LUMO of **1** is basically a  $\pi_{C=O}^*$  orbital (see Figure 3). In the different conformers, the orientation of the substituents promotes relative stabilization or destabilization of the respective frontier orbitals, thus resulting in different values of  $\eta$ . For example, the hardest conformer is **1F**, which in turn is the most polar and the less stable one. In **1F**, the synperiplanar oxygen atom O4 has an in-phase stabilizing interaction with the O1–C2(H)–C3 moiety, thus resulting in a low-energy HOMO. On the other hand, the anticlinal methyl group of **1F** has an anti-phase hyperconjugative interaction with the  $\pi_{C=O}^*$  subunit, thus resulting in a destabilized LUMO. The high HOMO–LUMO gap resulting from these interactions yields the high value of  $\eta$  for this conformer.

Given that in **1** there are two basic oxygen atoms, different open or chelated cation–molecule complexes can be formed. We have studied several structures **2**, derived from the interaction between the lithium cation and  $\alpha$ -methoxypropanal (see Chart 1). The chief geometric features of two representative examples are shown in Figure 4. According to our results, complexation with lithium promotes a higher C=O bond distance, thus yielding a more electrophilic species. For instance, in **2A** and **2F** the O1–C2 bond distances are found to be 0.023 Å larger than in **1A** and **1F** at the B3LYP/6-31G\* level, respectively. The critical point density associated to the Li $\cdots$ O1 critical point in **2A** is found to be  $H(\mathbf{r}_c) = +0.0190$  au at the HF/6-31G\* level. Similarly, the  $H(\mathbf{r}_c)$  magnitudes associated to the Li $\cdots$ O1 and Li $\cdots$ O4 critical points



**Figure 3.** Canonical frontier orbitals of conformer **1A**, computed at the HF/6-31G\* level.

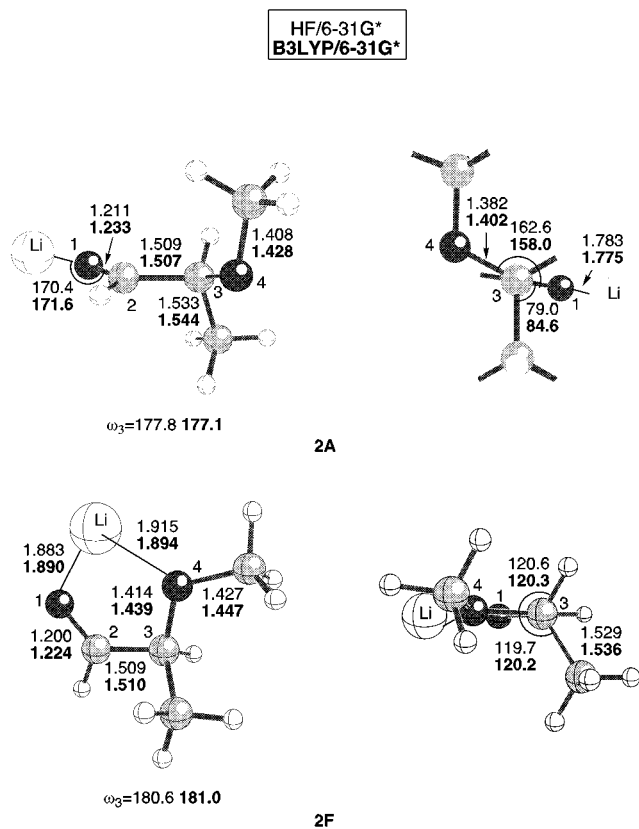
of **2F** are +0.0131 au and +0.0115 au at the same level. These results clearly indicate that the lithium–oxygen interactions in these ion–molecule complexes are electrostatic in nature.<sup>39</sup>

The respective relative energies of these compounds, computed at several theoretical levels, are shown in Table 4. From our results, it is clear that the complex **2F**, with a dicoordinated lithium cation, is significantly more stable than open ion–molecule complexes such as **2A**, in which the lithium cation is almost linearly complexed with the carbonyl group<sup>40</sup> (see Figure 4). Therefore, the conformational analysis of lithium-complexed  $\alpha$ -methoxypropanal is dominated by the cyclic complex **2F**. This

(38) See, for example: (a) Roa, G.; Ugalde, J. M.; Cossio, F. P. *J. Phys. Chem.* **1996**, *100*, 9619. (b) Sponer, J.; Leszczynski, J.; Hobza, P. *J. Phys. Chem.* **1996**, *100*, 1965.

(39) For recent examples on the characterization of lithium–oxygen interactions by means of the  $H(\mathbf{r}_c)$  criterion, see: (a) Lecea, B.; Morao, I.; Arrieta, A.; Cossio, F. P. *Eur. J. Chem.* **1997**, *3*, 20. (b) López, X.; Ugalde, J. M.; Cossio, F. P. *J. Am. Chem. Soc.* **1996**, *118*, 2718.

(40) (a) Wiberg, K. B.; Marquez, M.; Castejon, H. *J. Org. Chem.* **1994**, *59*, 6817. (b) Shambayatti, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 283–324.



**Figure 4.** Ball-and-stick representation of conformers **2A**, **F** of lithium cation-(*S*)-methoxypropanal complex. See Figure 1 caption for additional details.

**Table 4. Relative Energies ( $\Delta E_{\text{rel}}$ , kcal/mol) between the Lithium- $\alpha$ -Methoxypropanal Complexes **2A** and **2F** (See Figure 4)**

level	$\Delta E_{\text{rel}}^a$ (kcal/mol)	
	<b>2A</b>	<b>2F</b>
HF/6-31G* + $\Delta$ ZPVE	0.00	-16.82
MP2/6-31G*//HF/6-31G* + $\Delta$ ZPVE	0.00	-20.36
B3LYP/6-31G* + $\Delta$ ZPVE	0.00	-18.34

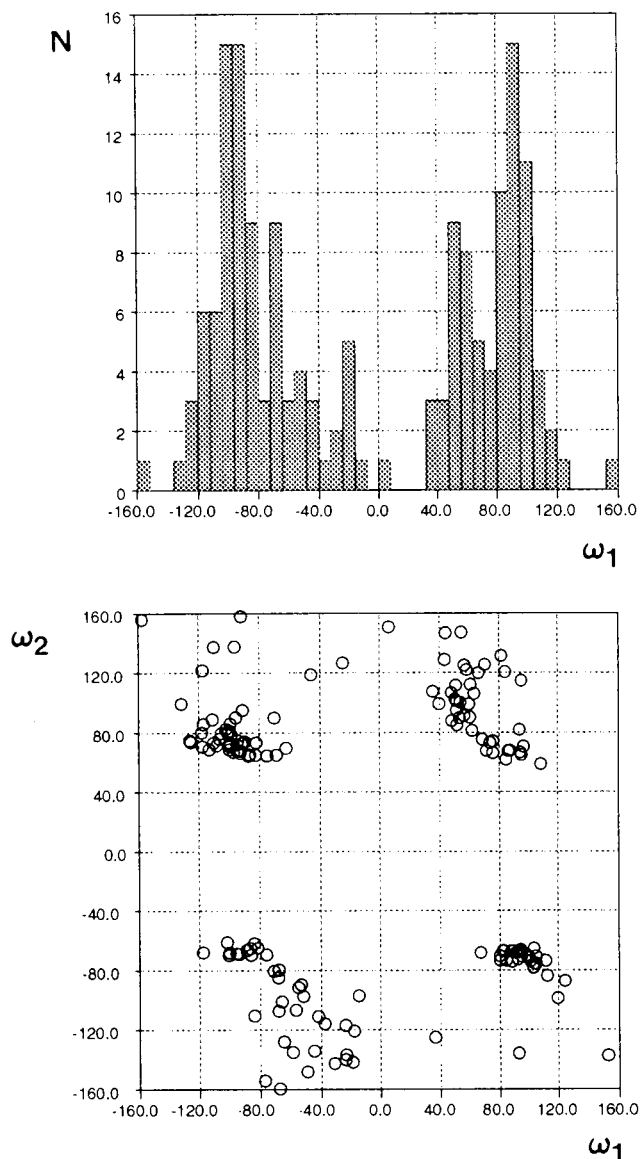
<sup>a</sup> HF/6-31G\* zero-point vibrational energies are scaled by 0.89.

conformational restriction is in line with the higher stereocontrol observed in the nucleophilic addition to chelated  $\alpha$ -alkoxycarbonyl compounds, according to the Cram's cyclic model.<sup>41</sup> It is expected that appropriate solvents such as ethers should solvate the cation, and therefore the computed energy differences reported in Table 4 are probably lower in solution. However, it is not expected that solvation will overcome the large  $\Delta E_{\text{rel}}$  values. On the other hand, in **2F** there is one position less available for coordination, thus enhancing the entropy of the system *via* liberation of a solvent molecule.

To summarize up the discussion on our results obtained in the gas phase, we can conclude that, in the absence of Lewis acids, 2-methoxypropanal is preferably in the conformation **1A**. In this conformation, the methyl and the methoxy groups are isoclinal and antiperiplanar, respectively.

As we have noted above, there are no experimental data on the structure of this compound. In order to check

(41) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) For a mechanistic study on the effective participation of chelated complexes in nucleophilic additions to the carbonyl group, see: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.



**Figure 5.** Histograms and scattered histograms of carbonyl compounds **3**. The dihedral angles  $\omega_1$  and  $\omega_2$  are defined in Chart 1.  $N$  stands for the number of structures with a given value of  $\omega_1$ .

the generality of the results obtained from our calculations, we performed a search in the Cambridge Structural Database (CSD) including the structures **3** indicated in Chart 1. Under the conditions indicated in the previous section, 164 structures were found. The summary of this search is represented in Figure 5. The first graphic is the histogram corresponding to the  $\omega_1$  dihedral angle. As can be seen, the majority of the structures have isoclinal or nearly isoclinal  $R^2$  substituents ( $\omega_1 \cong \pm 90^\circ$ , since both (*R*) and (*S*) enantiomers were included in the search). Besides, the  $\omega_1$  vs  $\omega_2$  bidimensional representation shows that the majority of the structures are grouped around the  $\omega_1$  and the  $\omega_2$  values of **1A**. Therefore, we can conclude that this conformation is the predominant one in the crystalline state and in the gas phase.

We have also optimized the structures of conformers **1A–F** in dichloromethane solution ( $\epsilon = 9.08$ ), a representative solvent widely used in the chemistry performed with this kind of compounds. The chief geometrical features of conformers **1A–F** obtained at both HF(L1A1)/6-31G\* and B3LYP(L1A1)/6-31G\* levels are collected in Figures 1 and 2. The main geometrical difference

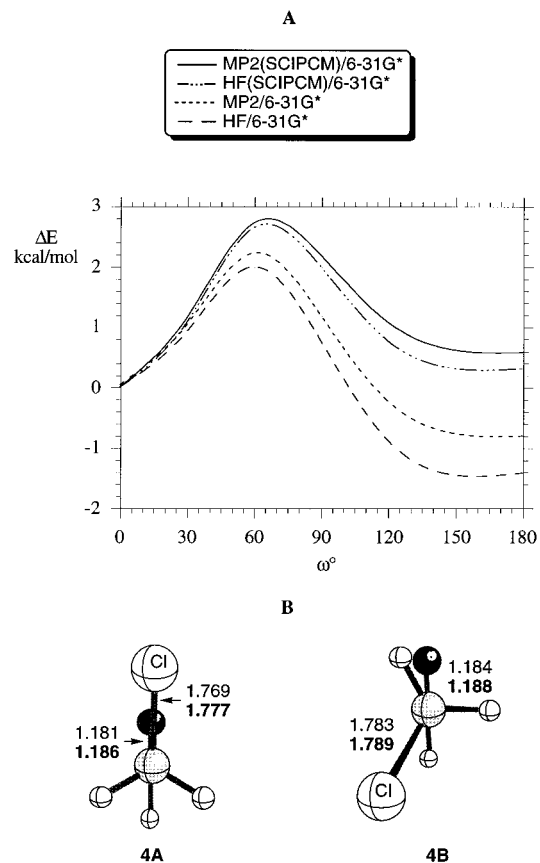
between the *in vacuo* and solvated structures is the difference in the O1–C2 bond distance, which is slightly elongated in solution, although this effect is less pronounced than in the case of Lewis acid complexation. This result is corroborated by the monotonically higher dipole moments and lower C=O bond orders of the solvated structures (see Table 3). In addition, the computed relative hardnesses are approximately in the same order as the values obtained in the gas phase, although the numerical values of  $\Delta\eta$  are slightly higher. The stereo-electronic effects are similar in character to those computed *in vacuo*, although the magnitude of the second-order energies associated to the two-electron interactions are higher in magnitude. For example, in **1A** the  $\Delta E^{(2)}$  values for the  $\sigma_{C-Me} \rightarrow \pi_{C=O}^*$  interaction in the gas phase and in solution are 4.36 and 4.54 kcal/mol, respectively (see Table 2). In summary, the geometric and electronic effects present in the gas phase for the different conformers are enhanced in solution. The combination of these effects has, however, different consequences for each structure.

We have found that the relative energies of conformers **1A–F** are sensitive to the SCRF method. The L1A1 method predicts that **1B** is the most stable conformer, and the polar isomers **1E** and **1F** are significantly stabilized with respect to the gas phase (see Table 1). Inclusion of higher multipoles according to eq 5 results in a relative destabilization of conformer **1B**; this local minimum is found to be 1.14 kcal/mol less stable than **1A** at the MP2(L6A3)/6-31G\* level. The polar conformer **1D** is significantly stabilized with this method, being only 0.52 kcal/mol higher in energy than **1A**.

It is noteworthy that, at the L6A3 level, the relative contributions to the solvation energy of the different multipoles vary substantially for the different conformers. Thus, in the case of conformers **1A–C**, which have antiperiplanar methoxy groups, the most important term in eq 5 is found at  $l = 2$  (quadrupole component). On the other hand, for conformers **1D–F**, which have synperiplanar methoxy groups, the most important components of  $\Delta G_s$  correspond to the dipole terms ( $l = 1$ ). These results reflect the importance of the relative orientation of the carbonyl and alkoxy dipoles in each conformer.<sup>13</sup> In view of these results, the PCM methods, which can be considered as equivalent to an infinite expansion in the multipole series, seem to be the most appropriate ones for this problem.

As can be seen from the data collected in Table 1, the IPCM and SCIPCM methods yield results which are between the L1A1 and the L6A3 approaches. Thus, **1B** is 0.23 kcal/mol less stable than **1A** at the MP2(SCIPCM)/6-31G\* level. In addition, the polar conformer **1D** is only 0.35 kcal/mol less stable than **1A** at the same theoretical level. The remaining polar conformers **1E** and **1F** are also significantly stabilized with respect to the *in vacuo* values (see Table 1). As a consequence, the combination of the geometrical, electronic, and polar effects in the different conformers yields a quite complex distribution of conformers, since steric and polar effects are opposite each other and the latter are relatively more important in solution.

In order to test the reliability of our SCRF results, we computed the conformational profile of chloroacetaldehyde (**4**), since for this compound experimental data are available in dichloromethane solution.<sup>10</sup> In Figure 6A we have collected the data obtained *in vacuo* and in solution using the SCIPCM method. The different conformers of



**Figure 6.** (A) Conformational profiles for chloroacetaldehyde **4** in the gas phase and in dichloromethane solution ( $\epsilon = 9.08$ ).  $\omega$  is the dihedral angle O=C–C–Cl. (B) Newman projection of synperiplanar (**4A**) and antiperiplanar (**4B**) conformers of chloroacetaldehyde. Plain and bold numbers correspond to HF/6-31G\* and HF(SCIPCM)/6-31G\* data, respectively. See Figure 1 caption for additional details.

**Table 5. Relative Energies (kcal/mol) of the Synperiplanar (**4A**) and Antiperiplanar (**4B**) Conformers of Chloroacetaldehyde in the Gas Phase ( $\epsilon = 1.00$ ) and in Dichloromethane Solution ( $\epsilon = 9.08$ )**

method	$\Delta E$	
	<b>4A</b>	<b>4B</b>
	$\epsilon = 1.00$	
HF/6-31G*	0.00	-1.46 <sup>a</sup>
MP2/6-31G*	0.00	-0.85 <sup>b</sup>
	$\epsilon = 9.08$	
HF(SCIPCM)/6-31G*	0.00	+0.31
MP2(SCIPCM)/6-31G*	0.00	+0.57
expt <sup>c</sup>	0.00	+0.71

<sup>a</sup> Data taken from ref 6d. <sup>b</sup> Data taken from ref 8a. <sup>c</sup>  $\Delta G^\circ$  taken from ref 10.

**4** were fully optimized at the HF(SCIPCM)/6-31G\* level, and the energies were evaluated at the MP2(SCIPCM)/6-31G\*/HF(SCIPCM)/6-31G\* level of theory. The results are reported in Figure 6B and in Table 5. The corresponding gas phase results computed at the MP2/6-31G\*/HF/6-31G\* level are coincident with those reported by Frenking *et al.*<sup>8a</sup> and are given for comparison. It is found that in the gas phase conformation **4A**, which has a synperiplanar chlorine atom, is 0.85 kcal/mol less stable than conformation **4B**, in which the chlorine atom is antiperiplanar. Interestingly, one of the hydrogen atoms attached to the  $\alpha$  carbon is isoclinal in this conformer. Therefore, in the gas phase the dipole–dipole repulsion is minimized and the donating effect of the C–H bond is

very efficient, thus resulting in a net stabilization of **4B** with respect to **4A**. This situation is reversed in solution and now the parallel orientation of the carbonyl and C–Cl dipoles results in a relative stabilization *via* the high value of  $\Delta G_s$ . Thus, at MP2(SCIPCM)/6-31G\*//HF(SCIPCM)/6-31G\* level it is found that **4A** is now 0.57 kcal/mol more stable than **4B**. This result is in excellent agreement with the experimental result of  $\Delta G^\circ = 0.71$  kcal/mol found in dichloromethane solution.<sup>10</sup> Therefore, the SCRF approach is adequate for the evaluation of solvent effects on the conformational equilibria of this kind of compounds.

### Conclusions

From the studies reported in this work, the following conclusions can be drawn:

(a) In the gas phase, the more populated conformer of  $\alpha$ -methoxypropanal is that which incorporates a methyl group in an isoclinal disposition with respect to the carbonyl group. However, there is another hydrogen isoclinal conformer which is very close in energy.

(b) In solution, there are three predominant conformations; that found in the gas phase, one in which the  $\alpha$ -hydrogen atom and the methoxy group are isoclinal and antiperiplanar, respectively, and one in which the methoxy group is synperiplanar.

(c) Polar conformations are significantly stabilized in solution. Contributions of multipole effects including those higher than dipole to the solvation energy must be taken into account, given the sensitivity of the energy of solvation to the relative orientation of the polar groups.

(d) The SCIPCM method describes correctly the conformational profile of  $\alpha$ -chloroacetaldehyde both qualitatively and quantitatively, and thus we place confidence in predictions of the method concerning other compounds.

(e) The conformational analysis of lithium-complexed  $\alpha$ -methoxypropanal is dominated by a chelated complex in which the methoxy and carbonyl groups are synperiplanar.

Finally, our results suggest that any mechanistic rationalization on the stereochemical outcome of reactions involving this kind of compounds should include at least nonspecific solvent effects.<sup>42</sup> Very likely methods more sophisticated than those based on the Onsager model (L1A1) will be required for a realistic description of these phenomena.<sup>43</sup> These implications are currently under study in our laboratory.

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**Supporting Information Available:** Table including the total energies (in atomic units) of all stationary points discussed in the text. Complete listing of the references used in the analysis of the crystallographic data (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(42) For recent interesting studies on temperature and solvent effects on the nucleophilic additions to aldehydes and related compounds, see: (a) Cainelli, G.; Giacomini, D.; Perciaccante, F. *Tetrahedron: Asymmetry* **1994**, *5*, 1913. (b) Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150. (c) Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2849.

(43) For a computational study on cyanide additions to monosubstituted acetaldehydes using the L1A1 model, see: Cieplak, A. S.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 9226.