Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5713–5718

TETRAHEDRON

Conformational analysis of *N*-Boc-*N*,*O*-isopropylidene-α-serinals. A combined DFT and NMR study

Alberto Avenoza,* Jesús H. Busto, Francisco Corzana, Gonzalo Jiménez-Osés and Jesús M. Peregrina*

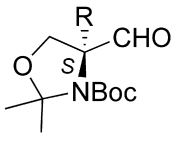
Grupo de Síntesis Química de La Rioja, Departamento de Química, Universidad de La Rioja, Madre de Dios, 51, U.A.-C.S.I.C., E-26006 Logroño, Spain

Received 7 April 2003; revised 16 May 2003; accepted 30 May 2003

Abstract—This work describes an extensive conformational analysis of Garner's aldehyde and its α-methylated homologue—two important chiral building blocks that are widely used in organic synthesis. A combination of density-functional theory and NMR spectroscopy confirmed the existence of a dynamic equilibrium between two possible conformers of the carbamate group in these compounds. The calculated properties such as conformer populations and rotational barriers around the (C═O)–N bond are in good agreement with the experimental values. Finally, the dipole moments of the molecules appear to be a decisive factor in the stabilization of the conformers in solution.

1. Introduction

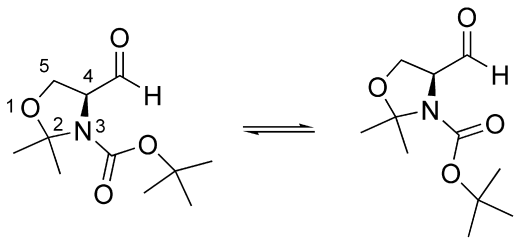
Garner's aldehyde (**1**) and its α-methylated homologue (**2**) (Fig. 1) are compounds of special interest due to their wide versatility as chiral building blocks in stereocontrolled organic synthesis.[1] The formyl group and the suitably protected amino and hydroxyl groups in the oxazolidine ring have been used in several synthetic strategies that involve stereochemical control, transformation and/or deprotection reactions to form a part of an essential backbone in biologically active compounds.



1: R = H
2: R = Me

Figure 1. Garner's aldehyde (**1**) and its α-methylated homologue (**2**).

A peculiar feature of these oxazolidines is that their NMR spectra show two sets of signals at 298 K due to the presence of a dynamic equilibrium between two conformers (α and β) generated by rotation of the conjugated C–N bond of the carbamate[2] (Scheme 1). In conformer α the carbonyl of the carbamate group is *syn* to the C2–N bond, while in conformer β the two bonds adopt an *anti* orientation. This dynamic equilibrium is not restricted to Boc carbamates and has recently been experimentally studied in the Cbz derivatives of Garner's aldehyde.[3]



1α 1β

Scheme 1. Dynamic equilibrium in Garner's aldehyde due to the rotation of the conjugated C–N bond of the carbamate.

The *cis*/*trans* isomerization in amides has been the subject of substantial investigations in recent years.[4] In contrast, the closely related carbamate group has been relatively ignored despite its occurrence in biologically active compounds[5] such as anticonvulsants, local anaesthetics, sedatives, hypnotics and muscle relaxants. Fortunately, a number of rigorous theoretical and experimental studies have been recently performed and these have established significant differences between the amide and carbamate groups.[6] For instance, it is known that the barriers to rotation around the

Keywords: Garner's aldehyde; density-functional theory; dipole moment.
* Corresponding authors. Tel./fax: +34-941-299655;
e-mail: alberto.avenoza@dq.unirioja.es;
jesusmanuel.peregrina@dq.unirioja.es

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00852-4

conjugated C–N bonds are somewhat lower in carbamates and that these barriers, in contrast to the case of amides, show very little solvent dependence.[6]

Bearing all these studies in mind, and taking into account the role that this special 'flexibility' could play in the asymmetric induction of these building blocks, we decided to carry out a thorough study on the dynamic equilibrium present in oxazolidines **1** and **2** by NMR spectroscopy and density-functional theory (DFT). The aim of this study was to elucidate the conformational preferences of these rather large and complex molecules in order to facilitate subsequent theoretical studies on the asymmetric induction mechanisms. These latter investigations are already underway.

2. Experimental

2.1. NMR experiments

^{1}H NMR spectra were acquired on a Bruker ARX-300 spectrometer at 300 MHz (^{1}H) in $CDCl_3$ and are reported in ppm downfield from TMS.

2.2. Calculations

All calculations were carried out by means of the B3LYP hybrid functional.[7] Full optimizations and transition structure searches, using the 6-31G(d) basis set, were carried out with the Gaussian 98 package.[8] Analytical frequencies were calculated at the B3LYP/6-31G(d) level and the natures of the stationary points were determined in each case according to the appropriate number of negative eigenvalues of the Hessian Matrix. Scaled frequencies were not considered since significant errors on the calculated thermodynamical properties are not found at this theoretical level.[9] In all cases single-point calculations at the B3LYP/6-311++G(2d,p) level were carried out on the B3LYP/6-31G(d) geometries. Furthermore, solvent effects were taken into account through single point energy calculations with the IPCM method,[10] as implemented in Gaussian 98, using the dielectric permittivity of $CDCl_3$ (4.81), which was the solvent used in the experiments.

Unless otherwise stated, only Gibbs free energies are used for the discussion on the relative stabilities. These energies were obtained using the following correction formula:

$$\Delta\Delta G = \Delta\Delta E_{\text{basis}} + \Delta\Delta G_{298} + \Delta\Delta G_{\text{solv}} \quad (1)$$

where $\Delta\Delta E_{\text{basis}}$ is the relative energy at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level, $\Delta\Delta G_{298}$ represents the thermal and entropic corrections at 298 K, calculated at the B3LYP/6-31G(d) level, and $\Delta\Delta G_{\text{solv}}$ is the solvation correction (relative solvation free energies), calculated at the IPCM/B3LYP/6-31G(d) level.

3. Results and discussion

First, and in order to obtain the optimized geometry of conformers α and β, DFT relaxed potential-energy surface (PES) scans were performed at the B3LYP/6-31G(d) level

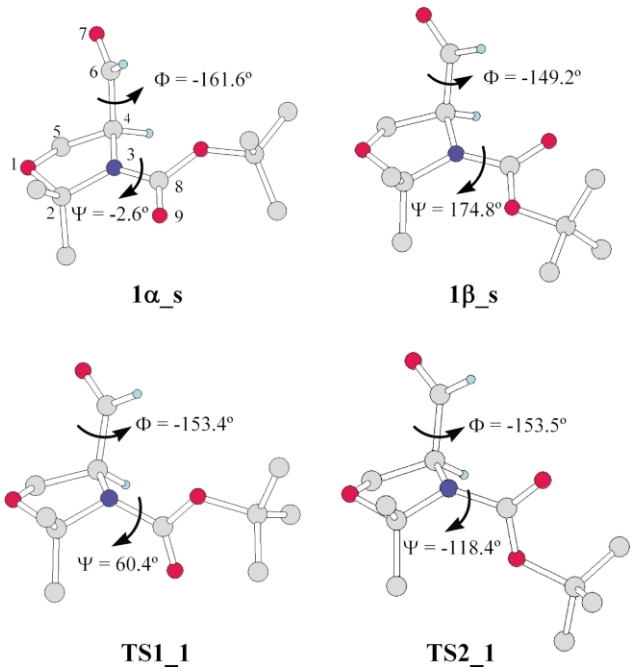


Figure 2. B3LYP/6-31G(d) geometries of the minimum energy conformations and transition states of compound **1**.

by simultaneously varying Φ (N3–C4–C6–O7) and Ψ (C2–C3–C8–O9) dihedral angles, with step-sizes of 60 and 180°, respectively (Fig. 2). Two different envelope conformations of the oxazolidine ring, namely those in which the oxygen atom is puckered up either towards (*syn*) the formyl group or in the opposite direction (*anti*), were taken into account throughout the PES scans. The lowest energy structures found in these preliminary calculations were fully optimized in order to obtain the minimum energy conformers of each structure.

Figure 2 shows some relevant features of the minimum energy structures of conformers α and β found for oxazolidine **1**. Table 1 contains the principal energetic results obtained from the theoretical study. As can be seen, in this case the favoured conformation of the oxazolidine ring is always *syn* (**1**α_s and **1**β_s). Furthermore, the relative stability calculated for conformers α and β does not change when solvation energy is taken into account, with the lowest energy corresponding to conformer α (Fig. 3). This situation has been assumed by other authors for studies of similar carbamates.[3]

The free energy difference between the two conformers ($\Delta\Delta G$=0.52 kcal/mol) was used to estimate the conformer population from the Maxwell–Boltzmann distribution. The calculated ratio of **1**α/**1**β=7:3 is in good agreement with the experimental value of 6:4, which was obtained at 25°C by integrating the signal of the aldehyde proton. Unfortunately, we could not determine which signal corresponds to each conformer by nOe experiments due to the complexity of the ^{1}H NMR spectrum.

The next step was to estimate the rotational barrier for the transformation of **1**α to **1**β by locating the corresponding transition structures. In a first approximation a semi-

Table 1. Relative energies, free energies (both in kcal/mol) and dipole moments (Debye) of the minima and transition structures described in this work

	ΔE_0[a]	$\Delta\Delta E_{basis}$[b]	$\Delta\Delta G_{298}$[a,c]	$\Delta\Delta G_{solv}$[d]	Dipole moment[b]	$\Delta\Delta G$[e]
1α_a	0.14	0.28	0.34	0.62	0.67	1.24
1β_a	1.22	1.26	0.50	-0.61	4.70	1.15
1α_s	0.00	0.00	0.00	0.00	2.55	**0.00**
1β_s	0.75	0.78	0.20	-0.46	4.35	0.52
TS1_1	17.38	16.51	0.27	-1.75	3.81	15.03
TS2_1	18.86	18.09	0.06	-2.77	5.15	15.38
2α_a	0.00	0.00	0.00	0.00	0.44	1.47
2β_a	0.89	0.72	-0.24	-1.75	4.41	0.19
2α_s	1.65	1.34	-1.01	-1.68	1.33	0.11
2β_s	2.24	1.88	-0.85	-2.50	4.54	**0.00**
TS1_2	18.35	17.01	-0.71	-3.16	2.38	14.61
TS2_2	19.91	18.80	-1.64	-2.31	4.47	16.33

[a] Calculated at the B3LYP/6-31G(d) level.
[b] Calculated at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level.
[c] Thermal and entropic corrections at 298 K.
[d] Calculated at the IPCM/B3LYP/6-31G(d) level.
[e] Calculated using Eq. (1).

empirical calculation (PM3) was used, starting from **1**α and varying the angle Ψ in increments of 10°. The geometries of the two maxima found in these calculations were optimized at the B3LYP/6-31G(d) level to obtain the transition structures **TS1_1** and **TS2_1** (Fig. 2). The energetic results for these transition states in the gas phase and in solution are shown in Table 1.

In **TS1_1** the nitrogen lone pair is *anti* to the carbonyl oxygen, a situation that is—as in the case of amides—more stable than **TS2_1** (Fig. 3). This feature is attributed to a repulsive interaction between the nitrogen non-bonded electron pair and one of the carbonyl electron pairs in **TS2_1**.[6] The rotational barrier was estimated as the difference between conformer **1**α and the most stable transition state **TS1_1** (0.35 kcal/mol more stable than **TS2_1**), which gives a value of 15.0 kcal/mol in $CDCl_3$. In

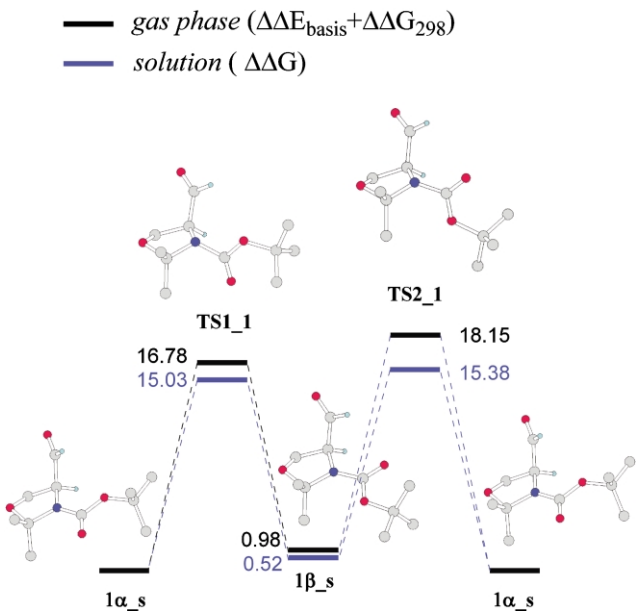


Figure 3. Theoretical energies for conformers α and β and transition states of compound **1**.

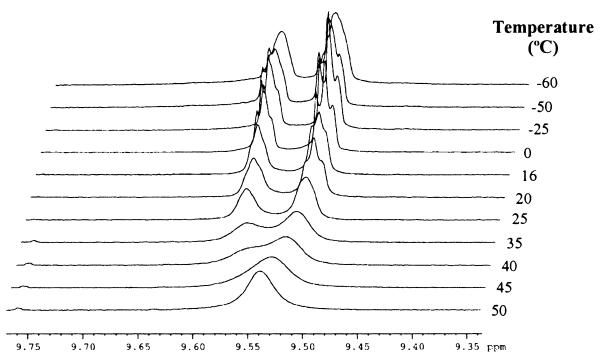


Figure 4. ^{1}H NMR spectrum of CHO group of compound **1** at different temperatures in $CDCl_3$.

order to validate this result, the ^{1}H NMR spectrum of compound **1** was recorded in $CDCl_3$ at several temperatures in the range −60 to 50°C (Fig. 4) and the Gibbs energy of activation ($\Delta G_c^{\neq}$) was estimated using Eyring's equation:

$$\Delta G_c^{\neq} = 4.58 T_c[10.32 + \log(T_c/k_c)] \quad (2)$$

$$k_c = (\pi\Delta\nu/2)^{1/2} \quad (3)$$

where $\Delta\nu$ is the maximum separation between the signals of the exchanging nucleus, T_c is the coalescence temperature and k_c is the rate constant for the exchange process at T_c.[11] Although this equation is generally applied to equally populated signals, it has also been used for moderately unequally populated signals.[12] According to Eq. (2), the experimental value of $\Delta G_c^{\neq}$ was calculated to be 16.1 kcal/mol, which is in good agreement with the value previously calculated.

The protocol described for compound **1** was also applied to calculate the conformer population and the rotational barrier for the α-methylated derivative **2**. From the energy viewpoint, the gas phase calculations led to conclusions similar to those obtained for compound **1**, i.e. conformers **2**α are more stable than conformers **2**β. However, the conformations of the formyl group and the oxazolidine ring

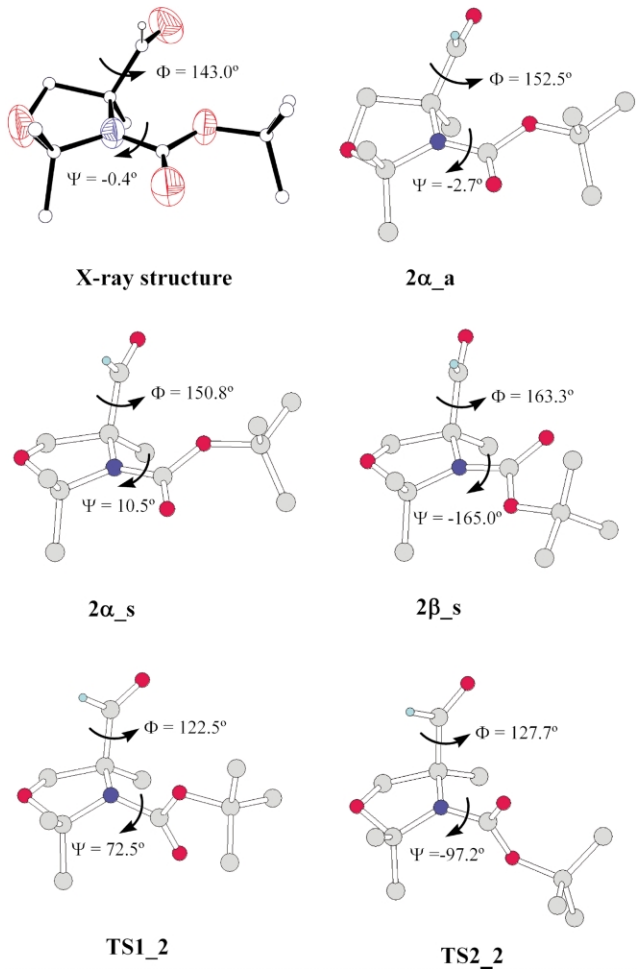


Figure 5. X-Ray structure, B3LYP/6-31G(d) geometries of the minimum energy conformations and transition states of compound **2**.

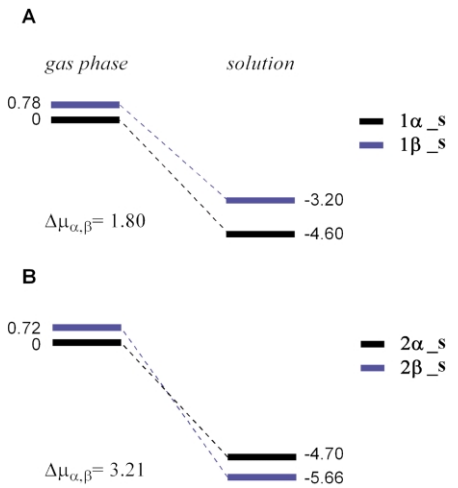


Figure 6. Theoretical relatives energies (in kcal/mol) of conformers α and β in gas phase and in solution for (A) compound **1** and (B) compound **2**.

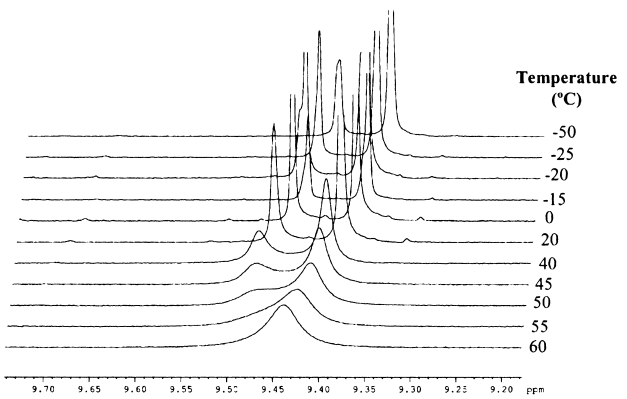


Figure 7. ^{1}H NMR spectrum of CHO group of compound **2** at different temperatures in $CDCl_3$.

change, with the conformer **2**α_a now being the most stable. The geometry of this conformer is analogous to that found in the crystal structure of oxazolidine **2**,[†] which was obtained by slow evaporation of a $CDCl_3$ solution (Fig. 5).

In contrast to the situation observed for Garner's aldehyde, the relative stabilities of the conformers change dramatically when solvent effects are taken into account. For example, in solution the two *syn* conformers, **2**α_s and **2**β_s, were found to be more stable than their respective *anti* counterparts. In fact, conformer **2**β_s was found to be the most stable structure in solution. This behavior can be explained by considering the difference in the dipole moments between the different conformers of both molecules. As a rule of thumb the solvation energy in a polarizable continuum model is expected to be proportional to the square of the dipole moment of the solute, as predicted by the Onsager equation:[13]

$$\Delta G_{\text{solv}} = -(\varepsilon - 1)\mu^2/(2\varepsilon + 1)a_0^3 \qquad (4)$$

where μ is the dipole moment of the solute, ε is the dielectric constant of the medium, and a_0 is the radius of the cavity in which the solute is situated.

As can be seen from the results in Table 1, conformers β have larger dipole moments than conformers α. This signifies, in accordance with the Onsager equation, a preferential solvation of the former species. In compound **2** the difference in the dipole moment between the two conformers ($\Delta\mu_{\alpha,\beta}$=3.21) is particularly significant, and results in a differential stabilization of **2**α_s and **2**β_s that is sufficiently marked to invert the energy of the conformers in solution. In contrast, the value of $\Delta\mu_{\alpha,\beta}$ for Garner's aldehyde is not sufficiently high to change the relative energy observed in gas phase (Fig. 6).

Unfortunately, in a similar way to compound **1**, the signals

[†] Crystal data: (a) $C_{12}H_{21}NO_4$, M_w=243.30, colourless prism of 0.50×0.20×0.10 mm^3, T=293(2) K, orthorhombic, space group $P2_12_12_1$, Z=4, a=8.7480(3) Å, b=10.5540(7) Å, c=14.9850(9) Å, V=1383.51(9) Å^3, d_{calc}=1.168 g cm^{-3}, $F(000)$=528, λ=0.71070 Å (Mo Kα), μ=0.095 mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.36–27.91°, 3217 collected reflections, 3217 unique (R_{int}=0.000), full-matrix least-squares, R_1=0.0682, wR_2=0.1687, (R_1=0.1104, wR_2=0.1970 all data), goodness-of-fit=1.025, residual electron density between 0.251 and −0.203 e Å^{-3}. Hydrogen atoms were located from mixed methods. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 203691. (b) Sheldrick, G. M. *SHELXL97*: *Program for the refinement of crystal structures*; University of Göttingen, Germany, 1997.

corresponding to each conformer of oxazolidine **2** could not be assigned—again due to the complexity of the ^{1}H NMR spectrum. However, the theoretical population ratio of **2**β/**2**α=5.5:4.5 is in very good agreement with the experimental value (6:4) obtained by integrating the signals of the CHO group.

The rotational barrier of oxazolidine **2** was estimated by calculating the two transition states in the gas phase and in solution. The geometries of these species are shown in Figure 5. Once again, as in the case of compound **1**, **TS1_2** was found to be more stable than **TS2_2** (Table 1). The energy of the rotational barrier was calculated to be 14.6 kcal/mol, a value in fairly good accordance with the experimental value of 16.5 kcal/mol, which was obtained in a similar way as for oxazolidine **1**. The results of the dynamic NMR study on oxazolidine **2** are represented in Figure 7.

4. Conclusions

The conformer population and the rotational barrier around the (C=O)–N bond for oxazolidines **1** and **2** were studied by NMR spectroscopy and DFT theory. Good agreement was obtained between the two techniques. In both compounds conformer α is the most stable one in the gas phase. However, the situation changes when solvent effects are taken into account. In this sense, and in contrast to the behavior observed in Garner's aldehyde, the relative stabilities of the minima found in the gas phase differ from those calculated in solution. Thus, conformers **2**β appear to be more stable than conformers **2**α in solution. This fact can be explained by considering the significant difference in the dipole moments of the two conformers, which contribute significantly to the stabilization of conformer **2**β_s.

The complexity of the ^{1}H NMR spectrum precluded assignment of the signals corresponding to each conformer. However, if we take into account the good accordance between the experimental and theoretical results, it can be proposed that the calculations carried out in this work may shed considerable light on the conformers present in solution.

It can be concluded that both compounds are rather flexible in solution and this property could play an important role in the asymmetric induction of these building blocks. This conformational study has allowed the identification of the conformational preferences in this kind of molecule, both in the gas phase and in solution. This situation considerably simplifies further modelling studies that are currently being carried out to explain the high induction generated by these oxazolidines in asymmetric reactions.

Acknowledgements

We thank the Ministerio de Ciencia y Tecnología (project PPQ2001-1305), the Gobierno de La Rioja (project ANGI-2001/30) and the Universidad de La Rioja (project API-02/03) for financial support. The authors also thank Dr José I. García for his assistance in the theoretical calculations.

References

1. (a) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136, and references cited therein. (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220. (c) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653. (d) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195. (e) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949. (f) Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **2002**, *67*, 598. (g) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Acros Org. Acta* **2002**, *9*, 9. (h) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 399. (i) Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. Preparation and Synthetic Applications of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals. *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2002; Vol. 6. (j) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 1037.
2. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
3. Monache, G. D.; Di Giovanni, M. C.; Maggio, F.; Misiti, D.; Zappia, G. *Synthesis* **1995**, 1155.
4. (a) Stewart, W. E.; Siddal, T. H., III. *Chem. Rev.* **1970**, *70*, 517. (b) Ross, B. D.; True, N. S. *J. Am. Chem. Soc.* **1984**, *106*, 2451. (c) Lim, K.; Francl, M. M. *J. Phys. Chem.* **1987**, *91*, 2716. (d) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1992**, *114*, 831. (e) Wiberg, K. B.; Cameron, L. M. *J. Am. Chem. Soc.* **1993**, *115*, 9234. (f) Laidig, K. E.; Cameron, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 1737. (g) Lauvergnat, D.; Hiberty, P. C. *J. Am. Chem. Soc.* **1997**, *119*, 9478. (h) Vassilev, N. G.; Dimitrov, V. S. *J. Mol. Struct.* **1999**, *484*, 39. (i) Drakenberg, T.; Dahlquist, K. J.; Forsen, J. *J. Phys. Chem.* **1972**, *76*, 2178. (j) LeMaster, C. B.; True, N. S. *J. Phys. Chem.* **1989**, *93*, 1307. (k) Duffi, E. M.; Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 7235. (l) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261. (m) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849.
5. (a) Burger's Medicinal Chemistry. In *Parts II and III, The Basis of Medicinal Chemistry*; 4th ed. Wolff, M. E., Ed.; Wiley: New York, 1979; p 1981. (b) O'Brien, D. R. In *The Design of Organophosphonate and Carbamate Inhibition of Cholinesterases*; *Drug Design*, Ariëns, E. J., Ed.; Academic: London, 1971; Vol. II, pp 162–212. (c) Hartley, G. S. *Drug Design*; Ariëns, E. J., Ed.; Academic: London, 1975; Vol. VI, pp 298–351.
6. (a) Basso, E. A.; Pontes, R. M. *J. Mol. Struct. (Theochem)* **2002**, *594*, 199. (b) Rablen, P. R. *J. Org. Chem.* **2000**, *65*, 7930. (c) Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426. (d) Deetz, M. J.; Forbes, C. C.; Jonas, M.; Malerich, J. P.; Smith, B. D.; Wiest, O. *J. Org. Chem.* **2002**, *67*, 3949.

7. (a) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
8. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaroni, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; González, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revisions A.7 and A.11; Gaussian, Inc.: Pittsburgh, PA, 1998.
9. Bauschlicher, C. W., Jr. *Chem. Phys. Lett.* **1995**, *246*, 40.
10. Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.
11. (a) Kincaid, J. F.; Eyring, H.; Stearn, A. E. *Chem. Rev.* **1941**, *28*, 301. (b) Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 3185.
12. Sandström, J. *Dynamic NMR Spectroscopy*; Academic: London, 1982; Chapter 6, pp 79–80, and references cited therein.
13. (a) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486. (b) Kirkwood, J. G. *J. Chem. Phys.* **1934**, *2*, 351. (c) Born, M. *Z. Phys.* **1920**, *1*, 45.