MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2004; **42**: 973–976
Published online 6 September 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mrc.1479

Note

Conformational insights into furo- and thieno[2,3-*b*]indolines derived from coupling constants and molecular modeling

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Received 15 May 2004; Revised 9 July 2004; Accepted 12 July 2004

The extent to which conformational preferences of fused heterocyclic five-membered rings change with the nature of the heteroatom (O and S) was investigated in furo- (1, 2) and thieno[2,3-*b*]indolines (3, 4) by the combined use of ^{1}H NMR spectroscopy and density functional theory (DFT) calculations. In contrast to the behavior observed for pyrroloindolines, the furo- and thienoindolines exist in solution in only one conformer, with structures in the ^{2}E–^{2}T$_3$ (1,2) and ^{2}T$_3$–E (3,4) North/West region of the pseudorotational wheel, and with pseudorotation phase angles (*P*) of 315.8, 311.6, 337.2 and 331.6°, respectively. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; pyrrolo[2,3-*b*]indolines; furo[2,3-*b*]indolines; thieno[2,3-*b*]indolines; conformation; molecular modeling

INTRODUCTION

Furobenzofurans and pyrroloindolines are an important class of natural products with both toxic and therapeutic properties (for reviews, see Ref. 1). With the advances being made in their binding to protein receptors, there is significant interest, from the drug-design perspective, in establishing the conformational preferences of these compounds. Recent theoretical studies lead to only one minimum energy conformation for furobenzofurans,[2] whereas pyrroloindolines, namely the alkaloids physostigmine and debromoflustramine B, are characterized by two minimum energy conformations for the considerably constrained pyrrolidine C-ring.[3] Hence, these two alkaloids exist in solution in a dynamic conformational equilibrium between two extreme low-energy structures labeled North/West and South/East conformations, while a fixed South/East conformation is found for physostigmine hydrochloride. It was shown that the umbrella inversion through N-1 in the free base appears to be a major factor in determining the pseudorotation[4] in the pyrrolidine ring.

In this work, we extended these studies to examine the extent to which conformational preferences in solution of fused five-membered indolines change with the nature of the heteroatom (O and S) in ring C. For this purpose, the furoindolines **1** and **2** and the thienoindolines **3** and **4** were prepared from the methiodide derivative of the corresponding pyrroloindoline. The solution conformation of indolines **1**–**4** in $CDCl_3$ was assessed with the aid of 1D and 2D NMR (COSY, HETCOR, gHMBC, NOESY) techniques, DFT calculations and subsequent determination of pseudorotational parameters. The results reveal that replacement of the N-1 nitrogen atom by oxygen or sulfur results in drastic changes in the conformational preferences of these tricyclic compounds. These studies are in line with our interest in defining the molecular conformation in solution of natural products.[5]

RESULTS AND DISCUSSION

Furo- and thienoindolines **1**–**4** were obtained by reaction of the methiodide of the corresponding pyrroloindolines **5** and **6** with NaOH or NaSH, respectively (Scheme 1), by using published procedures.[6] Although the tricyclic systems possessed a certain amount of flexibility, the presence of a heteroatom in rings B and C could predispose these molecules to a preferred conformation, which may be ascertained by NMR studies. In all cases, the expected *cis* B/C ring junction stereochemistry was deduced by the NOESY correlation between H-8a and the alkyl protons at C-3a. Conformation **A** (Fig. 1) was established by a detailed analysis of the ^{1}H NMR spectra. For example, the methylene protons

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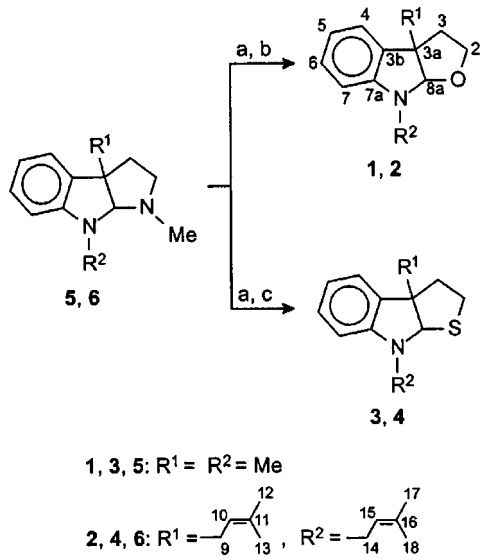
Contract/grant sponsor: CONACYT; Contract/grant number: 34405-N; G-32631-N.



Scheme 1. Preparation of furo-(**1**, **2**) and thienoindolines (**3**, **4**). (a) MeI; (b) NaOH; (c) NaSH.

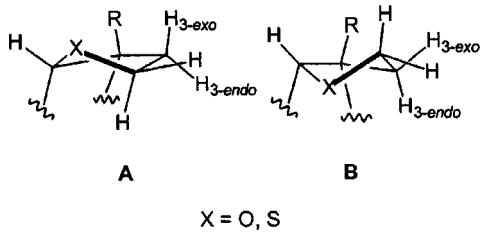


Figure 1. Conformations **A** and **B** for the C-ring.

Table 1. ^{1}H NMR chemical shifts of the C-ring for **1**–**4**[a]

	Atom				
Compound	2-*exo*	2-*endo*	3-*exo*	3-*endo*	8a-*exo*
1	3.95 ddd	3.45 ddd	2.05 ddd	2.14 ddd[b]	5.07 s
2	3.92 ddd	3.45 ddd	2.13 ddd	2.04 ddd[b]	5.18 s
3	2.80 ddd	2.65 ddd	2.21 ddd	2.60 ddd[b]	5.07 s
4	2.75 ddd	2.63 ddd	2.25 ddd	2.55 ddd[b]	5.19 s

[a] ^2J(H,H) and ^3J(H,H) values are given in Table 2.
[b] $^4J_{(3\text{-}endo,8a\text{-}exo)} \approx 0.4$ Hz.

of **1** exhibited four sets of well-resolved signals at δ 3.95, 3.45, 2.14 and 2.05 (Table 1) with an integral ratio of 1 : 1 : 1 : 1. Signal connectivities were confirmed by a COSY experiment. The existence of NOESY correlations between the methyl protons at C-3a and both methylene protons at C-3 indicates a quasi-axial conformation of H-3-*exo* and a quasi-equatorial disposition of H-3-*endo*, as shown in Fig. 1, **A**. The stereospecific assignment of these methylene protons was allowed by the observation of a weak zig-zag coupling interaction (ca 0.4 Hz) between the ring junction hydrogen H-8a and the less shielded H-3 proton (δ 2.14). Hence this signal corresponds to the *endo* and quasi-equatorial H-3 proton. The vicinal coupling constant values allowed the assignment of H-2-*exo* (δ 3.95) at higher frequency than H-2-*endo* (δ 3.45) (Table 1).

On the other hand, H-2-*exo* shows vicinal coupling constants with the methylene protons at C-3 of 7.0 and 1.5 Hz, reflecting dihedral angles approaching 40° and 60°, respectively (Table 2), with accordingly the H-2-*exo* proton being in a quasi-equatorial orientation. In principle, these coupling constants are consistent with conformational rigidity of the molecule in solution and only conformation **A** can accommodate these coupling constant derived constraints. It is worth mentioning that substitution of the methyl groups in **1** for the prenyl groups in **2** reverses the chemical shift of the C-3 pair of protons (*endo* and *exo*) (Table 1), as was supported on the basis of the magnitude of the vicinal coupling constants [^3J(H,H), Table 2] and selective decoupling experiments. Irradiation of the H-8a signal enhanced the H-3-*endo* signal. Likewise, for compounds in which the C-ring oxygen is replaced by sulfur, **3** and **4**, the NOE spectra clearly show the spatial proximities between the C-3 pair of protons (*endo* and *exo*) and the alkyl protons at C-3a. Additionally, a four-bond coupling constant [^4J(H,H)] between H-8a-*exo* and H-3-*endo* protons was found (Table 1). Close inspection of the data in Table 2 reveals that sulfur introduces small distortions in conformation **A**, as shown by small changes in J values, but overall conformer identification is still possible.

According to theoretical calculations using the molecular mechanics (MMX force field[7]) method, compounds **1**–**4** have two low-energy conformations resulting from the C-ring inversion **A** and **B**, with the former preferred between 1.5 and 3.0 kcal mol^{-1} (1 kcal = 4.184 kJ). Geometry optimizations by use of a density functional theory (DFT) method lead to only one minimum energy conformation (**A**) for **1** and two low-energy conformations (**A, B**) for **2**–**4**. The prenyl side-chains were rotated in order to establish all minimum conformations. The computed structures are shown in Fig. 2, and the corresponding relative energies are listed in Table 2. The theoretical coupling constants were obtained by means of a generalized Karplus-type relationship.[8] The observed and calculated couplings are given in Table 2. The calculated couplings give excellent agreement for thienoindolines, suggesting that the conformation in $CDCl_3$ solvent is predominantly **A**. However, we noted that, for furoindolines, the calculated coupling $^3J_{2,3\text{-}endo-exo}$ is larger than expected by as much as 1.2 Hz, and this is presumably due to the electronegativity effect of the oxygen atom.[9] The remaining ^3J couplings are in agreement with predictions. Hence the assignment of the spectra given above was confirmed.

The low-energy conformation **A** in **1**–**4** can be conveniently described using the Altona–Sundaralingam pseudorotational parameters.[10] With the knowledge of the five endocyclic torsion angles of a given conformer (τ_0–τ_4, Table 3), defined in Fig. 3, the phase angle (P) was calculated by solving the equation

$$\tan P = \frac{(\tau_2 + \tau_4) - (\tau_1 + \tau_3)}{3.077\ \tau_0} \quad (1)$$

The τ_0–τ_4 values were derived from structures calculated by a DFT method. The puckering amplitude τ_m is related to P and τ_0 through the equation

$$\tau_m = \frac{\tau_0}{\cos P} \quad (2)$$

For furoindolines **1** and **2**, the tetrahydrofuran C-ring was biased toward a North/West structure that is intermediate

Table 2. Density functional theory (B3LYP/6–31G*) relative energy (kcal mol^{-1}), calculated dihedral angles (φ, degrees, in parentheses) and calculated and observed vicinal coupling constants ($^3J_{2,3}$, Hz) of the C-ring for **1**–**4**

			$^3J_{2,3}$ (φ)							
			exo–exo		*exo–endo*		*endo–endo*		*endo–exo*	
Compound	Conformation	E_{rel}	Calcd	Obs.	Calcd	Obs.	Calcd	Obs.	Calcd	Obs.
1[a]	**A**	0.0	7.6 (−38)	7.0 (−41)	0.3 (84)	1.5 (62)	5.7 (−39)	5.3 (−40)	11.5 (−161)	11.4 (−160)
2[b]	**A**	0.0	7.7 (−37)	8.3 (−33)	0.3 (84)	1.5 (62)	5.4 (−39)	5.4 (−39)	11.5 (−161)	11.0 (−157)
	B	2.6	6.6 (33)	—	10.6 (153)	—	8.7 (31)	—	0.4 (−90)	—
3[c]	**A**	0.0	6.6 (−42)	6.2 (−44)	0.8 (77)	1.5 (69)	5.7 (−46)	4.9 (−50)	12.5 (−165)	12.7 (−166)
	B	2.3	6.9 (40)	—	11.8 (159)	—	7.7 (37)	—	0.4 (−82)	—
4[d]	**A**	0.0	6.4 (−43)	6.4 (−43)	0.8 (76)	1.4 (71)	5.6 (−47)	4.9 (−50)	12.6 (−165)	12.2 (−162)
	B	2.5	6.5 (42)	—	12.0 (161)	—	7.3 (38)	—	0.5 (−80)	—

[a] $^2J_{2,2} = 8.8$ Hz; $^2J_{3,3} = 11.7$ Hz.
[b] $^2J_{2,2} = 8.3$ Hz; $^2J_{3,3} = 11.7$ Hz.
[c] $^2J_{2,2} = 11.4$ Hz; $^2J_{3,3} = 12.2$ Hz.
[d] $^2J_{2,2} = 10.7$ Hz; $^2J_{3,3} = 11.7$ Hz.

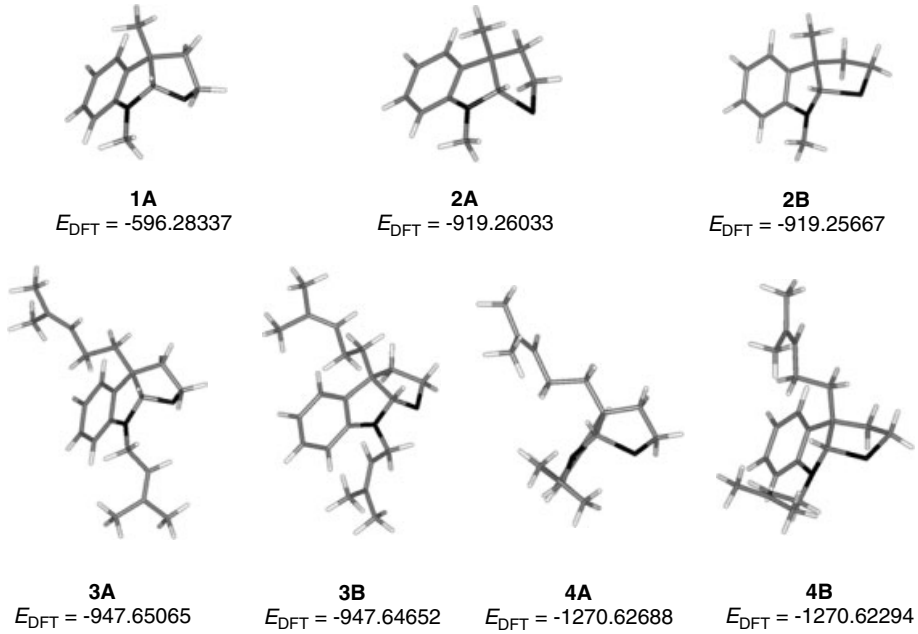


Figure 2. Density functional theory molecular models (B3LYP/6–31G*, *E* in hartrees) for **1**–**4**.

Table 3. Endocyclic torsion angles (τ) and pseudorotational parameters (P_A, τ_m) for **1**–**4**

	Endocyclic torsion angle (°)							
Compound	τ_0	τ_1	τ_2	τ_3	τ_4	Conformation **A**	P_A (°)	τ_m (°)
1	34.2	−37.7	26.9	−7.7	−16.3	^2E–$^2T_3$	315.8	37.5
2	35.8	−37.7	25.2	−5.1	−19.1	^2E–$^2T_3$	311.6	38.0
3	26.5	−43.2	41.3	−20.0	−3.8	$^2T_3$–E_3	337.2	44.8
4	29.5	−44.3	39.3	−16.1	−7.8	$^2T_3$–E_3	331.6	44.7

between the idealized envelope ^2E and half chair $^2T_3$ conformers (P = 315.8° for **1** and 311.6° for **2**), whereas in thienoindolines **3** and **4**, the tetrahydrothiophene C-ring adopts a $^2T_3$-type form deformed towards the envelope E_3 conformation (P = 337.2° for **3** and 331.6° for **4**). In thienoindolines **3** and **4**, the conformers populated by the C-ring differ only slightly from those present in **1** and **2**. The P values vary by ca 20°. Table 3 describes the **A** conformers which best fit the NMR data.

EXPERIMENTAL

NMR measurements were performed on Varian Mercury spectrometers operating at 300 MHz (proton) or 75 MHz

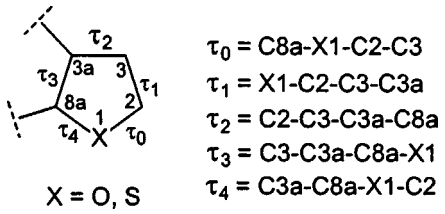


Figure 3. Definition of endocyclic torsion angles $\tau_0-\tau_m$.

(carbon). Data were obtained from $CDCl_3$ solutions. Spectra were of ca 28 mg cm^{-3} solutions with a probe temperature of ca 22 °C. Typical operating parameters for ^{1}H-detected experiments were an f_2 (^{1}H) spectral window of 2278 Hz with 1024 data points. For phase-sensitive gHSQC spectra, f_1 (^{13}C) was 12 500 Hz, 256 time increments were collected and linearly predicted to 1024, with 64 transients per increment; for gHMBC spectra, f_1 (^{13}C) was 18 188 Hz with 128 transients per increment and 256 time increments. Phase-sensitive NOESY spectra used the same ^{1}H spectral windows and f_2 data points with 256 increments linearly predicted to 1024 using a mixing time of 0.8 s and a relaxation delay of 1.0 s.

Calculations were carried out using a Pentium IV-based PC. For molecular mechanics calculations, the PCMODEL program (Serena Software, Bloomington, IN, USA) was used. A systematic conformational search for the five-membered C-ring was carried out with the aid of Dreiding models and considering dihedral angle rotations of ca 10°: the E_{MMX} value was used as the convergence criterion. All DFT calculations were performed using Spartan'04.[11] Each conformer was optimized at the B3LYP/6–31G* level of theory.[12]

3a,8-Dimethyl-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (1)

Colorless oil; R_f 0.71 [AcOEt–hexane (2 : 3)]; IR, $CHCl_3$ (cm^{-1}), 3052, 2932, 1462, 1378; ^{1}H NMR ($CDCl_3$), δ 7.10 (1H, td, J = 7.6, 1.5 Hz, H-6), 7.05 (1H, dd, J = 7.3, 1.5 Hz, H-4), 6.78 (1H, ddd, J = 7.6, 7.3, 1.0 Hz, H-5), 6.37 (1H, d J = 7.6 Hz, H-7), 5.07 (1H, s, H-8a), 2.92 (3H, s, NMe), 1.46 (3H, s, CMe), for the methylene proton data (H-2 and H-3) see Table 1; ^{13}C ($CDCl_3$), δ 150.4 (C-7a), 134.5 (C-3b), 128.1 (C-6), 122.4 (C-4), 117.3 (C-5), 105.0 (C-8a), 104.8 (C-7), 67.3 (C-2), 52.3 (C-3a), 41.7 (C-3), 30.9 (NMe), 24.7 (CMe).

3a,8-Bis(3-methylbut-2-enyl)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (2)

Colorless oil; R_f 0.82 [AcOEt–hexane (2 : 3)]; IR, $CHCl_3$ (cm^{-1}), 3050, 2932, 1462, 1380; MS (EI, 70 eV), m/z 297 M^+ (100), 283 (18), 230 (33), 160 (68); HRMS (EI), calcd for $C_{20}H_{27}NO$ 297.2096, found 297.2096; ^{1}H NMR ($CDCl_3$), δ 7.06 (1H, td, J = 7.6, 1.2 Hz, H-6), 7.02 (1H, d, J = 7.6, Hz, H-4), 6.64 (1H, td, J = 7.6, 1.0 Hz, H-5), 6.36 (1H, d, J = 7.6 Hz, H-7), 5.22 (1H, tq, J = 6.6, 1.5 Hz, H-15), 5.18 (1H, s, H-8a), 5.06 (1H, tq, J = 7.6, 1.5 Hz, H-10), 3.83 (2H, m, H-14,14′), 2.47 and 2.42 (2H, dd, J = 15.4, 7.6 Hz, H-9,9′), 1.73 (3H, s, Me-17), 1.72 (3H, s, Me-18), 1.67 (3H, s, Me-12), 1.56 (3H, s, Me-13), for the methylene proton data (H-2 and H-3) see Table 1; ^{13}C NMR ($CDCl_3$), δ 150.3 (C-7a), 134.8 (C-16), 134.2 (C-11), 133.5 (C-3b), 127.9 (C-6), 123.1 (C-4), 120.8 (C-15), 119.8 (C-10), 117.0 (C-5), 105.1 (C-7), 101.1 (C-8a), 66.8 (C-2), 56.3 (C-3a), 42.3 (C-14), 39.6 (C-3), 36.3 (C-9), 25.9 (Me-12), 25.7 (Me-17), 18.0 (Me-13), 17.9 (Me-18).

3a,8-Dimethyl-2,3,3a,8a-tetrahydro-8*H*-thieno[2,3-*b*]indole (3)

Colorless oil; R_f 0.82 [AcOEt–hexane (2 : 3)]; IR, $CHCl_3$ (cm^{-1}), 3060, 2926, 1606, 1376; MS (EI, 70 eV), m/z 205 M^+ (100), 177 (38), 158 (36), 144 (60); ^{1}H NMR ($CDCl_3$), δ 7.11 (1H, td, J = 7.8, 1.5 Hz, H-6), 6.99 (1H, dd, J = 7.3, 1.0 Hz, H-4), 6.70 (1H, td, J = 7.3, 1.0 Hz, H-5), 6.44 (1H, d J = 7.8 Hz, H-7), 5.07 (1H, s, H-8a), 2.81 (3H, s, NMe), 1.43 (3H, s, CMe), for the methylene proton data (H-2 and H-3) see Table 1; ^{13}C ($CDCl_3$), δ 149.7 (C-7a), 135.0 (C-3b), 128.1 (C-6), 121.4 (C-4), 117.8 (C-5), 107.3 (C-7), 86.6 (C-8a), 56.7 (C-3a), 44.5 (C-3), 33.1 (NMe), 32.2 (C-2), 24.8 (CMe).

3a,8-Bis(3-methylbut-2-enyl)-2,3,3a,8a-tetrahydro-8*H*-thieno[2,3-*b*]indole (4)

Slightly yellow oil; R_f 0.93 [AcOEt–hexane (2 : 3)]; IR, $CHCl_3$ (cm^{-1}), 3050, 2930, 1460, 1380; MS (EI, 70 eV), m/z 313 M^+ (100), 244 (70), 176 (97); ^{1}H NMR ($CDCl_3$), δ 7.09 (1H, ddd, J = 7.8, 7.3, 1.2 Hz, H-6), 6.96 (1H, dd, J = 7.3, 1.2 Hz, H-4), 6.67 (1H, td, J = 7.3, 1.0 Hz, H-5), 6.48 (1H, d, J = 7.8 Hz, H-7), 5.26 (1H, tsept, J = 6.9, 1.3 Hz, H-15), 5.19 (1H, tsept, J = 6.9, 1.3 Hz, H-10), 5.19 (1H, s, H-8a), 3.87 (1H, dd, J = 14.2, 5.4 Hz, H-14), 3.63 (1H, dd, J = 14.2, 8.3 Hz, H-14′), 2.39 and 2.34 (2H, dd, J = 15.1, 7.0 Hz, H-9,9′), 1.76 (3H, s, Me-17), 1.75 (3H, d, J = 1.1 Hz, Me-18), 1.69 (3H, d, J = 1.0 Hz, Me-12), 1.51 (3H, s, Me-13), for the methylene proton data (H-2 and H-3) see Table 1; ^{13}C NMR ($CDCl_3$), δ 150.0 (C-7a), 136.3 (C-16), 134.8 (C-3b), 134.2 (C-11), 128.3 (C-6), 122.5 (C-4), 120.2 (C-15), 120.1 (C-10), 117.8 (C-5), 107.7 (C-7), 82.1 (C-8a), 60.8 (C-3a), 44.3 (C-14), 42.1 (C-3), 36.3 (C-9), 32.2 (C-2), 26.4 (Me-12), 26.3 (Me-17), 18.5 (Me-18), 18.2 (Me-13).

Acknowledgement

This research was supported by CONACYT, México (34405-N, G-32631-N).

REFERENCES

1. (a) Wogan GN. *Bacteriol. Rev.* 1966; **30**: 460; (b) Grieg NH, Pei XF, Soncrant TT, Ingram DK, Brossi A. *Med. Res. Rev.* 1995; **15**: 3; (c) Sano M, Bell K, Marder K, Stricks L. *Clin. Pharm.* 1993; **16**: 61; (d) Brossi A, Pei X-F, Greig NH. *Aust. J. Chem.* 1996; **49**: 171.
2. Alemán C, Donate PM, da Silva R, da Silva GVJ. *J. Org. Chem.* 1999; **64**: 5712.
3. (a) Morales-Ríos MS, Santos Sánchez NF, Suárez-Castillo OR, Joseph-Nathan P. *Magn. Reson. Chem.* 2002; **40**: 677; (b) Morales-Ríos MS, Santos Sánchez NF, Joseph-Nathan P. *J. Nat. Prod.* 2002; **65**: 136.
4. Kilpatrick JE, Pitzer KS, Spitzer R. *J. Am. Chem. Soc.* 1947; **69**: 2483.
5. (a) Reyes-Trejo B, Morales-Ríos MS, Alvarez-Cisneros EC, Joseph-Nathan P. *Magn. Reson. Chem.* 2003; **41**: 1021; (b) Flores-Sandoval CA, Cerda-García-Rojas CM, Joseph-Nathan P. *Magn. Reson. Chem.* 2001; **39**: 173.
6. Dale FJ, Robinson B. *J. Pharm Pharmacol.* 1970; **22**: 889.
7. Burket U, Allinger NL. *Molecular Mechanics*. *ACS Monograph* 177. American Chemical Society: Washington, DC, 1982.
8. (a) Haasnoot CAG, de Leeuw FAAM, Altona C. *Tetrahedron* 1980; **36**: 2783; (b) Cerda-García-Rojas CM, Zepeda LG, Joseph-Nathan P. *Tetrahedron Comput. Methodol.* 1990; **3**: 113.
9. Abraham RJ, Parry K, Thomas WA. *J. Chem. Soc. B* 1971; 446.
10. (a) Altona C, Sundaralingam M. *J. Am. Chem. Soc.* 1972; **94**: 8205; (b) Altona C, Sundaralingam M. *J. Am. Chem. Soc.* 1973; **95**: 2333.
11. Kong J, White CA, Krylov AI, Sherrill CD, Adamson RD, Furlani TR, Lee MS, Lee AM, Gwaltney SR, Adams TR, Ochsenfeld C, Gilbert ATB, Kedziora GS, Rassolov VA, Maurice DR, Nair N, Shao Y, Besley NA, Maslen PE, Dombroski JP, Daschel H, Zhang W, Korambath PP, Baker J, Byrd EFC, Van Voorhis T, Oumi M, Hirata S, Hsu CP, Ishikawa N, Florian J, Warshel A, Johnson BG, Gill PMW, Head-Gordon M, Pople JA. *J Comput. Chem.* 2000; **21**: 1532.
12. (a) Becke AD. *Phys. Rev. A* 1988; **38**: 3098; (b) Becke AD. *J. Chem. Phys.* 1993; **98**: 5648; (c) Lee C, Yang W, Parr RG. *Phys. Rev. B* 1988; **37**: 785; (d) Perdew JP. *Phys. Rev. B* 1986; **33**: 8822.