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PRONOUNCED CONFORMATIONAL PREFERENCE OF THE 3′-α-CUMYL SUBSTITUENT IN 2-(2′-METHOXY-3′-α-CUMYLPHENYL)BENZOTRIAZOLE

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A pronounced conformational preference of the 3′-α-cumyl substituent in 2-(2′-methoxy-3′-α-cumylphenyl)benzotriazole is suggested from the results of molecular dynamics simulations. This suggestion is supported by both solution NMR spectral and solid-state x-ray crystallographic data. The orientation of the α-cumyl substituent may have implications on the relative performance of 3′-substituted 2′-hydroxyphenylbenzotriazole light stabilizers in polar media. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Derivatives of 2-(2′-hydroxyphenyl)benzotriazole are commonly used industrially to provide enhanced light stability to polymeric resins and coatings.[1] According to the theory of Förster,[2] these molecules undergo an efficient excited-state intramolecular proton transfer process.[3] The proton transfer is followed by rapid internal conversion to the ground state, which regenerates the starting material. This mechanism provides the compound with high photochemical stability.

In the course of our research on the 3′-substituted versions of these compounds, molecular dynamics simulations were carried out on the methyl ether derivative **A** (see Figure 1), a model compound for benzotriazole UV absorbers. The methyl ether derivative was found to provide a useful NMR spectral probe sensitive to the orientation of the aromatic portion of the α-cumyl substituent in the 3′-position. Use of the methyl ether also prevents spectral shifts due to differences in hydrogen bonding as found for the hydroxylated compounds. We report here the results of the simulations as well as corroborating experimental data obtained in both solution and the solid state.

EXPERIMENTAL

NMR spectroscopy

^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a Varian UNITY 500 NMR spectrometer. All solutions were dilute and of proximate molar equivalence in the substrate. The chemical shifts are reported relative to TMS, where a positive shift is downfield from the standard. The identity of the aromatic methoxy signal was established in each case by observation of the $^1J_{C-H}$ coupling, via the ^{13}C satellite sidebands, or by difference NOE work.

Syntheses

The hydroxyphenylbenzotriazole starting materials are well known, readily available compounds.

2-(2-*Methoxy*-5-*methylphenyl*)-2-*H*-*benzotriazole* (1). To a stirred solution of 45·0 g (0·2 mol) of 2-(2-hydroxy-5-methyl)-1,2,3-2*H*-benzotriazole and 17·6 g (0·21 mol) of sodium hydroxide in 500 ml of ethanol heated at reflux was added 18·7 g (0·3 mol) of methyl iodide over 40 min. The reaction mixture was heated for an additional 5 h, concentrated to *ca* 200 ml and added to 500 ml of water. The resulting precipitate was collected and recrystallized from 2-propanol to yield 37·4 g of the methyl ether **1** as white crystals; m.p. 91–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8·01–7·96 (nfom, 2 H), 7·51 (d, J = 2·18 Hz, 1 H), 7·47–7·42 (nfom, 2 H), 7·31 (dd, J = 8·39, 2·18 Hz, 1 H), 7·05 (d, J = 8·39 Hz, 1 H), 3·86 (s, $^1J_{C-H}$ = 144·7 Hz, 3 H), 2·38 (s, $^1J_{C-H}$ = 126·7 Hz, 3 H); IR (CH_2Cl_2), 2595, 1500, 1330, 1065, 1015 cm^{-1}. Analyses: calculated for $C_{14}H_{13}N_3O$, C 70·28, H 5·48, N 17·56; found, C 70·17, H 5·15, N 17·69%.

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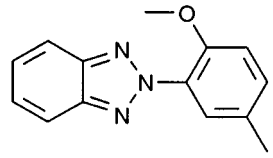

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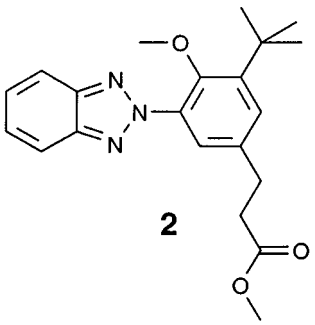

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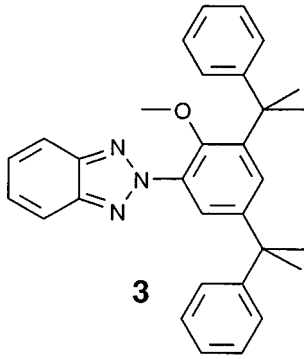

3

Methyl 3-(3-*benzotriazol*-2-*yl*-5-tert-*butyl*-4-*methoxyphenyl*)*propionate* (2). To a stirred, orange suspension of 10·0 g (28·3 mmol) of methyl 3-(3-benzotriazol-2-yl-5-*tert*-butyl-4-hydroxyphenyl)propionate ester and 8·0 g (57·9 mmol) of potassium carbonate in 30 ml of DMF heated at 60 °C was added an excess of methyl iodide. The now yellow reaction mixture was stirred at 60–70 °C for 16 h, then allowed to cool to room temperature. The reaction mixture was acidified with 10% HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated to yield 9·8 g of an orange solid which was purified by MPLC on silica gel using heptane–EtOAc (10 : 1) to yield 7·6 g of the methyl ether **2** as a white solid; m.p. 83–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8·02–7·98 (nfom, 2 H), 7·49–7·45 (nfom, 2 H), 7·38 (*meta* doublet, J = 2·33 Hz, 1 H), 7·33 (d, J = 2·33 Hz, 1 H), 3·70 (s, $^1J_{C-H}$ = 146·7 Hz, 3 H), 3·08 (s, $^1J_{C-H}$ = 144·8 Hz, 3 H), 2·98 (t, 2 H), 2·68 (t, 2 H), 1·45 (s, 9 H) (irradiation of the *tert*-butyl signal at 1·45 ppm produced an NOE for the methoxy resonance at 3·08 ppm); IR ($CDCl_3$), 2940, 1720, 1420, 1345, 1230, 1095, 980 cm^{-1}. Analysis: calculated for $C_{21}H_{25}N_3O_3$, C 68·63, H 6·86, N 11·44; found, C 68·77, H 6·98, N, 11·48%.

2 - [2 - *Methoxy* - 3, 5 - *bis*(1 - *methyl* - 1 - *phenylethyl*) *phenyl*] - 2*H* - *benzotriazole* (3). To a stirred, orange suspension of 10·0 g (22·4 mmol) of 2-[2-hydroxy-3,5-bis(1-methyl-1-phenylethyl)phenyl]-2*H*-benzotriazole and 6·2 g (44·9 mmol) of potassium carbonate in 30 ml of DMF heated at 60 °C was added an excess of methyl iodide. The now yellow reaction mixture was stirred at 60–70 °C for 16 h, then allowed to cool to room temperature. The reaction mixture was acidified with 10% HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated to yield 9·9 g of a tan solid. The crude product was dissolved in EtOAc, filtered through a small pad of silica gel, concentrated and recrystallized from EtOAc to yield 7·1 g of the methyl ether **3** as white crystals; m.p. 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7·97–7·92 (nfom, 2 H), 7·50 (AB, 2 H), 7·44–7·39 (nfom, 2 H), 7·36–7·30 (ms, 4 H), 7·25–7·15 (ms, 5 H), 7·08 (t, 1 H), 2·04 (s, $^1J_{C-H}$ = 145·2 Hz, 3 H), 1·78 (s, 6 H), 1·69 (s, 6 H); IR (CH_2Cl_2), 2920, 1470, 1335, 1020, 980 cm^{-1}. Analysis: calculated for $C_{31}H_{33}N_3O$, C 80·30, H 7·18, N 9·07; found, C 80·61, H 6·78, N 9·08%.

Parametrization

The MacroModel AMBER* force field contains high-quality, specific parameters for 2-(2′-hydroxyphenyl) benzotriazole. In contrast, calculations on the methyl ether 2-(2′-methoxyphenyl)benzotriazole revealed that the relative energies of the three lowest energy conformers (as determined by *ab initio* calculations) were poorly reproduced. Therefore, we used a combination of solid-state x-ray diffraction data[4] and *ab initio* calculations (using Spartan[5] software) to determine higher quality molecular mechanical parameters for the system. The *ab initio* calculations were performed on the unsubstituted 2-(2′-methoxyphenyl)benzotriazole. The resulting parameters are given in Table 1. The C═N, N—N and N—C bond lengths were taken from the solid-state structure, as was the N—C—C bond angle. The constants for bond stretching, angle bending and torsional rotation for the triazine ring system were chosen to be somewhat rigid, such that the benzotriazole ring system would remain fairly planar and with nearly constant bond lengths and angles determined from the x-ray data. Partial atomic charges were assigned from a fit to the molecular electrostatic potential of the HF/

Table 1. Derived AMBER* parameters used in this work

Bond	r_0	k_s				
C1=N2	1·347	600				
C7=N8	1·347	600				
N2–N9	1·334	500				
N8–N9	1·334	500				
N9–C10	1·430	400				
Angle	θ_0	k_θ				
C7–C1=N2	107·4	75·0				
C1–C7=N8	131·3	75·0				
Torsion	V_1	V_2	V_3	V_4	V_5	V_6
C14–C15–O16–C17	−1·0921	1·8257	−0·1623	0·3304	0·0066	−0·0326
C10–C15–O16–C17	0·0	0·0	0·0	0·0	0·0	0·0
N2–N9–C10=C11	0·0	0·0692	0·0	−0·1058	0·0	0·0071
N2–N9–C10=C15	0·0	0·0692	0·0	−0·1058	0·0	0·0071
N8–N9–C10=C11	0·0	0·0692	0·0	−0·1058	0·0	0·0071
N8–N9–C10=C15	0·0	0·0692	0·0	−0·1058	0·0	0·0071
C1=N2–N9–C10	0·0	10·0	0·0	0·0	0·0	0·0
C1=N2–N9–C8	0·0	10·0	0·0	0·0	0·0	0·0
C7=N8–N9–C10	0·0	10·0	0·0	0·0	0·0	0·0
C7=N8–N9–C2	0·0	10·0	0·0	0·0	0·0	0·0
Atom	**Charge**	**Atom**	**Charge**			
C1, C7	+0·350	N2, N8	−0·55			
C3, C6	−0·320	C4, C5	−0·127			
N9	+0·620	C10	−0·150			
C11	−0·110	C12	−0·170			
C13	−0·100	C14	−0·310			
C15	+0·460	O16	−0·440			
C17	+0·179					

Table 2. Conformational energies of 2-(2′-methoxyphenyl)benzotriazole[a]

	Ab initio torsions		HF/6–31G*//HF/6–31G*		HF/6–31G*//MP2/6–31G*	
Conformer	2–9–10–15	10–15–16–17	*E* (hartree)	*E* (rel) (kcal)	*E* (hartree)	*E* (rel) (kcal)
1	+50	−106	−736·84014	0·00	−739·15406	0·00
2	+62	−178	−736·83994	0·13	−739·15377	0·18
3	+55	+79	−736·83854	1·00	−739·15209	1·24
	AMBER* torsions			AMBER*		
	2–9–10–15	10–15–16–17		*E*(rel) (kcal)		
1	+59	−97		0·0		
2	+63	−178		0·0		
3	+64	+85		0·8		

[a] Conformers were verified as energy minima by normal coordinate analysis by *ab initio* calculation and with the derived molecular mechanics parameters (**1** and **2**, HF/3–21G*; **3**, HF/6–31G*).

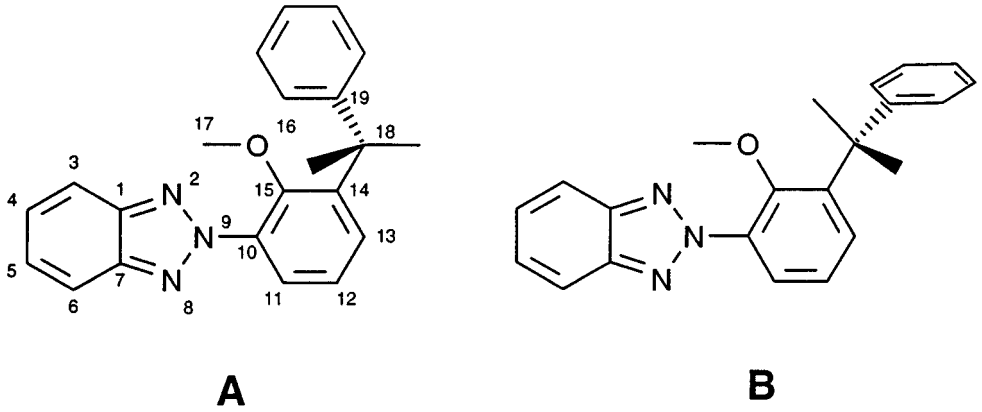

Figure 1. Atom numbers and conformer labels for 2-(2′-methoxy-3′-α-cumylphenyl)benzotriazole

6–31G* wavefunction at the HF/6–31G* structure. Torsional parameters for the inter-ring N—N—C—C and the methoxy C—C—O—Me torsion were developed by fitting to the HF/6–31G*//HF/6–31G* rotational profile. All other parameters were taken from the standard AMBER* force field. The final parametrization gave the results shown in Table 2 for the relative energies of the three lowest-energy conformers of 2-(2′-methoxyphenyl)benzotriazole.

Simulations

The simulations were performed on 2-(2′-methoxy-3′-α-cumylphenyl)benzotriazole using the MacroModel version 5.0 software.[6] We used the AMBER* all-atom force field and a GB/SA simulated chloroform solvent.[7] Equilibration for 50 ps was followed by 14·5 ns of mixed-mode Monte Carlo/stochastic dynamics[8] at a constant temperature of 300 K. A Monte Carlo trial was attempted every dynamics time step. This gave rise to an acceptance ratio for the simulations of about 2%, which amounts to *ca* 50 fs of dynamics per successful Monte Carlo step. The final average potential energy scaled to 300 K for the simulation was 260·0 kJ mol^{-1}. Two duplicate simulations were carried out, starting from conformations with different dihedral angles to both the methoxy and α-cumyl groups. All simulations gave virtually identical results with respect to average scaled potential energy and conformer populations.

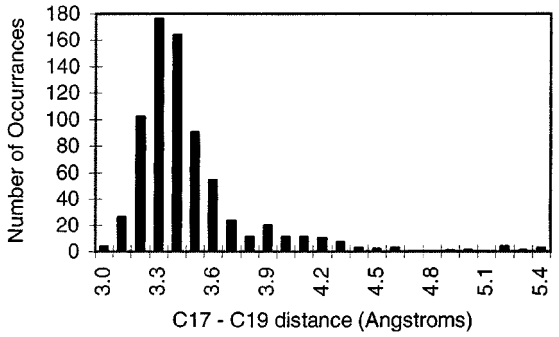

Figure 2. Histogram of C(17)–C(19) distance for 2-(2′-methoxy-3′-α-cumylphenyl)benzotriazole. The structure was sampled every 20 ps during the simulation

RESULTS AND DISCUSSION

The orientation of the α-cumyl substituent in 2-(2′-methoxy-3′-α-cumylphenyl) benzotriazole can be partially characterized by the dihedral angle to the aromatic ring of the α-cumyl substituent, the C(15)—C(14)—C(18)—C(19) torsion. In orientation **A** (Figure 1) the C(15)—C(14)—C(18)—C(19) torsion is near ±60°. Orientation **B** has this torsion near ±120°. For orientation **A**, if the C(10)—C(15)—O(16)—C(17) dihedral has the same sign as the C(15)—C(14)—C(18)—C(19) torsion, such that the methyl group of the ether and the phenyl ring of the α-cumyl are on the same side of the molecule, the distance from the methyl ether carbon C(17) to the *ipso* carbon of the α-cumyl aromatic ring C(19) is about 3·3 Å. In the **B** orientation, the corresponding distance is over 4·0 Å. During the simulations, the C(17)—C(19) distance was monitored. A histogram of the results is given in Figure 2. The peak near 3·3 Å is due to the population of a conformation in which the α-cumyl group is oriented as in **A**, and the methyl ether carbon lies on the same side of the molecule as C(19). Orientation **B** has a small population. In fact, integration of the peaks yields a ratio of about 92:8. If we only consider the orientation of the α-cumyl group, without regard to the position of the methoxy, the ratio increases to 98:2. This corresponds to a free energy difference of about 2·3 kcal mol^{-1} at 300 K. In addition, visual inspection of structures sampled during the simulations indicates that in most samples the methyl ether lies mostly in a position normal to the planes of the α-cumyl and benzotriazole aromatic systems.

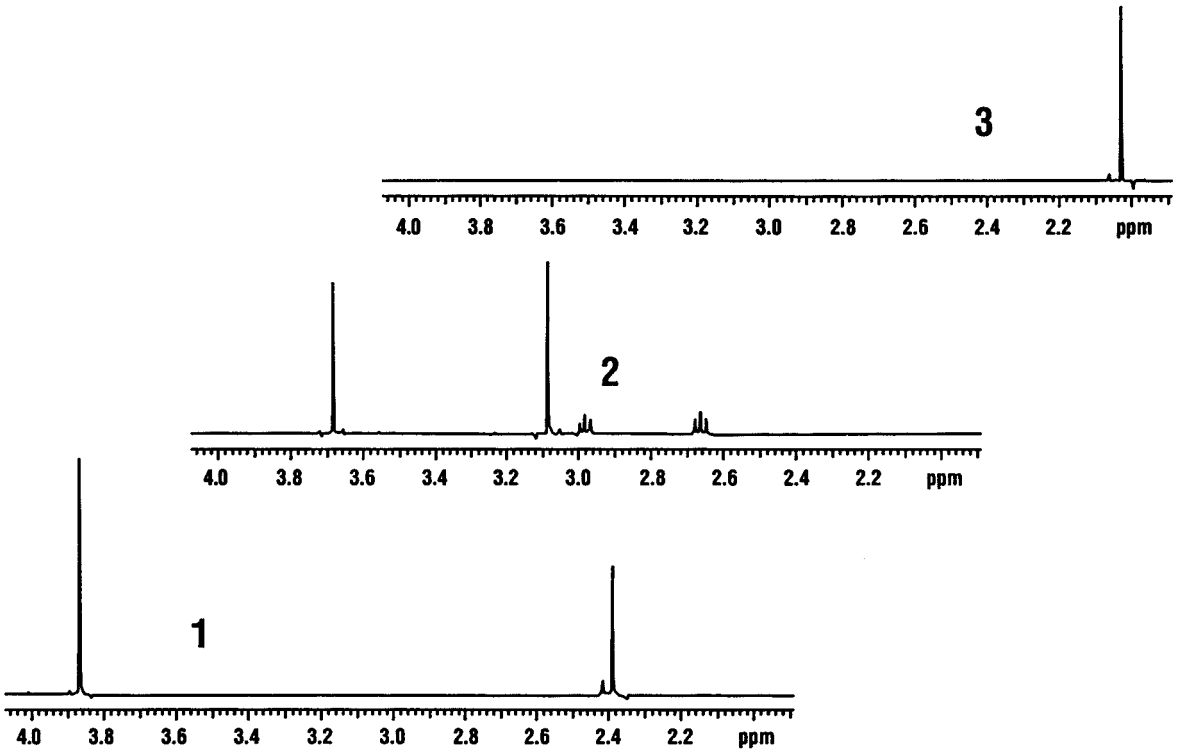

Figure 3. ^{1}H NMR spectra of model compounds **1**–**3** in the 4·0–2·0 ppm range

The ^{1}H NMR spectra of the three model compounds **1**, **2** and **3** are shown in Figure 3. In the spectrum of **1**, a singlet is observed at 3·86 ppm, which is assigned to the protons of the methoxy substituent. The observed chemical shift is ±0·1 ppm of the chemical shift for the methyl protons of anisole.[9] This is the region expected for the protons of an aromatic methoxy group. In the spectrum of **2** the methoxy resonance has moved upfield to 3·08 ppm. This dramatic shift is almost out of the standard range of expectation for any methoxy resonance. This observation is interpreted by noting that the aromatic rings separated by the C—N single bond are not coplanar in these systems and, that the 3′-*tert*-butyl group hinders rotation about the C(15)—O(16) bond such that the methyl protons spend most of the time in the shielding region of the benzotriazole aromatic system. The spectrum of **3** indicates an even more pronounced upfield shift of the methyl protons to 2·04 ppm. This constitutes a virtually unprecedented chemical shift for the protons of the methoxy group. A reasonable explanation of this observation is that the shift is due to an overwhelming conformational preference, even in solution, of the 3′-α-cumyl substituent which places the methyl substantially in the shielding region of both aromatic systems. Interestingly, the simulated time-averaged distance between the centroid of the phenyl ring and the centroid of the methoxy protons is 3·72 Å. According to a derived shielding function developed by Johnson and Bovey[10] based on free electron theory, the predicted change in chemical shift due to the presence of the phenyl ring is about 1·0 ppm. The observed change is 1·04 ppm from the already shielded methoxy protons of **2**.

Additional support for the conformational preference of the α-cumyl group in these compounds can be seen in the x-ray crystal structure of a related compound, 2,4,6-tri(α,α-dimethylbenzyl)phenol.[11] The orientation of the 2- and 6-substituents are identical to the orientation shown in conformer **A**.

This pronounced preference of the α-cumyl substituent is initially surprising, considering the steric requirements of the phenyl group relative to methyl. MacPhee *et al.*[12] and Charton[13] have published revised Taft steric parameters E_s which include the phenyl group. In both cases, the steric requirements of the methyl group were less than phenyl. Given this, one might expect that an orientation of the α-cumyl group such as that depicted in **A**, which places the phenyl in the vicinity of the methoxyl, would be destabilized relative to orientation **B**. However, one must note that the steric requirement of a phenyl substituent is highly anisotropic.[14] The values of E_s and related steric parameters are derived from relative rates of acid-catalyzed ester hydrolysis and/or rates of esterification of carboxylic acids. For a substituent such as a phenyl group, parameters derived

in this manner would represent an appropriately averaged quantity over the rotameric conformations of the phenyl group. As a result, comparison of such steric parameters is misleading in the present case, as correlations with conformer stabilities should not hold in situations where the structural surroundings induce an important conformational preference of a group.[15] Additionally, an electronic contribution to the stabilization of orientation **A** is consistent with what has been reported by Nishio *et al.*[16] They discussed a stabilization arising from a CH—π interaction which is largely understood in terms of delocalization from the phenyl π system to a C—H σ^* orbital. The enthalpy for a single CH–π interaction is estimated to be around 1 kcal mol^{-1}. The free energy of interaction will contain a favorable additional entropic contribution of R ln 3 (0·65 kcal mol^{-1} at 300 K) due to the three identical C—H bonds. It should be noted, however, that this interaction is not explicitly taken into account in the simulations.

It has been suggested by Heller[17] that the introduction of large groups *ortho* to the hydroxyl of 2-(2′-hydroxyphenyl)benzotriazoles could shield the intramolecular hydrogen bond, which is a key structural feature for photostability, from being disrupted in basic, polar media. In addition, Catalan *et al.*[18] have observed the dramatic effect on the UV absorption spectrum and photostability of an *ortho-tert*-butyl-substituted 2-(2′-hydroxyphenyl)benzotriazole in DMSO solution. In the light of the previous suggestions and observations, we feel that the observed conformational preference may have an effect on the performance of an appropriately substituted 2-(2′-hydroxyphenyl)benzotriazole UV absorber in a polar environment. The performance, as UV stabilizers, of model compounds of this type is currently under study in some coating systems of high polarity.

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REFERENCES

1. B. Ranby and J. F. Rabek, *Photodegradation, Photooxidation, and Photostabilization of Polymers: Principles and Applications.* Wiley, New York (1975).
2. Th. Förster, *Z. Elektrochem. Angew. Phys. Chem.* **54**, 42–46 (1950).
3. J.-E. A. Otterstedt, *J. Phys. Chem.* **58**, 5716–5725 (1973).
4. J. Rieker, E. Lemmert-Schmitt, G. Goeller, M. Roessler, G. J. Stueber, H. Schettler, H. E. A. Kramer, J. J. Stezowski, H. Hoier, S. Henkel, A. Schmidt, H. Port, M. Wiechmann, J. Rody, G. Rytz, M. Slongo and J.-L. Birbaum, *J. Phys. Chem.* **96**, 10225–10234 (1992).
5. *Spartan Version 4.0.* Wavefunction, Irvine, CA (1995).
6. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.* **11**, 440–467 (1990).
7. W. C. Still, A. Tempczyk, R. C. Hawley and T. Hendrickson, *J. Am. Chem. Soc.* **112**, 6127–6129 (1990).
8. F. Guarnieri and W. C. Still, *J. Comput. Chem.* **15**, 1302–1310 (1994).
9. *Varian Atlas of NMR Spectral Data*, spectrum No. 162.
10. C. E. Johnson, Jr, and F. A. Bovey, *J. Chem. Phys.* **29**, 1012–1014 (1958).
11. M. V. Kurashev, Y. T. Struchkov, T. G. Veretyakhina, V. E. Shklover, *Izv. Akad. Nauk SSSR, Ser. Khim.* 1843–1846 (1986).
12. J. A. MacPhee, A. Panaye and J.-E. Dubois, *Tetrahedron* **34**, 3553–3562 (1978).
13. M. Charton, *J. Am. Chem. Soc.* **97**, 1552–1556 (1975).
14. R. Gallo, *Prog. Phys. Org. Chem.* **14**, 115–163 (1983).
15. A. Babadjamian, M. Chanon, R. Gallo and J. Metzger, *J. Am. Chem. Soc.* **95**, 3807–3808 (1973).
16. M. Nishio, Y. Umezawa, M. Hirota and Y. Takeuchi, *Tetrahedron* **51**, 8665–8701 (1995).
17. H. J. Heller, *Eur. Polym. J. Suppl.* 105–132 (1969).
18. J. Catalan, P. Perez, F. Fabero, J. F. K. Wilshire, R. M. Claramunt and J. Elguero, *J. Am. Chem. Soc.* **114**, 964–966 (1992).

