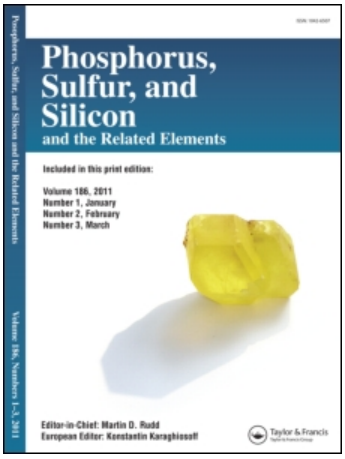


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

CONFORMATIONAL ANALYSIS OF 2-SUBSTITUTED ALKYLPHOSPHORYL COMPOUNDS. PART 2. ^{1}H NMR, IR AND MOLECULAR MECHANICS MODELLING STUDIES OF THE SOLVATION OF 2-HYDROXYPENTYLPHOSPHONATES

Daniel G. Genov[a]; John C. Tebby[a]
[a] Division of Chemistry, School of Sciences, Staffordshire University, United Kingdom

To cite this Article Genov, Daniel G. and Tebby, John C.(1996) 'CONFORMATIONAL ANALYSIS OF 2-SUBSTITUTED ALKYLPHOSPHORYL COMPOUNDS. PART 2. ^{1}H NMR, IR AND MOLECULAR MECHANICS MODELLING STUDIES OF THE SOLVATION OF 2-HYDROXYPENTYLPHOSPHONATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 114: 1, 91 — 98
To link to this Article: DOI: 10.1080/10426509608046414
URL: http://dx.doi.org/10.1080/10426509608046414

Phosphorus, Sulfur, and Silicon, 1996, Vol. 114, pp. 91–98
Reprints available directly from the publisher
Photocopying permitted by license only

CONFORMATIONAL ANALYSIS OF 2-SUBSTITUTED ALKYLPHOSPHORYL COMPOUNDS. PART 2. ^{1}H NMR, IR AND MOLECULAR MECHANICS MODELLING STUDIES OF THE SOLVATION OF 2-HYDROXYPENTYLPHOSPHONATES

DANIEL G. GENOV and JOHN C. TEBBY

Division of Chemistry, School of Sciences, Staffordshire University, Stoke-on-Trent, ST4 2DE, United Kingdom

(Received February 28, 1996)

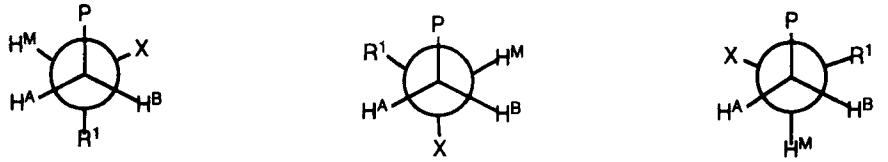
IR, molecular weight and molecular mechanics modelling studies of 2-hydroxypentylphosphonates indicate that intramolecular hydrogen bonding has a significant influence on the position of the conformational equilibrium. IR spectroscopy and elevation of boiling point shows similar degrees of intramolecular and intermolecular hydrogen bonding with a small proportion of non-hydrogen bonded molecules. Molecular mechanics (MM) modelling indicates that the intramolecular hydrogen bond may involve the ester oxygens of the phosphonate group as well as the phosphoryl oxygen. MM modelling was also used to calculate HCCH dihedral angles for the staggered conformers of diisopropyl 2-hydroxypentylphosphonate with and without docked solvent molecules. Utilisation of these angles in place of the perfectly staggered 60° and 180° angles made changes of up to 6% to the NMR estimate of the position of the conformational equilibrium. Conformational changes induced by different solvents, appear to operate mainly by moderating the intramolecular interactions. MM modelling indicates that the relationship between the ^{1}H NMR chemical shift difference of the diastereotopic α-methylene protons and the population of the major conformer *ga* is due to specific solvation—with aromatic solvents associating preferentially with the hydrophobic face, and chloroform and methanol preferentially solvating the polar groups.

Key words: 2-hydroxypentylphosphonates, conformational analysis.

INTRODUCTION

Previously we reported the synthesis and conformational analysis of a series of 2-hydroxyalkylphosphonates and their carboxylic esters in six solvents with different polarities and in the presence of metal ions (Li^+, Na^+ and Zn^{2+}).[1] Vicinal ^{1}H NMR proton-proton coupling constants were used to calculate the relative populations of the conformers *ga*, *ag* and *gg* (Figure 1) on the assumption that the conformers were perfectly staggered. Steric effects were studied by variation of the sizes of the alkyl groups R^1 and R^2 and intramolecular interactions were studied by derivatisation of the hydroxy group. Marked conformational preferences were observed for 2-hydroxyalkylphosphonates which were attributed to stabilising intramolecular hydrogen bonds, involving the phosphoryl oxygen and hydroxyl hydrogen.

In the work presented here, IR spectroscopy and boiling point elevation together with MM modelling have been used to estimate the extent to which the HCCH dihedral angles deviate from the perfectly staggered conformations and to investigate the relative importance of specific interactions in the conformers identified by NMR spectroscopy for two phosphonates (**1a** and **1b**).



ga *ag* *gg*

$(R^2O)_2P(O)CH_2CHXR^1$

1a: X = OH, R^1 = Pr^n, R^2= Me

b: X = OH, R^1 = Pr^n, R^2= Pr^i

FIGURE 1 Three staggered conformers in phosphonates **1a, b** (P = phosphonate group).

RESULTS AND DISCUSSION

Conformational Analysis

It has previously been shown by NMR spectroscopy that the dimethyl and diisopropyl 2-hydroxy-pentylphosphonates **1a, b** (Table I) favour conformer *ga* in all solvents and this is particularly marked in less polar solvents such C_6D_6 and $CDCl_3$, e.g. 79% for phosphonate **1b** in $CDCl_3$.[1] This preference was attributed to the stabilising effect of an intramolecular hydrogen bond between the phosphoryl oxygen and the hydroxyl hydrogen in this conformer.

Further information on the extent and type of hydrogen bonding was sought using infrared spectroscopy focussing on the OH absorption band (3000–3800 cm^{-1}) of phosphonates **1a, b** in the condensed phase and in solutions of different concentrations in tetrachlomethane and chloroform-d (Table II). In the neat liquid phase the IR spectra of both compounds exhibited a single band in the OH stretching region at 3370 cm^{-1}. Solutions in tetrachlomethane at concentrations from 4.3 mol% to 3 × 10^{-3} mol% gave a broad band at 3460 ± 10 cm^{-1} which had a shoulder in the spectra of the

TABLE I

Chemical shifts δ (ppm) of the α-methylene protons H^A and H^B and relative populations P (%) of the conformers *ga*, *ag* and *gg* for **1a, b**

Compd	Solvent	δ_A	δ_B	P_{ga}	P_{aa}	P_{gg}
1a	C_6D_6	1.80	1.90	71	9	20
	$CLCl_3$	1.90	1.86	77	2	21
	$(CD_3)_2CO$	1.96	1.90	64	17	19
	C_5D_5N	2.23	2.30	58	22	20
	$(CD_3)_2SO$	1.88	1.86	49	30	21
	CD_3OD	2.01	1.99	51	28	21
1b	C_6D_6	1.83	1.87	70	8	22
	$CDCl_3$	1.92	1.83	79	0	21
	$(CD_3)_2CO$	1.89	1.82	63	16	21
	C_5D_5N	2.19	2.24	53	27	20
	$(CD_3)_2SO$[a]	1.80	1.83	35	42	23
	CD_3OD	1.93	1.95	43	35	22

[a]The H^A and H^B signals can be assigned in two opposite ways since the chemical shifts and the HH coupling constants are similar. See text for this assignment.

TABLE II

Hydroxyl stretching frequencies of phosphonates **1a, b** *in condensed phase and in solutions in tetrachloromethane and chloroform-d*

Compound	Solvent	Concentration	Bonded OH	Free OH
1a	—	Neat	3370	*
	CCl_4	4.3	3460, 3390 (sh)	*
		2.2	3460, 3390 (sh)	*
		0.9	3466, 3390 (sh)	*
		0.2	3465	*
		3.10^{-3}	3477	*
	$CDCl_3$	4.3	3448	3604
		2.2	3456	3606
		0.2	3475	3608
1b	—	Neat	3370	*
	CCl_4	4.3	3460, 3370 (sh)	3582
		2.2	3458, 3371 (sh)	3582
		1.5	3458, 3369 (sh)	3584
		0.9	3460	3584
		0.5	3465	3587
		0.2	3467	3587
		3.10^{-3}	3465	*
	$CDCl_3$	4.3	3446	3568
		2.2	3448	3570
		1.1	3447	3570
		0.5	3448	3570
		0.2	3454	3571

*A band was not observed in this region.

more concentrated solutions at 3390 cm^{-1} for dimethyl phosphonate **1a** and 3370 cm^{-1} for diisopropyl phosphonate **1b**. The shoulders disappeared upon dilution and are therefore attributed to intermolecular hydrogen bonded associates e.g. dimers, trimers etc. Thus it can be concluded that in 4.3 mol% tetrachloromethane solutions of phosphonates **1a** and **1b**, intramolecular hydrogen bonded monomers exist in equilibrium with intermolecular hydrogen bonded species. This conclusion was confirmed by determinations of the molecular mass of phosphonate **1b** in a 4.3 mol% tetrachloromethane solution by boiling point elevation. The averaged molecular mass was 377 cf monomer molecular mass 252.3. The close similarity of the position of the 3370 cm^{-1} bands in neat liquid phase and concentrated tetrachloromethane solution indicates similar structures for the associates. The spectra of phosphonate **1b** across a wide range of concentrations (4.3 to 0.2 mol%) also possessed a weak higher frequency band at 3580 cm^{-1} corresponding to non-hydrogen bonded hydroxyl groups. As expected for intramolecular hydrogen bonded species there was no significant shift of the absorption band down to very dilute tetrachloromethane solutions (3.10^{-3} mol%).

When the solvent was changed to chloroform-d the IR spectra of dimethyl and diisopropyl phosphonates **1a, b** exibited two bands (Table II), one at 3460 ± 15 cm^{-1} and one at 3585 ± 15 cm^{-1} indicating the presence of both hydrogen-bonded and free hydroxyl groups. In contrast to the tetrachloromethane solutions, low frequency shoulders were not observed on the bands at 3460 cm^{-1} even at high concentration showing that chloroform does not support the formation of associates. By comparing the integrated intensities of the two bands for the diisopropyl phosphonate **1b** it was estimated that the relative population of the hydrogen bonded species was

TABLE III

MM calculated dihedral angles $H^AC(1)C(2)H^M$ ($H^BC(1)C(2)H^M$) for phosphonate **1b**

Solvent	*ga1*[a]	*ga2*	*ag*	*gg1*	*gg2*
Vapour	63.6 (−175.9)	66.9 (−172.4)	−172.5 (−54.7)	−63.4 (55.4)	−63.5 (55.1)
C_6D_6	63.7 (−176.6)	70.6 (−169.1)	−174.7 (−57.2)	−56.5 (61.8)	−61.9 (56.3)
$CDCl_3$	61.2 (−177.9)	69.4 (−170.0)	−174.5 (−56.5)	−63.1 (55.6)	−61.3 (57.0)
$(CD_3)_2CO$	63.7 (−176.1)	73.1 (−166.9)	−177.6 (−59.1)	−57.1 (61.2)	−61.6 (56.8)
C_5D_5N	60.9 (−179.2)	66.3 (−173.3)	177.9 (−65.2)	−60.1 (58.3)	−61.3 (57.1)
CH_3OH	63.0 (−176.7)	68.0 (−172.2)	177.0 (−64.2)	−62.0 (56.6)	−61.7 (56.3)

[a]Conformers *ga1* and *gg1* are stabilized by an intramolecular hydrogen bond between the hydroxyl hydrogen and a phosphonic ester oxygen; conformers *ga2* and *gg2* are stabilized by an intramolecular hydrogen bond involving the hydroxyl hydrogen and the phosphoryl oxygen.

98% in tetrachloromethane and 90% in chloroform-d and this did not alter from 4.3 to 0.2 mol%.

Information about the possible specific nature of the interactions and energies involved was investigated by MM modelling.[2] Since X-ray diffraction studies have shown that these compounds adopt distorted dihedral angles in the crystal,[3] MM modelling also presented an opportunity to test the errors introduced by the use of perfectly staggered conformers (i.e., dihedral angles of 60°, −60° and 180°) in the earlier NMR based conformational analyses. The phosphonate **1b** was chosen for study and optimised structures determined for each of the conformers *ga*, *ag* and *gg*. In the vapour phase modelling two low energy froms (within <1 kcal/mol) were obtained for the staggered *ga* and *gg* conformers—one possessing an intramolecular hydrogen bond to an ester oxygen, the other possessing an intramolecular hydrogen bond to the phosphoryl oxygen. Multiple docking of three or four solvent molecules with conformers *ga*, *ag* and *gg* was carried out for both types of H-bonded phosphonate **1b**. Whilst such modelling covers only the initial stages of solvation this should reveal the most important substrate-solvent interactions since it has been reported[4] that docking 5 or 6 solvent molecules was sufficient to complete the first solvation shell of the substrate. It was found that the relative population of the conformers based on angles predicted by the MM modelling were dependent on the nature of the solvent. The phosphoryl hydrogen-bonded series, with and without solvent, were the most distorted from the perfectly staggered dihedral angles (Table III). The barrier separating each pair of *ga* and *gg* conformers must be low and therefore a weighted average of the dihedral angles for these conformers was calculated on the basis of 2/3 of the ester bonded conformer to 1/3 phosphoryl bonded conformer. The vicinal HCCH coupling constants were then re-calculated using the Haasnoot equation.[5] The populations of the MM conformers were then calculated using the observed vicinal proton-proton coupling constants, obtained by spectroscopic analysis of the signals from the α-methylene protons in the ^1H NMR spectra.[1] In the vapour phase the average population of the conformer *ag* was raised by about 5.5% (Table IV) at the almost equal expense of the other two conformers, compared to the estimates based on perfectly staggered dihedral angles. Use of the solvated models also raised the average estimate for conformer *ag* by about +4.5%, however the estimate of conformer *ga* was increased (ca. 1%) but the largest effect was a decrease in the population of conformer *gg* by an average of −6% (Table V). Thus moderate errors in the conformational analyses, in addition to those due to inaccurate

TABLE IV

Relative populations P_{ik} (%) of the conformers *ga*, *ag* and *gg* for **1b** calculated with the dihedral angles predicted by MM modelling in gas phase

Conformer	Solvent	$P_{ik}(E)^a$	$P_{ik}(P)$	$P_{ik}(A)$
ga	C_6D_6	69	70	69
	$CDCl_3$	79	80	79
	$(CD_3)_2CO$	60	61	60
	C_5D_5N	50	51	50
	CH_3OH	38	39	38
ag	C_6D_6	13	16	14
	$CDCl_3$	5	8	6
	$(CD_3)_2CO$	21	24	22
	C_5D_5N	31	33	32
	CH_3OH	40	41	40
gg	C_6D_6	18	14	17
	$CDCl_3$	16	12	15
	$(CD_3)_2CO$	19	15	18
	C_5D_5N	19	16	18
	CH_3OH	22	20	22

[a] $P_{ik}(E)$ represents the conformational populations calculated with the MM dihedral angles in the cases when *ga* and *gg* were stabilized by an intramolecular hydrogen bond between the hydroxyl hydrogen and a phophonic ester oxygen; $P_{ik}(P)$ are the relative populations for the cases when the intramolecular hydrogen bond involved the phosphoryl oxygen; and $P_{ik}(A)$ are the averaged populations.

TABLE V

Populations of the conformers P_{ik} (%) for **1b** calculated with the dihedral angles predicted by the docking simulation

Conformer	Solvent	$P_{ik}(E)$	$P_{ik}(P)$	$P_{ik}(A)$
ga	C_6D_6	71	73	71
	$CDCl_3$	78	82	79
	$(CD_3)_2CO$	63	67	64
	C_5D_5N	55	57	56
	CH_3OH	44	46	44
ag	C_6D_6	11	19	14
	$CDCl_3$	3	11	5
	$(CD_3)_2CO$	19	27	22
	C_5D_5N	28	32	29
	CH_3OH	36	40	39
gg	C_6D_6	18	8	15
	$CDCl_3$	19	7	16
	$(CD_3)_2CO$	18	6	14
	C_5D_5N	17	11	15
	CH_3OH	20	14	17

coupling data (e.g. due to second order spin-spin coupling effects) and imperfections in the Haasnoot equation, may occur when using the perfectly staggered conformer basis on molecules possessing polar functionalities.

With respect to the nature of the specific interactions, MM modelling also predicted conformer *ga* to be the most stable in the vapour phase and when solvated. This conformer was stabilized by an intramolecular hydrogen bond involving the hydroxyl hydrogen and either a phosphonic ester oxygen (1.9 Å) (conformer *ga1*) or the phosphoryl oxygen (1.9 Å) (conformer *ga2*), the former being slightly more favoured in the vapour phase and when docked with chloroform, acetone or meth-

anol, the latter being slightly more favoured when docked with benzene or pyridine. The higher energies of conformers *ag* and *gg* relative to conformer *ga* were due to less coulombic stabilisation of conformer *ag* and higher torsion strain in conformer *gg*. Conformer *gg* was also stabilized by intramolecular hydrogen bonding to an ester oxygen (*gg1*) or to the phosphoryl oxygen (*gg2*), the former being slightly preferred in the vapour phase, the latter—when docked with solvent molecules. Thus despite an unfavourable orientation between the large groups, intramolecular hydrogen bonding appears to be largely responsible for the relatively high population (~16–20%) of the *gg* conformers.

^{1}H NMR studies had shown that polar solvents (C_5D_5N, CD_3OD, DMSO-d6 and $(CD_3)_2CO$ to a lesser extent) decreased the population of conformer *ga* and increased the population of conformer *ag*. MM modelling provided evidence that this trend is due to strong solvation of the hydroxyl group and weakening of the intramolecular hydrogen bond between the hydroxyl and the phosphoryl groups of the phosphonates, which reduces the energy difference between conformers *ga* and *ag*.

The difference in the relative MM energies of the conformers *ga* and *ag* was greater in the less polar solvents (C_6H_6 and $CHCl_3$) and was smaller in polar solvents. Polar solvents stabilised conformer *ag* through intermolecular hydrogen bonding. Thus the increase in the population of conformer *ag* relative to conformer *ga* shown by the ^{1}H NMR spectra of **1b** (see above) can be attributed to solvent-solute association.

MM modelling of the dimethyl phosphonate **1a** which was performed without solvent docking showed the same trends.

Chemical Shifts of the α-Methylene Protons H^A and H^B

The diastereotopic protons H^A and H^B were non-equivalent in most spectra (Table I). The spectra from solutions in non-aromatic solvents showed the signal of H^A at lower field compared to that of H^B. MM docking investigations of the solvation of each of the individual conformers of phosphonate **1b** in methanol and chloroform showed, as expected, that these solvents have a preference for association with the polar $P(O)(OPr^i)_2$ and OH groups, forming intermolecular hydrogen bonds. The docking simulation with acetone showed an intramolecular hydrogen bonding between OH and O=C in conformer *ag* (1.9 Å) and close location of the carbonyl oxygen of acetone to the α-methylene protons of phosphonate **1b** (~2.5 Å) in all conformers.

For benzene-d6 solutions upfield shifts of the H^A signal were observed for the alcohols **1a** and **1b**, resulting in the appearance of this signal at higher field relative to that of H^B. MM modelling study indicated close association of the benzene molecules with H^A and R^1, i.e. preferential solvation of the hydrophobic side of the major conformer *ga*, leaving H^B closer to the electron rich OH group and less influenced by the anisotropic effect of the benzene.

For pyridine-d6 solutions both of the α-methylene protons of **1a** and **1b** were deshielded relative to chloroform. The MM modelling predicted the involvement of both of the α-methylene protons in hydrogen bonding with the nitrogen atom (2.5 Å) of pyridine. When pyridine was associated with H^B (2.4 Å), one of the pyridine β-protons was in close contact with the oxygen atoms of the β-substituent in phos-

phonate **1b**. Such solvent-solute association may be responsible for the observed shifts in pyridine-d5.

Previously we found that for 2-hydroxyalkylphosphonates and their carboxylic esters the chemical shift difference between the α-methylene protons H^A and H^B ($\Delta\delta_{AB}$) is proportional to the population of conformer *ga*. Also it was observed that in all solvents the signal of H^A moves down-field relative to that of H^B with increase of the population of conformer *ga*.[1] Because the proportions of conformer *ga* for phosphonates **1a** and **1b** in benzene-d6, chloroform-d, acetone-d6 and pyridine-d5 are very similar, it is not possible to identify a good relationship between the chemical shift difference and the population of conformer *ga*. This is attributed to competing structural effects. However the trend is observed for spectra obtained on methanol-d4 solutions. For phosphonate **1b** in DMSO-d6, H^A and H^B can be assigned in two ways because the chemical shifts and the vicinal proton-proton coupling constants are similar. But by assigning H^A to the upfield signal the trend is maintained. We conclude that the specific solvation indicated by the MM modelling of conformer *ga* for phosphonate **1b** is probably the main reason for the trends above and those previously observed for the dimethyl 2-hydroxyalkylphosphonates and their carboxylic esters.[1]

EXPERIMENTAL

The synthesis of phosphonates **1a** and **1b** was previously described.[1] The IR spectra of the neat liquids were recorded on a Perkin Elmer 457 spectrometer using sodium chloride plates. The IR spectra of tetrachloromethane and chloroform-d solutions were recorded on a Nicolet Impact 400 spectrometer. For chloroform-d and the concentrated tetrachloromethane (4.3 to 0.2 mol%) 1 mm pathlength sodium chloride cell was used. The spectra of dilute tetrachloromethane solutions (3.10^{-3} mol%) were recorded using 5 cm pathlength quartz cell. The solvents were commercially obtained and used without further purification.

Determination of the molecular weight of phosphonate **1b** was carried out by boiling point elevation of 4.3 mol% tetrachloromethane solution using the Cottrell method. 1,4-Dichlorobenzene was used as standard of known molecular weight. Equivalent weights of both compounds were taken so that the molecular weight of phosphonate **1b** was caculated by the relation:

$$M_{ph} = \Delta T_{st}/\Delta T_{ph} \times M_{st},$$

where ΔT_{ph} is the boiling point elevation and M_{ph} the molecular weight of phosphonate **1b**. The experiment was carried out in duplicate and the same result was obtained.

The molecular mechanics modelling study was performed using the COSMIC-90 program.[2] The package was run on a VAX 8300 computer using PC terminal. The features of the software used by us were: 1) the molecular-modelling facility, 2) the molecular-energy minimization procedures, 3) the addition of atomic sharges by the Liverpool-2 method, 4) the conformational hunt, 5) the docking procedure.

The molecules were built and partial charges were added by the Liverpool-2 method.[6-8] This method is based upon an empirical breakdown of the transmission of charge into one-, two-, and three-bond additive contributions. The one-bond effect is proportional to the difference in electronegativities of the bonded atoms, and the two- and three-bonded effects are functions of the atomic electronegativity and polarizability. These partial charges are primarily independent of conformation and therefore appropriate for the initial energy minimization calculations. Each structure was then optimized by well established methods such as CONJUGATE GRADIENT and TORMIN. The different conformers, produced upon rotation of all rotatable bonds in 5° steps, were examined and the most stable of each well were saved and further minimized.

In the molecular-docking program the stationary molecule, in this case one of the conformers *ga*, *ag* and *gg*, is placed at the centre of 1 nm diameter sphere, and the mobile molecule (the single solvent molecule) is placed in turn at points on the sphere, in all a total of 204 of such starting points. At each starting point the mobile molecule is rotated about its axis in 60° steps about all three cartesian axes, and the lowest energy obtained is used as the starting orientation for a subsequent energy-minimization procedure involving 500 iterations or until the change in energy between successive iterations is <0.0001 kcal·mol^{-1}. The multiple docking simulation was carried out until no change of the torsional angles

$H^{A}C(1)C(2)H^{M}$ and $H^{B}C(1)C(2)H^{M}$ was found or the interactions become solvent-solvent. In this procedure the bimolecular species of lowest energy from the first docking process was stored, further minimised and used in the next run as the fixed species. In the case of CH_3OH four multiple dockings were performed, in the case of $CHCl_3$, C_6H_6, C_5H_5N and $(CH_3)_2CO$—three for each conformer.

ACKNOWLEDGEMENT

The authors thank Ceram Resarch for allowing use of their Nicolet Impact 400 spectrometer and particularly to Mr. Steven Withington for recording the spectra.

REFERENCES

1. D. G. Genov and J. C. Tebby, *J. Org. Chem.*, **61,** in the press (1996).
2. J. G. Vinter, A. Davis and M. R. Saunders, *Journal of Computer-Aided Molecular Design*, **1,** 31 (1987).
3. Unpublished results.
4. M. A. Beckett and J. G. Dawber, *J. Chem. Soc. Faraday Trans. 1*, **85,** 727 (1989).
5. C. A. G. Haasnoot, F. A. A. M. de Leeuw and C. Altona, *Tetrahedron*, **36,** 2783 (1980).
6. R. J. Abraham, L. Griffiths and P. J. Loftus, *J. Comput. Chem.*, **3,** 407 (1982).
7. R. J. Abraham and B. D. Hudson, *J. Comput. Chem.*, **5,** 562 (1984).
8. R. J. Abraham and B. D. Hudson, *J. Comput. Chem.*, **6,** 173 (1985).