Conformational Analysis of (2-Substituted-alkyl)phosphoryl Compounds. 1. NMR Spectroscopic Studies of Dialkyl (2-Hydroxyalkyl)phosphonates and Their Carboxylic Esters

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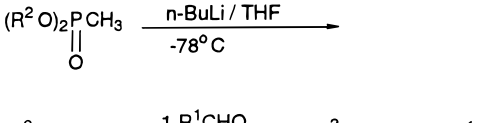
Twelve (2-substituted-alkyl)phosphonates (**2**, **3**) were synthesized and conformational analyses carried out by NMR spectroscopy. The conformational populations in six solvents with different polarities and in the presence of metal ions (Li^+, Na^+, Zn^{2+}), were studied. Steric effects were studied by variation of the sizes of alkyl groups R^1 and R^2 and intramolecular interactions studied by derivatization of the hydroxy group X. In (2-hydroxyalkyl)phosphonates the most stable conformer *ga*, in which the phosphoryl group is *gauche* to the hydroxy group and *anti* to the alkyl group (R^1), is favored particularly in less polar solvents such as C_6D_6 and $CDCl_3$. In polar solvents the population of the less stable conformer *ag*, in which the phosphoryl group is *gauche* to the alkyl group (R^1) and *anti* to the hydroxy group, is increased. Smaller alkyl groups R^1 (Me, Pr^n) allow more conformational freedom. Conversion of the hydroxy group to its carboxylic ester reduces the population of conformer *ga* so that, for $R^1 = Pr^n$, conformers *ga* and *ag* are approximately equally populated. The presence of metal salts in the acetone-d_6 solutions causes an increase in the population of conformer *ga* in both (2-hydroxyalkyl)phosphonates and their carboxylic ester derivatives. The chemical shift difference between the diastereotopic α-methylene protons has been shown to be proportional to the population of conformer *ga*.

Introduction

Continuing our previous studies on solvation effects,[1] we are interested in studying the solvation requirements of individual conformers and the contribution of solvation to changes in chemical shifts. Modro et al.[2] have noted marked changes in the NMR spectra of (2-hydroxyalkyl)- and (2-chloroalkyl)phosphonates in various solvents, which have been interpreted in terms of preferential conformational populations. These authors have shown that (2-substituted-alkyl)phosphonates exhibit nonequivalence of their diastereotopic α-methylene groups, which is dependent on the medium and the addition of alkali-metal salts. They have attributed the conformational preferences of three (2-substituted-alkyl)phosphonates (**1a,b** and **2b**) to strong attractive interactions between the phosphoryl group and the oxygen-containing substituent X—either an intramolecular hydrogen bond when X = OH or a donor−acceptor O → P effect when X = OCH_3 and, in the presence of salts, the coordination of a metal ion to both the phosphoryl oxygen and the oxygen from the hydroxy or the methoxy groups.[2] This type of compound seemed to provide an ideal model for our studies. In this paper we report the conformational analysis of 12 phosphonates, the stuctures of which vary with respect to the steric demand of the *β*-alkyl group and the phosphonic ester groups, as well as derivatizing the hydroxyl group. These structural variations were chosen to distinguish between the influence of intramolecular steric and polar effects as well as intermolecular solvent effects.

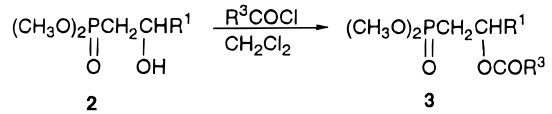
Results and Discussion

The alcohols **2a**−**h** were prepared in yields of 50−71% from the corresponding dialkyl methylphosphonate and appropriate aldehyde in THF (eq 1). The reactions were



(1)

carried out at low temperature (−78 °C) under nitrogen.[3] The esters **3a**−**d** were obtained in near-quantitative yields by the reaction of (2-hydroxyalkyl)phosphonate with carboxylic acid chloride in the molar ratio 1:2 in dichloromethane (eq 2). The structures of the products



(2)

2 and **3** were confirmed by IR spectroscopy and ^{31}P, ^{13}C, and ^1H NMR spectroscopy. The spectra also indicated the products to be pure.

The ^1H NMR spectra were recorded on solutions of the phosphonates in chloroform-*d*, benzene-d_6, pyridine-d_5, dimethyl-d_6 sulfoxide, methanol-d_4, and acetone-d_6 solutions with and without the presence of various concentrations of lithium chloride, sodium iodide, and zinc bromide. Generally the α-methylene group appeared as the AB part of an ABMX spin system. The chemical shifts of H^A and H^B and the vicinal couplings ($^3J_{AM}$ and $^3J_{BM}$) were obtained from the AB part of the spectra, which appeared

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(1) (a) Dawber, J. G.; Tebby, J. C.; Waite, A. A. C. *Phosphorus Sulfur Relat. Elem.* **1984**, *19*, 99. (b) Beckett, M. A.; Dawber, J. G. *J. Chem. Soc., Faraday Trans. 1* **1989**, *85*, 727. (c) Dawber, J. G.; Etemad, S.; Beckett, M. A. *J. Chem. Soc., Faraday Trans.* **1990**, *86*, 3725.

(2) (a) Modro, A. M.; Wessels, P. L.; Modro, T. A. *J. Chem. Res., Synop.* **1991**, 224. (b) Belciug, M.-P.; Modro, A. M.; Modro, T. A.; Wessels, P. L. *J. Phys. Org. Chem.* **1992**, *5*, 787.

(3) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691.

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Chart 1

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

2: X = OH
- **a**: $R^1 = t\text{-}C_4H_9; R^2 = CH_3$
- **b**: $R^1 = C_6H_5; R^2 = CH_3$
- **c**: $R^1 = i\text{-}C_3H_7; R^2 = CH_3$
- **d**: $R^1 = i\text{-}C_3H_7; R^2 = i\text{-}C_3H_7$
- **e**: $R^1 = n\text{-}C_3H_7; R^2 = CH_3$
- **f**: $R^1 = n\text{-}C_3H_7; R^2 = C_2H_5$
- **g**: $R^1 = n\text{-}C_3H_7; R^2 = i\text{-}C_3H_7$
- **h**: $R^1 = CH_3; R^2 = CH_3$

3: X = $OCOR^3$
- **a**: $R^1 = t\text{-}C_4H_9; R^2 = CH_3; R^3 = CH_3$
- **b**: $R^1 = n\text{-}C_3H_7; R^2 = CH_3; R^3 = CH_3$
- **c**: $R^1 = n\text{-}C_3H_7; R^2 = CH_3; R^3 = i\text{-}C_3H_7$
- **d**: $R^1 = n\text{-}C_3H_7; R^2 = CH_3; R^3 = t\text{-}C_4H_9$

$(CH_3O)_2P(O)CH_2CHXPh$

1a: X = OCH_3

1b: X = Cl

as a set of four AB subspectra. H^A and H^B in these ABMX spin systems normally gave rise to 16-line patterns. In some cases the chemical shift difference ($\Delta\delta_{AB}$) was very small. Thus, when $\Delta\delta_{AB}$ was 0.02 ppm, deceptively simple patterns (5 or 6 lines) were observed. When these spectra were recorded on a 500 MHz spectrometer, they were transformed to ABMX patterns. This enabled us to carry out spectral simulations and to obtain an accuracy of 0.1 Hz or better for the spectral parameters. The signals for the diastereotopic protons H^A and H^B were assigned on the basis of the relative magnitudes of $^3J_{AM}$ and $^3J_{BM}$, the signal with a smaller splitting being assigned to H^A. The values of the dihedral-angle-dependent vicinal phosphorus−carbon coupling constants, which are indicative of predominant *anti* $P(O)(OR^2)_2$- - - R^1 orientation, supported this assignment. Vicinal phosphorus−proton couplings have been shown to be dependent on dihedral angles,[4] but their usefulness in the present study was limited by the fact that the vicinal proton is further coupled in most of the compounds, making the coupling constant difficult to measure; also, the phosphorus and proton nuclei are *gauche* in the conformers of most interest and thus the coupling is little affected by changes in the populations of these two conformers. Finally, substituent effects on this coupling have been little studied.

Three stable conformers—*ga*, *ag*, and *gg*, and their enantiomeric forms—arise by rotation about the C(1)−C(2) bond (Figure 1). Their relative populations were estimated by relating the observed vicinal proton−proton coupling constants to the vicinal couplings of the individual staggered conformers calculated by a modified Karplus equation, formulated by Haasnoot et al.[5] (eqs 3−5). The estimation of the conformational populations

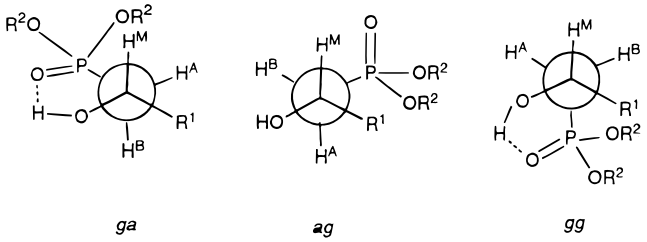

Figure 1. Three staggered conformers of (2-hydroxyalkyl)-phosphonates.

$$^3J_{AM} = P_{ga}\,^3J_g(ga) + P_{ag}\,^3J_a(ag) + P_{gg}\,^3J_{g'}(gg) \quad (3)$$

$$^3J_{BM} = P_{ga}\,^3J_a(ga) + P_{ag}\,^3J_g(ag) + P_{gg}\,^3J_{g'}(gg) \quad (4)$$

$$P_{ga} + P_{ag} + P_{gg} = 1 \quad (5)$$

was based on the presence of perfectly staggered conformers (Figure 1). Molecular mechanics modeling performed by us[6] has indicated that the use of twisted versions of these conformers which take into account polar and VDW interactions can alter the estimated conformer populations by up to 6%.

Conformational Analysis. The magnitudes of the two vicinal proton−proton and the phosphorus−carbon coupling constants showed a marked dependence on the polarity of the solvent, the presence of metal ions, and the types of substituents X, R^1, and R^2 of phosphonates **2** and **3**.

Effect of Substituent X. For the (hydroxyalkyl)-phosphonates conformer *ga* was established as the most populated, e.g. 71% and 77% for phosphonate **2e** in C_6D_6 and in $CDCl_3$, respectively (Table 1). This preference is attributed to the absence of substantial steric repulsions between the bulky $PO(OR^2)_2$ and R^1 groups and the stabilizing effect of an intramolecular hydrogen bond between the phosphoryl oxygen and the hydroxyl hydrogen in this conformer. The phosphorus chemical shifts (Table 1) supported this conclusion, since the ^{31}P signals of the (2-hydroxyalkyl)phosphonates were deshielded relative to those of the corresponding carboxylic esters. The deshielding effect can be explained by the involvement of the phosphoryl oxygen in a hydrogen bond, which decreases the π-back-bonding to phosphorus.

Polar solvents (DMSO-d_6, CD_3OD, C_5D_5N) with hydrogen-acceptor properties and/or hydrogen-donor properties decreased the population of conformer *ga* and increased the population of conformer *ag*. This is attributed to strong solvation of the hydroxyl group and weakening of the intramolecular hydrogen bond between the hydroxyl and the phosphoryl groups of the phosphonates. The population of the third conformer *gg* for (hydroxyalkyl)-phosphonates was usually unchanged at about 20% (i.e., phosphonates **2e**−**h**. Conformer *gg* had a higher population than conformer *ag* in less polar solvents (C_6D_6 and $CDCl_3$), which can be attributed to the stabilizing influence of an intramolecular hydrogen bond in conformer *gg*. The difference in the populations of the conformers *ga* and *ag* was small for the carboxylic ester derivatives **3b**−**d**, in which intramolecular hydrogen bonding is not possible and the magnitudes of the repulsion between the $PO(OMe)_2$ and OAc groups and between the $PO(OMe)_2$

(4) Benezra, C. J. *J. Am. Chem. Soc.* **1973**, *95*, 6890.
(5) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, 36, 2783.
(6) Unpublished results.

Table 1. Chemical Shifts of the Diastereotopic α-Methylene Protons and the Phosphorus Nucleus (ppm), Vicinal Proton−Proton and Carbon−Phosphorus Coupling Constants (Hz) and Conformer Populations *P* (%) for 2 and 3

no.	solvent	δ_A	δ_B	$^3J_{AM}$	$^3J_{BM}$	P_{ga}	P_{ag}	P_{gg}	$^3J_{PC}$	δ_P
2a	$CDCl_3$	1.97	1.85	1.4	11.0	100	0	0	15.7	35.77
	$(CD_3)_2CO$	1.97	1.77	1.6	11.1	100	0	0	15.7	36.24
	C_6D_6	1.84	1.82	1.6	11.5	100	0	0	16.1	35.81
	C_5D_5N	2.13	2.07	1.7	11.1	100	0	0	15.2	37.39
	$(CD_3)_2SO$	1.89	1.71	1.5	10.7	100	0	0	15.2	35.75
	CD_3OD	2.01	1.85	1.5	10.8	100	0	0	15.7	36.46
2b	$CDCl_3$	2.16	2.25	3.1	10.2	84	9	7	15.7	32.24
	$(CD_3)_2CO$	2.15	2.22	4.0	9.5	75	19	6	14.7	32.44
	C_6D_6	2.05	2.24	3.2	10.0	81	10	9	16.1	32.56
	C_5D_5N	2.45	2.61	4.0	9.4	76	15	9	14.7	32.16
	$(CD_3)_2SO$	2.23	2.33	5.4	8.5	61	33	6	11.7	32.69
	CD_3OD	2.23	2.33	5.3	8.8	64	33	3	12.7	32.52
2c	$CDCl_3$	1.95	1.89	2.4	10.6	87	2	11	16.1	34.92
	$(CD_3)_2CO$	1.93	1.84	2.7	9.8	78	4	18	15.2	35.01
	C_6D_6	1.78	1.86	2.5	10.5	86	3	11	16.1	34.95
	C_5D_5N	2.13	2.17	3.1	9.7	77	8	15	15.7	34.73
	$(CD_3)_2SO$	1.88	1.80	3.6	9.1	69	13	18	13.7	34.38
	CD_3OD	2.00	1.92	3.2	9.6	75	9	16	14.7	35.22
2d	$CDCl_3$	1.90	1.79	1.8	10.5	100	0	0	16.6	30.34
	$(CD_3)_2CO$	1.89	1.76	2.9	9.8	78	6	16	15.7	30.84
	C_6D_6	1.82	1.84	2.4	10.6	87	2	11	17.1	30.81
	$(CD_3)_2SO$	1.81	1.73	4.2	8.5	62	19	19	12.2	29.63
	CD_3OD	1.94	1.86	3.9	8.8	66	16	18	13.7	30.01
2e	$CDCl_3$	1.90	1.86	2.7	9.6	77	2	21	16.1	33.75
	$(CD_3)_2CO$	1.96	1.90	4.0	8.7	64	17	19	13.7	33.80
	C_6D_6	1.80	1.90	3.3	9.2	71	9	20	16.1	33.91
	C_5D_5N	2.23	2.30	4.5	8.2	58	22	20	13.7	33.54
	$(CD_3)_2SO$	1.88	1.86	5.4	7.4	49	30	21	11.0	33.17
	CD_3OD	2.01	1.99	5.2	7.6	51	28	21	12.7	33.93
2f	$CDCl_3$	1.96	1.90	2.6	10.0	80	3	17	16.1	31.18
	$(CD_3)_2CO$	1.94	1.88	4.1	8.4	61	17	22	13.7	31.25
	C_6D_6	1.84	1.91	3.1	9.4	73	8	19	15.7	31.46
	C_5D_5N	2.24	2.29	4.7	8.0	56	23	21	13.7	30.84
2g	$CDCl_3$	1.92	1.83	2.4	9.8	79	0	21	16.6	29.24
	$(CD_3)_2CO$	1.89	1.82	4.0	8.5	63	16	21	14.2	29.52
	C_6D_6	1.83	1.87	3.2	9.1	70	8	22	16.1	29.76
	C_5D_5N	2.19	2.24	5.0	7.8	53	27	20	12.7	29.04
	$(CD_3)_2SO$	1.83	1.80	6.3	6.6	39	39	22	8.8	28.33
	CD_3OD	1.93	1.95	5.9	6.9	43	35	22	11.3	31.01
2h	$CDCl_3$	1.96	1.99	4.0	8.3	61	16	23	16.1	33.11
	$(CD_3)_2CO$	1.93	1.95	5.0	7.7	53	26	21	12.7	33.13
	C_6D_6	1.76	1.93	4.3	8.5	62	20	18	15.2	33.23
	C_5D_5N	2.16	2.31	5.6	7.1	45	32	23	12.2	34.23
	$(CD_3)_2SO$	1.88	1.95	6.9	6.4	35	46	19	9.8	32.48
	CD_3OD	1.97	2.05	5.9	7.0	44	35	21	11.7	33.19
3a	$(CD_3)_2CO$	1.98	1.90	1.8	10.9	100	0	0	14.2	31.87
	C_5D_5N	2.13	2.09	1.9	10.8	100	0	0	14.7	33.22
	$(CD_3)_2SO$	2.06	1.94	1.7	11.4	100	0	0	14.2	32.69
3b	$CDCl_3$	2.06	2.14	6.3	6.8	40	40	20	8.8	29.99
	$(CD_3)_2CO$	2.04	2.09	6.3	6.6	39	39	22	8.8	29.99
	$(CD_3)_2SO$	2.16	2.12	6.1	6.8	41	38	21	9.8	30.38
	CD_3OD	2.16	2.19	5.6	7.1	45	32	23	10.3	31.29
3c	$CDCl_3$	2.06	2.15	6.3	6.5	38	39	23	8.3	30.06
	$(CD_3)_2CO$	2.06	2.10	6.4	6.4	37	40	23	8.3	30.16
	C_6D_6	1.88	2.02	6.4	6.6	38	41	21	8.8	29.34
	C_5D_5N	2.22	2.30	6.1	6.6	39	37	24	8.8	29.97
	$(CD_3)_2SO$	2.14	2.12	6.0	7.0	43	37	20	9.8	30.34
3d	$CDCl_3$	2.04	2.15	6.6	6.3	35	42	23	7.8	30.10
	$(CD_3)_2CO$	2.04	2.10	6.7	6.3	35	43	22	8.3	30.16
	C_6D_6	1.84	2.00	6.4	6.6	38	41	21	8.3	29.24
	$(CD_3)_2SO$	2.12	2.10	6.1	6.8	41	38	21	9.3	30.30

and Pr^n groups are approximately equal. In contrast to the case for the (2-hydroxyalkyl)phosphonates dissolution of the esters **3b**−**d** in polar solvents such as DMSO-d_6 stabilized conformer *ga* to a greater extent than less polar solvents (C_6D_6 and $CDCl_3$); e.g. the ratio *ga:ag* for phosphonate **3c** is 43:37 in DMSO-d_6 and 38:39 in $CDCl_3$. This was also evident from the values of $^3J_{PC}$ (9.8 Hz in DMSO-d_6 and 8.3 Hz in $CDCl_3$ and **3c**) (Table 1). The effect could be due to preferential solvation of the phosphoryl and carboxylic ester groups by DMSO-d_6. A strong interaction between a phosphoryl group and DMSO was observed in the infrared spectrum of triethylphosphine oxide. Thus, DMSO caused a large increase in the phosphoryl stretch wavenumber ($\nu_{P=O}$) relative to its position in nonpolar solvents such as hexane.[7] A strong interaction between a carboxylic ester group and a sulfoxide group was also evident from a conformational study of the *O*-acetyl ester derivative of methyl (2-hydroxypropyl) sulfoxide. The preference for the conformer with a *gauche* orientation between the acetyl group and the sulfoxide group was attributed to electrostatic interactions, involving oxygen from the acetyl group and the sulfur atom.[8] We may therefore conclude that such attractive electrostatic interactions, including both the phosphoryl and the acetyl group from the carboxylic esters **3b**−**d** and a molecule of the solvent, may be responsible for the increase of the population of the conformer *ga* in DMSO-d_6.

Table 2. Chemical Shifts of the Diastereotopic α-Methylene Protons and the Phosphorus Nucleus (ppm), Vicinal Proton−Proton and Phosphorus−Carbon Couplings (Hz), and Rotamer Populations *P* (%) for 1 and 2 in Acetone-d_6 Solutions in the Presence of Metal Salts

no.	salt	δ_A	δ_B	$^3J_{AM}$	$^3J_{BM}$	P_{ga}	P_{ag}	P_{gg}	$^3J_{PC}$	δ_P
2a	LiCl (1:1)	2.04	2.12	2.1	11.1	100	0	0	16.1	37.71
	NaI (1:1)	2.04	2.01	1.5	10.9	100	0	0	15.7	36.76
	NaI (1:2)	2.04	2.12	1.4	11.3	100	0	0	15.7	36.89
	$ZnBr_2$ (1:1)	2.25	2.11	1.9	10.9	100	0	0	15.7	38.55
2b	LiCl (1:1)	2.31	2.54	3.5	10.1	81	16	3	15.7	34.14
	NaI (1:1)	2.23	2.47	3.3	10.1	82	13	5	15.2	33.09
	$ZnBr_2$ (1:1)	2.47	2.55	3.5	9.9	80	13	7	15.7	35.33
2c	LiCl (1:1)	2.02	2.18	2.7	10.5	85	6	9	16.1	37.04
	NaI (1:1)	2.00	2.07	2.6	10.6	86	5	9	15.7	35.90
	$ZnBr_2$ (1:1)	2.25	2.19	2.6	10.4	84	4	12	16.6	37.93
2d	LiCl (1:1)	1.95	2.09	2.7	10.3	83	5	12	15.7	32.33
	NaI (1:1)	1.90	1.98	2.4	10.6	87	2	11	16.1	31.35
2e	LiCl (1:1)	2.11	2.25	3.7	9.0	70	14	16	14.7	35.89
	NaI (1:1)	2.08	2.15	3.5	9.3	72	12	16	14.7	34.73
	NaI (1:2)	2.11	2.23	3.4	9.2	70	11	19	15.2	35.03
	NaI (sat.)	2.21	2.31	3.4	9.2	70	11	19	15.2	35.48
	$ZnBr_2$ (1:1)	2.33	2.27	3.3	9.5	74	10	16	15.7	36.91
2f	LiCl (1:1)	2.07	2.24	3.7	8.9	67	14	19	14.2	33.15
	NaI (1:1)	2.05	2.11	3.4	9.3	72	11	17	14.7	32.03
	NaI (1:2)	2.08	2.19	3.4	9.1	70	10	20	14.7	32.28
	NaI (sat.)	2.16	2.30	3.3	9.3	72	10	18	14.7	32.74
	$ZnBr_2$ (1:1)	2.30	2.26	3.3	9.3	72	10	18	14.7	33.86
2g	LiCl (1:1)	2.00	2.17	3.5	9.1	69	12	19	14.7	31.25
	NaI (1:1)	1.95	2.07	3.2	9.0	66	11	23	15.2	30.12
	NaI (1:2)	1.99	2.13	3.2	9.0	66	11	23	14.7	30.27
	NaI (sat.)	2.05	2.23	3.3	9.2	71	9	20	14.2	30.36
2h	LiCl (1:1)	2.07	2.23	4.0	8.7	64	17	19	15.7	35.27
	NaI (1:1)	2.04	2.14	4.7	8.5	61	24	15	14.7	34.10
	NaI (1:2)	2.12	2.26	4.2	8.6	63	18	19	15.2	34.56
	$ZnBr_2$ (1:1)[a]	2.27	2.27						14.7	36.05
3a	LiCl (1:1)	2.25	2.06	1.5	10.8	100	0	0	14.7	33.82
	NaI (1:1)	2.18	2.05	1.8	11.2	100	0	0	14.2	33.34
3b	LiCl (1:1)	2.29	2.25	5.5	7.2	47	31	22	10.3	31.83
3c	LiCl (1:1)	2.34	2.26	5.7	7.2	46	34	20	10.3	32.15
3d	LiCl (1:1)	2.29	2.23	6.0	7.0	43	38	19	9.3	31.89

[a] The vicinal proton−proton coupling constants cannot be measured accurately due to the equivalence of the α-methylene protons.

The addition of anhydrous lithium chloride, sodium iodide, and zinc bromide to acetone-d_6 solutions of the (2-hydroxyalkyl)phosphonates increased the population of conformer *ga* (Table 2). For phosphonate **2e** the population of *ga* was 70% when lithium chloride was present, compared to 64% in its absence. The trend was supported by $^3J_{PC}$, which was 14.7 Hz when lithium chloride was present and 13.7 Hz in its absence. Similar effects of Na^+ and Mg^{2+} on dimethyl (2-hydroxy-2-

(7) Symons, M. C. R.; Eaton, G. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 3033.

(8) Alcudia, F.; Ruano, J. L. G.; Rodriguez, J. *Can. J. Chem.* **1979**, *57*, 2426.

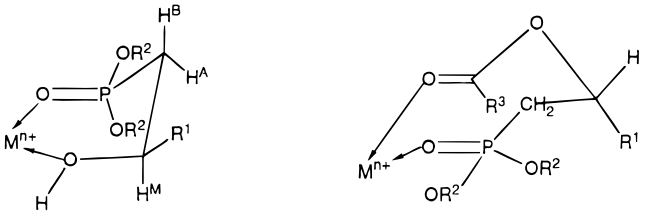

Figure 2. Coordination of (2-hydroxyalkyl)phosphonates and their carboxylic esters to metal ions.

phenylethyl)phosphonate **(2b)** were observed by Modro et al. and were explained by the chelation of the metal ions by the phosphoryl and the hydroxyl oxygen atoms (Figure 2).[2] The marked downfield shifts of the ^{31}P signals when salts were added to the acetone-d_6 solutions of the phosphonates confirmed the coordination of the metal ion to the phosphoryl oxygen (Table 2). The effect increased in the order $Na^+ < Li^+ < Zn^{2+}$.

Lithium chloride also increased the population of conformer *ga* for the carboxyl ester derivatives. Thus, the population of conformer *ga* in acetone-d_6 for phosphonate **3c** was shown to be 37% and it rose to 46% when an equimolar amount of lithium chloride was present. The trend was supported by the $^3J_{PC}$ coupling constants, which were 8.3 and 10.3 Hz, respectively. These observations can be taken as further support for the coordination of the metal ion by the carbonyl oxygen as well as the phosphoryl oxygen, as shown in Figure 2.

Effect of Substituent R[1]. The nature of substituent R^1 in the dimethyl (2-hydroxyalkyl)phosphonates had a marked influence on the conformational populations.

For phosphonate **2a** the bulk of the *tert*-butyl group was the major factor determining the conformational populations. The *tert*-butyl group strongly favored conformer *ga* due to the minimization of steric repulsion between the large groups in this conformer. While the population of conformer *ga* was estimated to be 100% in all solvents for phosphonate **2a,** both $^3J_{BM}$ and $^3J_{AM}$ were less than the calculated coupling constants for the perfectly staggered conformer *ga*, showing that the conformer is twisted. $^3J_{AM}$ and $^3J_{BM}$ varied for different solvents by up to 0.3 and 0.7 Hz, respectively, which was attributed to a slight variation of the dihedral angles and the bond angles.

For the phosphonates possessing smaller alkyl groups R^1 (Me, Pr^n), the populations of the conformers varied significantly with the polarity of the solvent, indicating greater conformational freedom. Modro et al.[2] have observed that for dimethyl (2-hydroxy-2-phenylethyl)-phosphonate **(2b)** in DMSO-d_6 conformer *ga* is more populated than conformer *ag* (*ga*:*ag* = 64%:22%) and have attributed the preference to stronger hydrogen-bonding acceptor properties of the phosphoryl group relative to the sulfoxide acceptor. However, when R^1 was Me (**2h**), conformer *ga* predominated in less polar solvents, e.g. 62% in C_6D_6 ($^3J_{PC}$ = 15.2 Hz), while in DMSO-d_6 the population of conformer *ag* was higher (35% *ga* and 46% *ag* with $^3J_{PC}$ = 9.8 Hz). This fact indicates the significant influence of the steric factors on the conformational equilibrium. Therefore, the higher population of the conformer *ga* in DMSO-d_6 for phosphonate **2b** (R^1 = Ph) cannot be attributed only to the strength of the electrostatic interactions. The destabilizing effect of the steric repulsion between the phosphoryl and the phenyl groups in conformer *ag* should also be taken into consideration.

The addition of salts to acetone-d_6 solutions of the phosphonates increased the populations of conformer *ga* for all compounds under study, the effect being stronger when R^1 was small. For example, the addition of an equimolar amount of lithium chloride to an acetone-d_6 solution of the phosphonate **2e** (R^1 = Pr^n) increased the population of *ga* from 64% to 70%, while for phosphonate **2h** (R^1 = Me) it resulted in greater difference (53% for **2h** in acetone-d_6 and 64% for **2h** in the presence of lithium chloride).

Effect of Substituent R[2]. Comparisons of the spectra of the (2-hydroxyalkyl)phosphonates **2c**−**g** allowed the effect of varying the phosphonic ester groups (OR^2) on the conformational populations to be studied. The NMR spectroscopic studies indicated that bulky alkoxy groups influence the involvement of the P═O group in intramolecular hydrogen bonding, depending on the polarity of the solvent. In $CDCl_3$ the population of conformer *ga* was approximately the same for diisopropyl (2-hydroxypentyl)phosphonate (**2g**) and for the corresponding dimethyl (2-hydroxypentyl)phosphonate (**2e**) (79% for **2g** and 77% for **2e**). However, it was found that in polar solvents, such as DMSO-d_6 and CD_3OD, the population of conformer *ga* decreased to a greater extent for the diisopropyl ester **2g** than for the corresponding dimethyl ester **2e**; e.g., in DMSO-d_6 the population of the conformer *ga* was 39% for **2g** and 49% for **2e**. Thus, it is concluded that the DMSO solvation of the hydroxyl group, which generally weakens the intramolecular hydrogen bond, is even more effective when larger phosphonic ester groups are present, reflecting the extra steric hindrance of these groups.

Chemical Shifts of the Diastereotopic α-Methylene Protons H[A] and H[B]. The diastereotopic protons H^A and H^B were nonequivalent for most compounds and in most solvents (Table 1). The chemical shift difference $\Delta\delta_{AB}$ ($\Delta\delta_{AB} = \delta_A - \delta_B$) between diastereotopic protons has been rationalized in terms of conformational preference,[9] the observed chemical shifts being time-averaged over the residence time for each of conformers, e.g. *ga*, *ag*, and *gg*. In Figure 3 $\Delta\delta_{AB}$ values for dimethyl (2-hydroxyalkyl)phosphonates **2a**,**c**,**e**,**h** (R^1 = alkyl) have been plotted against the populations of conformer *ga*. Although there will be variations caused by the change in the nature of substituent R^1, a consistent trend of increasing chemical shift with greater *ga* population was observed by giving $\Delta\delta_{AB}$ a positive value when H^A is downfield of H^B and a negative value when H^A is upfield of H^B. It can be seen that in all solvents the signal of H^A moves downfield relative to that of H^B with increase of the population of conformer *ga*. In contrast to the case for the nonaromatic solvents, $\Delta\delta_{AB}$ for the benzene-d_6 and pyridine-d_5 solutions was often negative. Presumably this arises from an aromatic solvent-induced shift of the resonances of the α-methylene protons. While the effects of benzene-d_6 and pyridine-d_5 on the chemical shift difference were similar, the actual chemical shifts of H^A and H^B relative to chloroform-*d* were in different directions. Thus in benzene-d_6 solutions upfield shifts of the α-methylene protons were observed. The shielding was stronger for H^A, so that its signal in most cases appeared at higher field relative to that of H^B. In pyridine-d_5 deshielding of H^A and H^B was observed. As the downfield shifts were stronger for H^B, its signal occurred at lower field compared to that of H^A.

(9) Jennings, W. B. *Chem. Rev.* **1975**, *75*(3), 307.

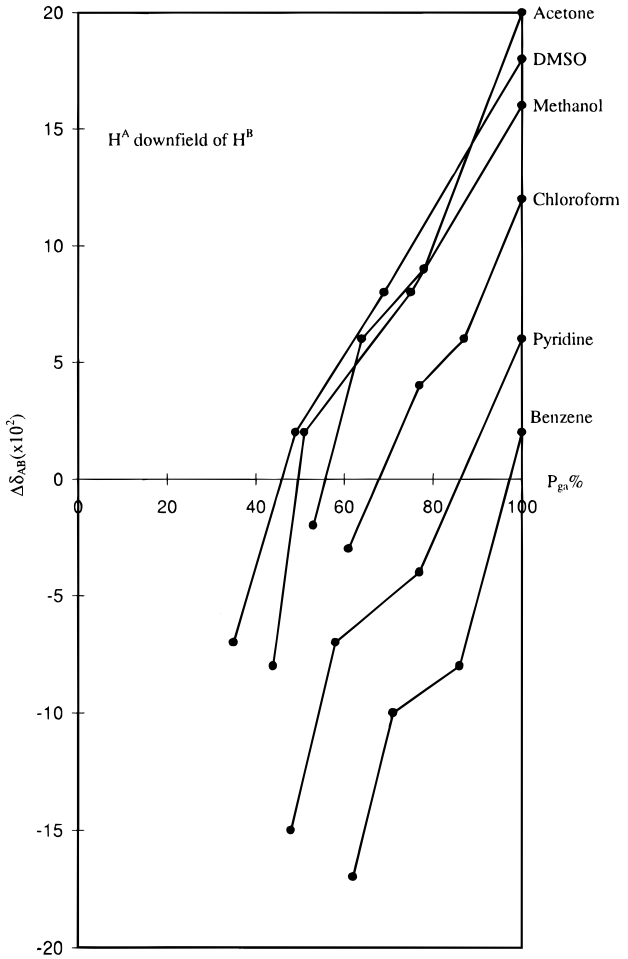

Figure 3. Plot of the chemical shift difference ($\Delta\delta_{AB}$) *vs* the population of conformer *ga* (P_{ga}) for phosphonates **2a**,**c**,**e**,**h**.

For the carboxylic esters **3b**−**d** the signal of H^A was observed upfield to that of H^B. Only in the spectra of DMSO-d_6 solutions did the signal of H^A occur at lower field. As for the 2-(hydroxyalkyl)phosphonates the trend is attributed to an increase of the population of conformer *ga* in these cases (Table 1).

The general effect of the metal ions was a downfield shift of the signals of both of the α-methylene protons (Table 2). The H^B signal was usually so strongly affected that it appeared downfield of H^A for most of the (2-hydroxyalkyl)phosphonates when lithium chloride and sodium iodide were added to their acetone-d_6 solutions. The observed deshielding was dependent on the concentration of M^{n+}, being stronger when the metal ion concentration was higher. A dependence of $\Delta\delta_{AB}$ on the conformational preference was found again. Thus, in the presence of zinc bromide, $\Delta\delta_{AB}$ was 0.14 ppm for phosphonate **2a** (100% *ga*) and 0.06 ppm for phosphonate **2e** (74% *ga*). When lithium chloride was added to the acetone-d_6 solutions of these phosphonates, $\Delta\delta_{AB}$ was −0.08 ppm for **2a** (100% *ga*) and −0.14 ppm for **2e** (70% *ga*).

In the spectra of the acetone-d_6 solutions of the carboxylic esters **3b**−**d** (X = OCOR[3]) the signal of H^A was observed upfield from that of H^B. The appearance of H^A at lower field than H^B in the presence of lithium chloride is attributed to an increase of the population of conformer *ga*.

The relative roles of specific solvation, the conformational populations, and intramolecular interactions on the chemical shifts of H^A and H^B are currently being studied.

Experimental Section

General Considerations. ^1H, ^{13}C, and ^{31}P NMR spectra were obtained on a JEOL GSX-270 spectrometer. The proton spectra were also recorded on a Bruker ACP-400 or JEOL ALPHA-500 spectrometer when the chemical shift difference between the α-methylene protons was ≤0.05 ppm. The solvents were obtained commercially and used without futher purification. Spectra were of 2.5 M solutions at room temperature. The subspectra of the α-methylene signals were analyzed as an AB part of an ABMX spin system and then calculated using the LAOCOON IV program. The parameters were accurate to 0.1 Hz or better.

All ^1H and ^{13}C measurements were referenced to Me_4Si as an internal standard. ^{31}P NMR spectra were referenced to 85% H_3PO_4. IR spectra of the neat liquids were recorded on a Perkin-Elmer 457 spectrometer using NaCl windows. IR spectra of the crystalline phosphonates **2b** and **3a** (KBr disks) were recorded on a Nicolet Impact-400 spectrometer. Boiling and melting points are uncorrected.

General Procedure for Preparation of (2-Hydroxyalkyl)phosphonates.[3] To a stirred solution of dialkyl methylphosphonate in dry THF was added a solution of 1.6 M *n*-butyllithium in hexane at −78 °C under N_2. The reaction mixture was stirred for 15 min at this temperature, and a solution of an appropriate aldehyde in THF was added dropwise at such a rate that the solution temperature was maintained at −78 °C. After 30 min of stirring the temperature was raised to −20 °C and the reaction mixture was neutralized with concentrated hydrochloric acid. The removal of the solvents gave a residue, which was dissolved in $CHCl_3$. After filtration the $CHCl_3$ solution was dried ($MgSO_4$) and evaporated under reduced pressure to give crude (2-hydroxyalkyl)phosphonate. In this way the following compounds were prepared.

Dimethyl (2-Hydroxy-3,3-dimethylbutyl)phosphonate (2a). Dimethyl methylphosphonate (6.15 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.9 mL), and trimethylacetaldehyde (0.055 mol) were reacted as above, giving an oil, which was purified by vacuum distillation (7.35 g, 70%): bp 97 °C/0.05 mmHg; IR (neat, cm^{-1}) 1231 (P═O), 1032 and 1050 (shoulder) (P—O—C), 3375 (OH). Anal. Calcd for $C_8H_{19}O_4P$: C, 45.71; H, 9.11. Found: C, 45.31; H, 9.12.

Dimethyl (2-Hydroxy-2-phenylethyl)phosphonate (2b). Dimethyl methylphosphonate (6.15 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and benzaldehyde (5.51 g, 0.052 mol) were reacted as above to produce an oil, which after washing with hexane crystallized. It was purified by recrystallization from benzene (white crystals, 7.95 g, 70%): mp 51 °C (lit.[2b] mp 56.1−56.5 °C); IR (KBr, cm^{-1}) 1216 and 1243 (shoulder) (P═O), 1045 and 1072 (shoulder) (P—O—C), 3309 (OH).

Dimethyl (2-Hydroxy-3-methylbutyl)phosphonate (2c). Dimethyl methylphosphonate (6.15 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and 2-methylpropanal (3.75 g, 0.052 mol), reacted as above, gave an oil which was purified by vacuum distillation (6.5 g, 67%): bp 80 °C/0.05 mmHg; IR (neat, cm^{-1}) 1224 and 1245 (shoulder) (P═O), 1030 and 1060 (shoulder) (P—O—C), 3370 (OH). Anal. Calcd for $C_7H_{17}O_4P$: C, 42.86; H, 8.73. Found: C, 42.48; H, 8.66.

Diisopropyl (2-Hydroxy-3-methylbutyl)phosphonate (2d). Diisopropyl methylphosphonate (9.00 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and 2-methylpropanal (3.75 g, 0.052 mol), reacted as above, gave an oil, which was purified by vacuum distillation (10.9 g, 71%): bp 112 °C/0.1 mmHg; IR (neat, cm^{-1}) 1223 and 1240 (shoulder) (P═O), 982 (P—O—C), 3370 (OH).

Dimethyl (2-Hydroxypentyl)phosphonate (2e). Dimethyl methylphosphonate (6.15 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and butanal (3.75 g, 0.052 mol), reacted as above, gave an oil, which was purified by

vacuum distillation (5.54 g, 57%): bp 100 °C/0.2 mmHg; IR (neat, cm^{-1}) 1225 and 1240 (shoulder) (P═O), 1030 and 1055 (shoulder) (P—O—C), 3368 (OH).

Diethyl (2-Hydroxypentyl)phosphonate (2f). Diethyl methylphosphonate (7.6 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and butanal (3.75 g, 0.052 mol), reacted as above, gave an oil, which was purified by vacuum distillation (7.6 g, 68%): bp 110 °C/0.1 mmHg; IR (neat, cm^{-1}) 1238 and 1255 (shoulder) (P═O), 1042 (O—Et), 975 (P—O—C), 3370 (OH).

Diisopropyl (2-Hydroxypentyl)phosphonate (2g). Diisopropyl methylphosphonate (9.0 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and butanal (3.75 g, 0.052 mol), reacted as above, gave an oil, which was purified by vacuum distillation (10.95 g, 71%): bp 108 °C/0.05 mmHg; IR (neat, cm^{-1}) 1223 and 1240 (shoulder) (P═O), 984 (P—O—C), 3370 (OH).

Dimethyl (2-Hydroxypropyl)phosphonate (2h). Dimethyl methylphosphonate (6.15 g, 0.05 mol), *n*-butyllithium (1.6 M in hexane, 32.82 mL, 0.0525 mol), and acetaldehyde (2.29 g, 0.052 mol), reacted as above, gave an oil, which was purified by vacuum distillation (4.3 g, 51%): bp 94 °C/0.1 mmHg; IR (neat, cm^{-1}) 1228 and 1250 (shoulder) (P═O), 1025 and 1050 (shoulder) (P—O—C), 3370 (OH).

General Procedure for Preparation of Carboxylic Esters of (2-Hydroxyalkyl)phosphonates. To a solution of (2-hydroxyalkyl)phosphonate in dichloromethane was added the carboxylic acid chloride, and the mixture was refluxed for 2 h. Removal of the solvent under reduced pressure gave the crude product. In this way the following carboxylic esters of (2-hydroxyalkyl)phosphonates were obtained.

Dimethyl [2-(Acetyloxy)-3,3-dimethylbutyl]phosphonate (3a). Dimethyl [2-hydroxy-3,3-dimethylbutyl]phosphonate (3.13 g, 0.015 mol) and acetyl chloride (2.36 g, 0.03 mol), reacted as above, gave a crude product, which was purified by recrystallization from benzene (3.0 g, 79%): mp 61 °C; IR (KBr, cm^{-1}) 1229, 1248, and 1288 (P═O), 1742 (C═O), 1038 and 1050 (P—O—C). Anal. Calcd for $C_{10}H_{21}O_5P$: C, 47.62; H, 8.39. Found: C, 47.60; H, 8.36.

Dimethyl [2-(Acetyloxy)pentyl]phosphonate (3b). Dimethyl (2-hydroxypentyl)phosphonate (2.95 g, 0.015 mol) and acetyl chloride (2.36 g, 0.03 mol), reacted as above, gave an oil, which was purified by vacuum distillation (3.1 g, 87%): bp 113 °C/0.5 mmHg; IR (neat, cm^{-1}) 1238 (P═O), 1022 and 1055 (shoulder) (P—O—C), 1733 (C═O).

Dimethyl [2-(Isobutyryloxy)pentyl]phosphonate (3c). Dimethyl (2-hydroxypentyl)phosphonate (2.96 g, 0.015 mol) and isobutyryl chloride (3.2 g, 0.03 mol), reacted as above, gave an oil, which was purified by vacuum distillation (2.9 g, 75%): bp 124 °C/0.5 mmHg.

Dimethyl [2-(Pivaloyloxy)pentyl]phosphonate (3d). Dimethyl (2-hydroxypentyl)phosphonate (2.95 g, 0.015 mol) and pivaloyl chloride (3.63 g, 0.03 mol), reacted as above, gave an oil, which was purified by vacuum distillation (3.1 g, 73%): bp 130 °C/0.5 mmHg. Anal. Calcd for $C_{12}H_{25}O_5P$: C, 51.42; H, 8.99. Found: C, 51.03; H, 8.99.

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Supporting Information Available: ^{13}C NMR spectra of **2a**—**h** and **3a**—**d** (12 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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