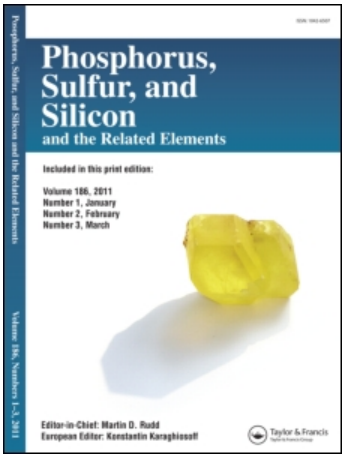

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Zdzisław Głowacki[a]; Maria Hoffmann[a]; Marek Topolski[a]; Janusz Rachoń[a]
[a] Department of Organic Chemistry, Technical University, GDANSK 6, POLAND

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SUBSTITUENT EFFECTS ON THE ^{31}P NMR CHEMICAL SHIFTS OF 1-AMINO- AND 1-HYDROXY-ALKYLPHOSPHONIC ACIDS

ZDZISŁAW GŁOWACKI, MARIA HOFFMANN, MAREK TOPOLSKI AND JANUSZ RACHOŃ

Department of Organic Chemistry, Technical University, Majakowskiego 11/12 str. 80-952 GDANSK 6, POLAND

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^{31}P chemical shifts are reported for twenty aminoalkylphosphonic acids (APAs), nine 1-hydroxyalkylphosphonic (HPAs) and six phosphonic acids (PAs). The protonation shifts and the substituent-induced effects (SCSs) of the amino and hydroxyl groups on the ^{31}P NMR and α-carbon ^{13}C NMR chemical shifts were calculated and discussed. Substituent shielding effects on phosphorus nucleus and deshielding effects on α-carbon are observed for both groups. Amino shielding effect on phosphorus nucleus is the sum of two interactions: 1) electron-withdrawing substituent effect propagated along the carbon chain, 2) hydrogen bonding and coulombic attaction between groups in the zwitterion forms. Both imply the increasing contribution of a P=O resonance structure leading to the upfield δ(P). Good linear correlation exist between chemical shifts of 1-hydroxyalkylphosphonic acids and the respective values of analogously constituted 1-aminoalkylphosphonic acids.

Key words: ^{31}P NMR chemical shifts; substituent effects; 1-hydroxyalkylphosphonic acids; aminoalkylphosphonic acids.

INTRODUCTION

Phosphonic acids and their α-hydroxy- and α-amino-derivatives are of chemical and biochemical interest in a number of ways. Thus, 1-aminophosphonic acids as analogs of 1-aminocarboxylic acids and from the fact that have been found in lower animals are important because of their potential biological activity and prospective medical applications.[1] Amino- and hydroxy-phosphonic acids act as substrates or inhibitors of enzymes involved in the metabolism of amino acids.[1,2,3] Furthermore, aminophosphonic and phosphonic acids form chelates.[4]

Several papers have been published in which their ^{31}P NMR chemical shifts were reported and discussed. Appleton et al.[5] studied the acid-base equilibria of 1,10,14 and I. Smith and co-workers[6] investigated the substituent effects of substituted diphenyl 1-phenylamino- 1-phenylmethanephosphonates. Anisotropy of chemical shifts in solid phosphonic, aminophosphonic acids and their esters were reported by Klose et al.[7] Harris and co-workers, in a series of investigations, studied the phosphonic and phosphinic acids,[8,9] their salts[10] and aminophosphonic acids (1,10,14)[11] with the solid state NMR.

In our previous works we investigated the phosphonate substituent-induced effects on the ^{13}C NMR chemical shifts of aminoalkylphosphonic acids[12] and 1-hydroxyalkylphosphonic acids.[13]

In order to study the substituent effects of amino and hydroxyl groups on the phosphonate δ(P) we have recorded ^{31}P NMR spectra of the homologues series of

aminoalkylphosphonic acids 1–20, 1-hydroxyalkylphosphonic acids 21–29 and the corresponding phosphonic acids I–VI.

TABLE I

^{31}P NMR chemical shifts (ppm), corresponding amino and hydroxyl substituent-induced chemical shifts (SCS(NH) and SCS(OH) in ppm) on the $\delta(P)$ and α-carbon $\delta(C)$ of aminoalkylphosphonic, hydroxyalkylphosphonic and related phosphonic acids

compound			SCS(NH_2)	
$H_2N-CHR^1-PO_3H_2$		δ(P)	P	α-C
1	R^1 = H	10.80	-13.63	23.00
2	Me	14.08	-19.63	25.33
3	Et	13.41	-18.33	22.39
4	Pr^n	13.62	-18.96	23.01
5	Pr^i	12.74		
6	Bu^n	13.62		
7	Bu^i	13.81		
8	Ph	10.23	-15.16	19.34
9	Bz	12.17		
$H_2N-R^1-PO_3H_2$				
10	$-(CH_2)_2-$	18.87	-14.84	6.66
11	$-CH_2-CHMe-$	23.16	-12.81	6.98
12	$-CH_2-CHPh-$	16.77		
13	$-CHMe-CH_2-$	18.74	-13.00	7.56
14	$-(CH_2)_3-$	23.86	-7.91	-3.67
15	$-(CH_2)_4-$	25.58	-7.00	1.21
$R^1-NH-CH_2-PO_3H_2$				
16	Me	8.91	-15.52	32.59
17	Et	9.07	-15.36	30.53
18	Pr^n	8.89	-15.54	30.88
19	Bz	8.83	-15.60	30.29
20	CH_2COOH	8.48	-15.95	30.75
$HO-CR^1R^2-PO_3H_2$				
	R^1 R^2		SCS(OH)	
21	H H	22.78	-1.65	43.62
22	Me H	24.91	-8.80	44.05
23	Pr^n H	24.66	-7.92	41.14
24	Pr^i H	24.18		
25	Bu^i H	24.88		
26	Ph H	20.17	-5.22	36.44
27	Me Me	27.06	-8.91	43.05
28	$-(CH_2)_4-$	26.79		
29	$-(CH_2)_5-$	26.76		
$HCR^1R^2-PO_3H_2$				
I	H H	24.43		
II	Me H	33.71		
III	Et H	31.74		
IV	Pr^n H	32.58		
V	Ph H	25.39		
VI	Me Me	35.97		

RESULTS AND DISCUSSION

All ^{31}P chemical shifts with the corresponding values of amino and hydroxyl substituent effects on the phosphonate δ(P) and δ(C) of α-carbon are given in Table I. SCS(NH_2) and SCS(OH) designate the differences between the ^{31}P chemical shifts of the 1-amino- or 1-hydroxy-alkylphosphonic acid and of the respective parent phosphonic acid (I–VI). Variations in δ(P) with pD for a D_2O solutions of 21, 25 and 26 are presented in Figure 1. Plot showing the correlation between δ(P) of 1-APAs and the respective values of analogously constituted 1-HPAs is given in Figure 2.

The 1-HPAs pD dependence of δ(P) follows the same trend as for PAs.[5] Deprotonation of phosphonate group cause a monotonic increase of shielding of the phosphorus nucleus, approximately -4 ppm for the first and -2.5 ppm for the second proton removed. The hydroxyl substitution leads to the strong deshielding of α-carbon atoms and shielding of P nucleus. In case of APAs the upfield shift of $\alpha-\delta$(C) is smaller whereas, phosphorus is highly shielded. The shielding of phosphorus in the zwitterion of aminophosphonic acids can be separated into two contributions. Previously we concluded from ^{13}C NMR data that the interaction between amino and phosphonate groups are negligible, if substituents are separated by more than two carbon atoms.[12] The amino SCS on δ(P) for 14 and 15 (-7.9 and -7.0 ppm) are the value of phosphorus shielding only due to hydrogen bonds

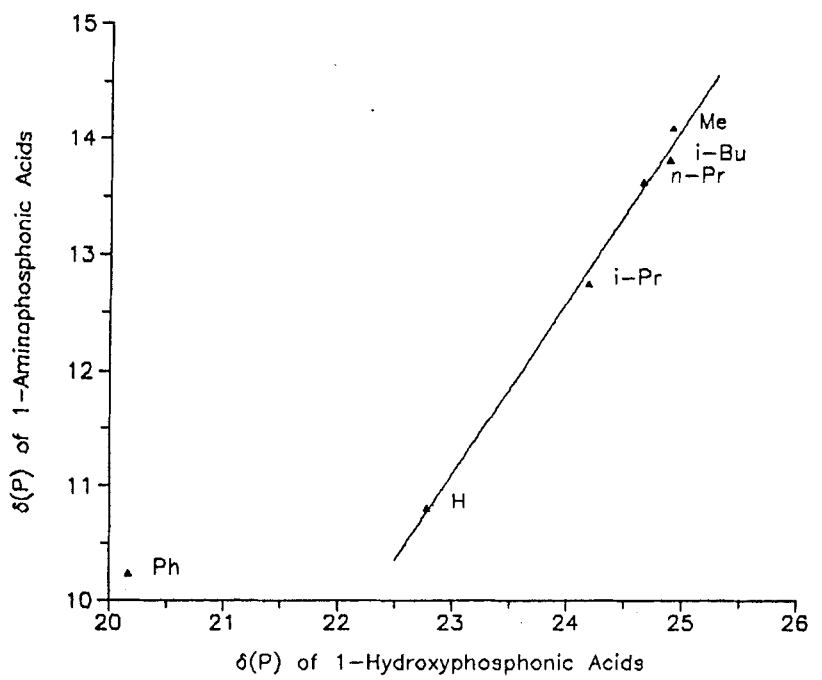

FIGURE 1 The ^{31}P NMR chemical shifts of 1-aminophosphonic acids (R—$CH(NH_2)PO_3H_2$) plotted against the respective values of 1-hydroxyphosphonic acids (R—$CH(OH)PO_3H_2$). The groups R are depicted on the plot.

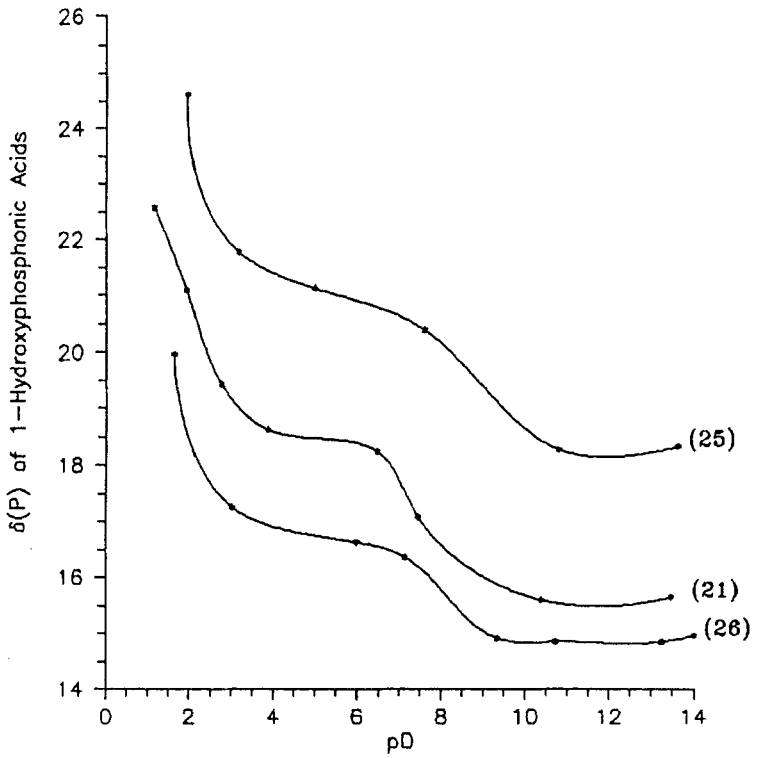

FIGURE 2 Variation of chemical shifts with pD for selected 1-hydroxyphosphonic acids (21, 25 and 26).

and coulombic attraction in the zwitterion forms. This value can be also measured from the plot of δ(P) vs. pD, as a downfield shift at pD > 11, it depends on pD and is proportional to the strength of interaction.[5] Both effects i.e., shielding effect of electron-withdrawing α-substituent and additional upfield shift observed in zwitterion form are oppositely correlated with charge density on phosphorus nucleus. This is not surprising, since it is known that δ(P) cannot be rationalized simply in terms of electron density. Supposedly, changes in $d\pi$—$p\pi$ bond order leading to an increase of the P=O resonance structure are responsible for enhancing in the d-orbital occupation on phosphorus and upfield shift of δ(P).[6,17-19]

These results are consistent with the available solid-state NMR studies.[7,11] The ^{31}P shielding asymmetry parameters implies an axial symmetry for the shielding environment of free phosphonate group for phosphonic acids (η = 0), which could arise from electronic equivalence of the three oxygen atoms. Under these circumstances, d-orbitals of the phosphorus are not involved in $d\pi$—$p\pi$ bonding. On the other hand, it should be noted that an axial symmetry can be interpreted also by assuming the bond fluctionality on the NMR time scale or the rapid rotation about C_3 axis. The asymmetry parameters for the APAs ($\eta > 0.9$ for 1, 10 and 14) provide evidence of the oxygens nonequivalence. Evidently, hydrogen bonds in zwitterion and electron-withdrawing α-substituent increase P=O bond order.

Good linear correlation exist between the ^{31}P chemical shifts of 1-amino- and 1-

hydroxy-alkylphosphonic acids except for the phenylphosphonic acid derivatives. Supposedly, due to rotation barrier of phenyl substituent in zwitterion of 1-aminophenylphosphonic acid. The regression coefficient (r), standard deviation (s), parameters A and B are as follows: 0.997, 0.15 ppm, 1.50 and −23.3 only considering five alkylphosphonic acids.

As expected, the linear correlation of ^{31}P vs.^{13}C α-carbon chemical shifts is not observed, the regression coefficients are 0.102 and −0.07, respectively for APAs and HPAs.

EXPERIMENTAL

Compounds 1–29 and I–VI were obtained by known general procedures.[14,15] A KOH or HCl solution in D_2O (0.2 mol L^{-1}) was used to change the pD. The pD values were measured on a Mera-Elmat N-517 pH meter. The meter readings were adjusted to pD values by applying a correction (pD = meter reading + 0.40).[16] The ^{31}P NMR spectra of 0.05–0.2 M D_2O solutions in 5 mm o.d. sample tubes were recorded at 36.27 MHz using a Jeol FX90Q spectrometer in the FT mode. An 85% aqueous H_3PO_4 solution was used as an external reference. Typical conditions were as follows: probe temperature of 303 K, spectral width 4000 Hz, 8 K data points and 50–100 accumulations.

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