Dependence of Vicinal ${}^{31}P-{}^{31}P$ and ${}^{31}P-{}^{13}C$ Coupling Constants on the Dihedral Angle of α,β -Diphosphonates

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Several α,β -diphosphonates with a norbornane or cyclohexane skeleton were prepared, and the ³¹P-³¹P coupling constants over three bonds for the ethyl or methyl esters, the acid and anion were obtained from the ¹³C NMR spectra or the ¹³C satellites in the ³¹P NMR spectra. The ³J(PP) values cover a range of about 90 Hz and are therefore well suited for conformational and configurational analysis. The dependence of ³J(PP) on the dihedral angle is well reflected by an extended Karplus relationship: ³J(PP) = A + B cos $\varphi + C \cos 2\varphi + D \cos 3\varphi$, with different parameters for the esters, acids and anions. For *trans* and *gauche* arrangements of the α,β -diphosphonic acids the dependence of ³J(PC) on the PCCC dihedral angle show that a good curve fitting is achieved using the Karplus relationship ³J(PC) = A + B cos $\varphi + C \cos 2\varphi$. A comparison of these curves with published data indicates smaller coupling constants for $\varphi \approx 0^\circ$. The coefficients of the Karplus equation for the ³J(PC) values obtained for esters are similar for acids and anions.

KEY WORDS Diphosphonates Vicinal P-P and P-C coupling constants Karplus relationship

INTRODUCTION

Diphosphonates are formed in addition to other products in the reaction of white phosphorus with alkenes in the presence of oxygen.¹⁻³ Structure elucidation of the reaction products by NMR spectroscopy in many cases shows different magnitudes for the vicinal coupling constants, ${}^{3}J(PP)$, of esters and diphosphonic acids. Further, a considerable change is observed for ${}^{3}J(PP)$ after the addition of alkali to the acid solution. A knowledge of the dependence of ${}^{3}J(PP)$ on the dihedral angle is required in order to draw conclusions regarding the conformation of the phosphoryl groups. Such a dependence has previously been obtained, to our knowledge, only by Couffignal et al.4 for diphenylphosphine sulphides. Ionin and co-workers^{5,6} and Hägele and coworkers^{7,8} have reported the ${}^{3}J(PP)$ values of several diphosphonates.

In this work we investigated the dependence of ${}^{3}J(PP)$ on the dihedral angle of esters, acids and anions of conformationally rigid diphosphonates. In addition, ${}^{3}J(PC)$ data were compared with the dihedral angle dependences published by Thiem and co-workers^{9,10} and Quin *et al.*¹¹ For this purpose several monophosphonates were included in the investigation.

RESULTS AND DISCUSSION

The following α,β -diphosphonates or monophosphonates were prepared and investigated as their ethyl or methyl esters, and as aqueous solutions of the

0749-1581/90/060500-05 \$05.00 © 1990 by John Wiley & Sons, Ltd. acids and their anions: the norbornane derivatives 1 (both 1d and 1e were formed in a ratio of 1:4 during the synthesis and were investigated without isolation), tetraethyl norborn-5-ene-trans-2,3-diphosphonate (2), tetraethyl bicyclo[2.2.2]octane-trans-2, 3-diphosphonate (3) and the cyclohexane derivatives 4. The compounds were chosen in such a way that the organic moiety of the phosphonate does not contain an electronegative substituent, which would decrease the vicinal coupling constant.

For the compounds with chemically equivalent phosphorus nuclei, i.e. **1a**, **3**, **4a** (at ambient temperature) and **4b**, the ³J(PP) values were obtained according to Refs 12 and 13 by spectral analysis of the AA'X spin system resulting for ¹³C-containing molecules. If $0.1 \leq |J_{AA'}/(J_{AX} - J_{A'X})| \leq 2.5$ is valid, then five lines can be observed in the ¹³C NMR spectrum. In these cases the coupling constant of interest can be determined from the distances between the normal lines, $2N = |J_{AX} + J_{A'X}|$, and between the combination lines, $4D = \sqrt{(J_{AX} - J_{A'X})^2 + 4J_{AA'}^2}$, taking into account the intensities of the normal lines (I_n) and combination lines (I_c) :

and

$$|J_{\mathbf{A}\mathbf{A}'}| = 2D\sqrt{1 - I_{\mathrm{c}}/I_{\mathrm{n}}}$$

$$|J_{\mathrm{AX}} - J_{\mathrm{A'X}}| = 4D\sqrt{I_{\mathrm{c}}/I_{\mathrm{n}}}$$

The relative signs of J_{AX} and $J_{A'X}$ are obtained simultaneously. Since the intensities cannot be determined very precisely, the coupling constants obtained from the ¹³C NMR spectra must be considered only as estimated values. Values of higher accuracy can be obtained from the ¹³C satellites of proton noise decoupled ³¹P spectra, where $J_{AA'}$ is a directly observable distance between

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lines. Although some of the eight lines of the AA' part are often covered by the base of the main line, or by signals from impurities, the coupling constant of interest can be determined in most cases because it appears four times in the AA' part. $J_{AA'}$ is measurable if $|J_{AA'}/(J_{AX} - J_{A'X})| \leq 1$ holds.

Satellite spectra for some diphosphonic acid solutions could not be interpreted owing to line broadening.

Dihedral angles

The ${}^{3}J(PP)$ values obtained for the diphosphonates and the assumed dihedral angles are given in Table 1. Compounds 1a, 1b, 2, 3 and 4c are conformationally rigid molecules. Their PCCP dihedral angles are not necessarily equal in the ester, acid and anion. Since experimental data from x-ray analysis are lacking, and the angles may vary in solution, we shall assume approximate values and discuss their deviations.

Owing to intramolecular hydrogen bonds between the two eclipsed phosphoryl groups, the dihedral angle of the acid **1a** is probably zero. The dihedral angle in esters and anions deviates from zero owing to steric hindrance or electrostatic repulsion. In accordance with an x-ray structural analysis of an *endo-endo*-substituted norbornane,¹⁴ the angle was assumed to be 20° . The significant increase in the coupling constant between the ester and the acid cannot be attributed only to changes in the dihedral angle.

In the *trans* compounds **1b** and **2** the coupling constants of the esters or the anions are of the same magnitude, whereas differences in the case of the acids indicate a smaller PCCP dihedral angle in the saturated compound. We assume a dihedral angle of 110° for **1b** and **2** (acid of **1b** 108°) by analogy with an *exo-endo*-substituted norbornane of known x-ray structural analysis.¹⁵

The ester and anion of bicyclooctanediphosphonate **3** show larger values for the coupling constants in comparison with those of **1b**, which suggests a larger dihedral angle (115°). The greater flexibility of the bicyclooctane skeleton obviously causes a significantly smaller angle (103°) in the acid.

Compounds 4a and 4b are conformationally flexible. In the case of the *cis*-diphosphonate 4a the *gauche* arrangement remains intact, despite a conformational change, so one can use a dihedral angle of approximately 60° for the calculation. In 4b, a conformational change from the bis-axial to the bis-equatorial arrangement of the phosphoryl groups has drastic consequences. The large J(PP) value (82.5 Hz) for the ester at ambient temperature indicates that the bis-axial conformation predominates. Unfortunately, even a lowering of the temperature during the measurement does not allow

		³ J(PP) (Hz)					
Compound		(0)	•	• • •			
No.	Diphosphonate	$\varphi(\circ)$	Ester	Acid	Anion		
1a	Norbornane-cis-2,3-endo-	20	26.1	35.0	21.4		
				(0°)			
4a	Cyclohexane- <i>cis</i> -1,2-	60	6.5	6.0	4.6		
1b	Norbornane-trans-2,3-	110	17.6	14.4	12.4		
				(108°)			
2	Norborn-5-ene-2,3-	110	17.6	15.2	12.4		
3	Bicyclo[2.2.2]octane-trans-2,3-	115	20.4	9.5	14.0		
				(103°)			
4c	Bicyclooxaphosphorinane-	170	91.4	86.4	70.3		
	(see text)		87.7				
4b	Cyclohexane-trans-1,2-	$\sim \! 180$	9094ª	—	67.0		
^a Estimated	I from low-temperature investigations	s (see text)	•				

Table 1. PCCP dihedral angles and coupling constants of α,β-diphosphonates

the observation of the signals of the bis-equatorially substituted conformer. The ratio of the conformers can be estimated by considering the dependence of the line width of C-1 and C-2 on temperature.^{16,17} On this basis the coupling constant of the bis-axial conformation is estimated¹⁸ to be 90-94 Hz. A coupling constant of 30 Hz in acid 4b indicates a remarkable change in the conformation relationships. Under these conditions the conformational equilibrium changes towards the bisequatorial form, which is stabilised by the formation of intramolecular hydrogen bonds. The use of water as solvent made it impossible to freeze the conformer equilibrium and to determine the proportions of the conformers. The anions of 4b should exist exclusively in a bis-axial conformation owing to repulsion of the negative charges. In the case of many conformationally flexible α,β -diphosphonates a coupling constant of 67 Hz has been observed in a strongly alkaline medium.¹⁹

The synthesis of a cyclohexane-trans-1,2-diphosphonate with a *tert*-butyl group in the 4-position failed. Such a compound with an equatorial position of the *tert*-butyl group would allow fixation of the phosphoryl groups in a bis-axial conformation. Rearrangement and condensation led to the conformationally rigid 2ethoxy-8- diethoxyphosphoryl- 4,4,5-trimethyl-2- oxo-3oxa-2-phosphabicyclo[3.3.1]nonane (4c), a compound well suited for the purpose of our experiment.



The signals of the two diastereomers, which differ in the arrangement of the terminal oxygen and the ethoxy group at P-2, were clearly seen in the NMR spectra. We assume that the diastereomer with the larger coupling constant has a PCCP dihedral angle of about 170°. Configurational differences vanish completely in the anion and are averaged in the acid owing to fast proton exchange. In contrast to the other diphosphonates with four negative charges, phosphorinane anion 4c contains only three negative charges; its coupling constant in alkaline solution cannot therefore be used for the general dependence of the ${}^{3}J(PP)$ coupling constants of α,β -diphosphonates on the dihedral angle.

Spin tickling experiments of the esters 4a and 4b were carried out in order to prove that the ${}^{3}J(PP)$ coupling constants of the two compounds have the same sign (in this case it should also be the same for all other dihedral angles). The ${}^{13}C{}^{1}H, {}^{31}P{}$ triple resonance technique proposed by Colquhoun *et al.*²⁰ was applied for this purpose. Irradiating with low power at the frequency of a ${}^{31}P{}$ satellite line of the AA' part causes a disturbance of the AA'X spin system. The following conclusion can be drawn from the line splitting induced in the ${}^{13}C{}$ spectrum:

$${}^{3}J(PP)[{}^{1}J(PC) + {}^{2}J(P'C)] > 0$$

Since ${}^{1}J(PC)$ is positive for phosphonates²¹ and ${}^{1}J(PC) \ge |{}^{2}J(P'C)|$, a positive value results for ${}^{3}J(PP)$.



Figure 1. Dependence of the ³*J*(PP) vicinal coupling constant on the dihedral angle in α,β -diphosphonates. The plotted curves were calculated using the equation ³*J*(PP) = $A + B \cos \varphi + C \cos 2\varphi + D \cos 3\varphi$. (\bigcirc) Ester, calculated with A = 32.06, B = -28.49, C = 29.41, D = -3.53; (\triangle) acid, calculated with A = 31.85, B = -25.12, C = 30.05, D = -1.79; (\square) anion, calculated with A = 23.40, B = -19.22, C = 22.25, D = -2.07.

Karplus-like curves

First we attempted to fit (least-squares approximation) the dependence of the measured ${}^{3}J(PP)$ values on the estimated dihedral angles to a Karplus-type function:

$$^{3}J(PP) = A + B\cos\varphi + C\cos 2\varphi$$
 (1)

This equation gives large deviations from the experimental data, particularly in the case of *gauche* coupling constants. A much better fit is obtained by expanding this function to

$${}^{3}J(PP) = A + B\cos\varphi + C\cos 2\varphi + D\cos 3\varphi \quad (2)$$

The calculated curves, together with the experimental data for the α,β -diphosphonates, are displayed in Fig. 1. It is obvious that the vicinal coupling constant, ${}^{3}J(PP)$, covering a range of more than 90 Hz in the case of α,β -diphosphonates, is well suited for the investigation of the configuration and conformation of these compounds.

The *trans* and *gauche* coupling constants given in Table 2 were used in the investigation of the

Table 2. Dependence of trans and gauche coupling constants of aqueous solutions of α , β - diphosphonates on the degree of titration						
	Coupling constant (Hz)					
Degree of	itration	J,(PCCP)	$J_g(PCCP)$			
0 1		86	6			
		80	5			
2	2	75	4			
3	}	71	3			
>4		67	3			

dependence of the conformer ratio of different α,β diphosphonates on the degree of titration.^{18,19} The J_t values for a degree of titration between 0 and 3 were directly obtained by simultaneously measuring and titrating an aqueous solution of 4c. All other values are based on our results obtained during the investigation of different α,β -diphosphonates.

The accuracy of the calculated curves and of the values proposed in Table 2 is limited by the errors resulting from the measurement of the coupling constants (usually ± 0.2 Hz) and the uncertainty of the dihedral angle (maximum 10°). The latter is larger owing to the utilization of only estimated values. In addition, apart from the dependence of the coupling constant on the dihedral angle, it is also influenced by the bond length, bond angle and type of substituents in the vicinity of the coupling nuclei. In order to suppress this last effect only compounds without electronegative substituents on the carbon skeleton were studied. The influence of the PCC bond angle is very marked in the case of a dihedral angle of zero. For example, the following ${}^{3}J(PP)$ values have been measured for intermediates in the synthesis of 1a; norborn-2enediphosponate 16.4 Hz (ester), about 20 Hz (acid) and 12.6 Hz (anion) and norbornadiene-2,3-diphosphonate 13.7, 19.6 and 11.4 Hz, respectively. There is probably the same qualitative bond angle dependence for ${}^{3}J(PP)$ as for ${}^{3}J(HH)$; this means that the coupling constants decrease with increasing bond angle.²²

Despite these uncertainties, ${}^{3}J(PP)$ values can be used for conformational investigations because the dependence on the dihedral angle predominates.

The PCCC dihedral angle dependence of the interesting ${}^{3}J(PC)$ coupling constant is shown in Table 3 for phosphonic acid esters. Similarly to **1a**, a dihedral angle (PCCC to the methyl group) of 20° was used for **1d** and, analogously to **1b**, of 110° for **1d** and **1e**. The dihedral angles of the norbornane skeleton were obtained from the x-ray structural data of norbornan-2-ol.²³ An angle of 60° was estimated for **4c**. The measured coupling constants can be approximated fairly well by a Karplus type function [Eqn (1)] using the parameters A = 7.23, B = -5.41 and C = 6.29. This function deviates from the curves published by Thiem and Meyer⁹ and Quin *et al.*¹¹ in the region of small dihedral angles, where our ${}^{3}J(PC)$ values are smaller.

The dihedral angle dependence obtained for esters can also be used for phosphonic acids and anions owing to the strong similarity of their ${}^{3}J(PC)$ values.

EXPERIMENTAL

The bicyclic and cyclohexanediphosphonates were prepared by a Diels-Alder reaction by analogy with published methods.²⁴⁻²⁷

Compounds 1a and 1c were prepared from cyclopentadiene (5) and ethynediphosphonate (6, prepared according to Ref. 24) or propyne-1-phosphonate (prepared according to Ref. 28) and twofold catalytic hydration of the norbornadiene products; 1b was prepared from 5 and *trans*-ethenediphosphonate (7, prepared according to Ref. 29), with formation of the norbornene intermediate 2; 1d and 1e were prepared from 5 and *trans*-propene-1-phosphonate (prepared according to Ref. 30); 3 was prepared from cyclohexa-1, 3-diene (8) and 7; 4a was prepared from 8 and 6 (the product of the Diels-Alder reaction is *o*benzenediphosphonate²⁴); 4b was prepared from butadiene and 7.²⁵

All Diels-Alder adducts were isolated from polymer side-products by rectification (10-cm Vigreux column) under vacuum (rotary oil pump).

For catalytic hydration of the unsaturated intermediate, either PtO_2 or Rh_2O_3/PtO_2 catalysts, according to Zymalkowski,³¹ were used. The spectra of the hydration products were recorded after separation of the catalyst and evaporation of the solvent (ethanol).

Compound 4c was formed during a 5-day reaction of 4-*tert*-butylcyclohex-4-ene-*trans*-1,2-diphosphonic acid with 20% hydrochloric acid and zinc. The reaction mixture was converted into the acid form of 4c by cation exchange. Reaction with triethyl orthoformate³² led to the formation of 4c after several days.

Table 3. PCCC dihedral angles and ³J(PC) values of phosphonates (coupling carbon atoms in parentheses)

Compound		Dihedral angle, $\varphi(^{\circ})$						
No.	Phosphonate	20	35	60	105	110	115	165
1a	Norbornane- <i>cis</i> -2,3- <i>endo</i> -di-				4.8 (C-4)			
1b	Norbornane- <i>trans</i> -2,3-di-		5.3 (C-6)					17.2 (C-5)
1c	3-endo-Methylnorbornane-2-endo-	6.8 (CH ₃)	5.9 (C-6)		4.8 (C-4)			
1d	3-exo-Methylnorbornane-2-endo-		5.1 (C-6)		4.0 (C-4)	4.8 (CH ₃)		
1e	3-endo-Methylnorbornane-2-exo-					4.1 (CH ₃)	5.3 (C-4)	18.0 (C-6)
	2- <i>endo</i> -Norbornane ^a		5.5 (C-6)		2.8 (C-4)			
	2-exo-Norbornane ^a						4.1 (C-4)	18.5 (C-6)
4c	Bicyclooxaphosphorinaned			≤0.4 (C-6) ^ь				
				≼0.4 (C-6)°				
				1.2 (C-9) [♭]				
				0.7 (C-9)°				
Average		6.8	5.5	0.7	4.1	4.4	4.7	17.9
^a Investig ^b Diastere ^c Diastere	ated by Quin <i>et al.</i> ¹¹ somer with ${}^{3}J(PP) = 91.4$ Hz. somer with ${}^{3}J(PP) = 87.7$ Hz.							

^d See text

Silylation of the esters using trimethylbromosilane, followed by hydrolysis with water,^{33–35} provided the phosphonic acids.

The ³¹P and ¹³C NMR spectra were recorded on a Bruker WH 90DS spectrometer operating at 36.44 and 22.63 MHz, respectively. The esters were dissolved in CDCl₃ (20%, v/v) and the acids in D₂O containing 15%

(v/v) CD₃OD (0.5–1 M). For the spectra of the anions the NMR samples were obtained by dissolving the acid in an excess of sodium hydroxide solution and adding 15% (v/v) CD₃OD (0.5–1 M). A digital resolution of 0.15 Hz for the ³¹P{¹H}–¹³C satellite spectra and of 0.4 Hz for the ¹³C NMR spectra was achieved.

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