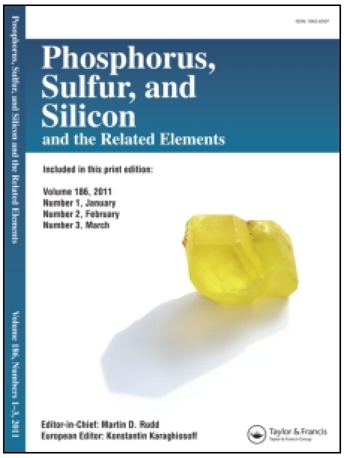

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TRANS-CYCLOHEXANE-1,2-DIPHOSPHONATES SYNTHESIS, STRUCTURAL AND NMR SPECTROSCOPIC INVESTIGATIONS

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TRANS-CYCLOHEXANE-1,2-DIPHOSPHONATES SYNTHESIS, STRUCTURAL AND NMR SPECTROSCOPIC INVESTIGATIONS

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A stereospecific addition of sodium diethylphosphite to cyclohexene-1-phosphonic acid diethyl ester 1 was used to synthesize *trans*-cyclohexane-1,2-diphosphonic acid tetraethyl ester 2b. Acidolysis of the ester yields the corresponding diphosphonic acid 2a. Dissociation constants pK_1-pK_4 of 2a were obtained in aqueous solutions by precision potentiometric titration. The molecular structure of solid 2a determined by X-ray diffraction shows a slightly disturbed chair form of the cyclohexane ring and a bisaxial conformation of the phosphonate groups with a P—C—C—P dihedral angle of 143°. Results of molecular modeling of 2a as well as of its anions (with and without consideration of Na^+ cations) obtained by semi-empirical MNDO methods and by empirical force field calculations including molecular dynamics are reported. The investigation of organic solutions of 2b and of aqueous solutions of 2a by NMR spectroscopy allows conclusions concerning the conformative state via a Karplus-type relation for the vicinal coupling constant $^3J_{PP}$ on the P—C—C—P dihedral angle. In 2b the preferred conformation is that with a bisaxial arrangement of the phosphonate groups, while in aqueous solutions of 2a the bisequatorial conformation dominates. By titration of 2a with a strong base the portion of the bisequatorial conformation rises to a maximum value at a degree of titration $\tau \approx 3$. Continuation of the titration leads to stabilization of the bisaxial conformation.

Key words: trans-Cyclohexane-1,2-diphosphonic acid; *trans*-cyclohexane-1,2-diphosphonic acid tetraethyl ester; crystal structure; molecular modeling; NMR; conformation.

INTRODUCTION

Trans-cyclohexane-1,2-diphosphonic acid is a four-basic acid of the general type H_4L as the simplest compound of this class of organic phosphorus acids, the ethane-1,2-diphosphonic acid. These acids dissociate in aqueous solution establishing a

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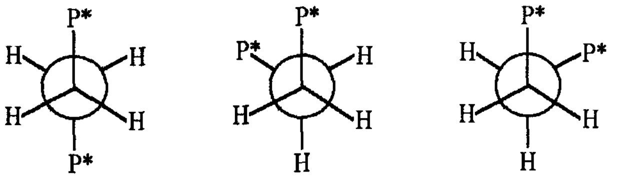
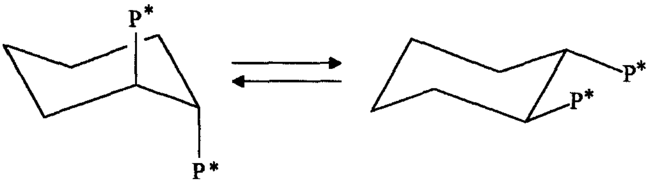


t g1 g2

P* = P(O)(OR)2

with R = H or -

SCHEME 1



aa ee

SCHEME 2

protolysis equilibrium including the anions $H_{4-i}L^{i-}$ (i = 1–4), which is characterized by the equilibrium constants K_1–K_4. Irani and Moedritzer[1] have determined the constants pK_1–pK_4 of ethane-1,2-diphosphonic acid to 1.50, 2.74, 7.42 and 8.96 (all for an ionic strength of 1), respectively.

We have studied the dependence of the vicinal coupling constant $^3J_{PP}$ on the degree of titration τ investigating the titration of this acid with a strong base.[2] The following data showing a minimum of the coupling constants $^3J_{PP}$ at $\tau \approx 3$ were found: 75.0 Hz for $\tau = 0$, 73.3 Hz for $\tau = 2$, 52.0 Hz for $\tau = 3.3$ and 69.6 Hz for $\tau = 5$.

These results may be explained by coupled equilibria of de- and reprotonation reactions and by changes of the ratios of the rotamers.

The free diphosphonic acid[3] and its tetrasodium salt[4] prefer the *trans* configuration in the solid state. In the opposite in solutions of diphosphonic acids the remarkable dependence of the vicinal coupling constant $^3J_{PP}$ on the dihedral angle[5] can be used to estimate the ratio of the conformers. As a $^3J_{PP}$ value of 75 Hz of an aqueous solution of ethane-1,2-diphosphonic acid confirms the dominance of the *trans* conformation, the decrease of this coupling constant to 52 Hz at a degree of titration $\tau \approx 3$ shows the existence of a remarkable portion of a gauche conformation with a P—C—C—P dihedral angle of about 60°. This can be explained by the possibility of the formation of intramolecular hydrogen bonds between the two phosphonate groups of one acid molecule if a gauche conformation is realized.

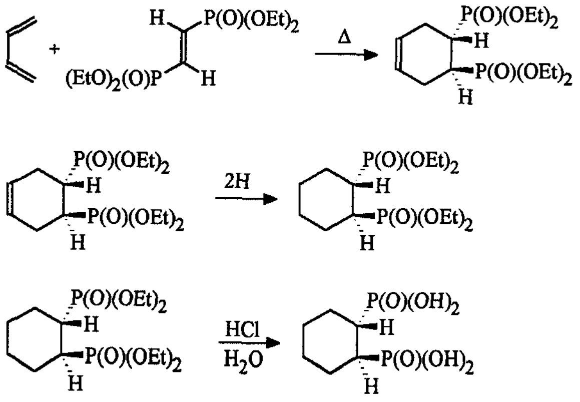
In the present work we investigate *trans*-cyclohexane-1,2-diphosphonic acid, a compound with a molecular skeleton that allows only two instead of three molecular arrangements. In this molecule the formation of an intramolecular hydrogen bond is possible in the bisequatorial conformation ee, which is also stabilized through the γ *trans* relation of both phosphonate groups to carbon atoms of the cyclohexane ring. On the other hand, in both conformations steric restrictions occur, in ee an interaction between the phosphonate groups and in aa γ gauche interactions of these groups with carbon atoms of the cyclohexane ring. Our studies deduced the preferential conformation in both the solid state and in solutions using X ray diffraction, potentiometric titration, and NMR spectroscopy. Theoretical calculations on an isolated molecule were performed using semi-empirical MNDO methods and by a force field method in DISCOVER.

The "Karplus-like" curves of the vicinal coupling constant $^3J_{PP}$ of α, β-diphosphonates obtained in paper[5] are based on estimated P—C—C—P-dihedral angles. The experimentally determined dihedral angle of *trans*-cyclohexane-1,2-diphosphonic acid is considered in our discussion concerning the ratio of conformers of α, β-diphosphonates.

RESULTS AND DISCUSSION

Preparation

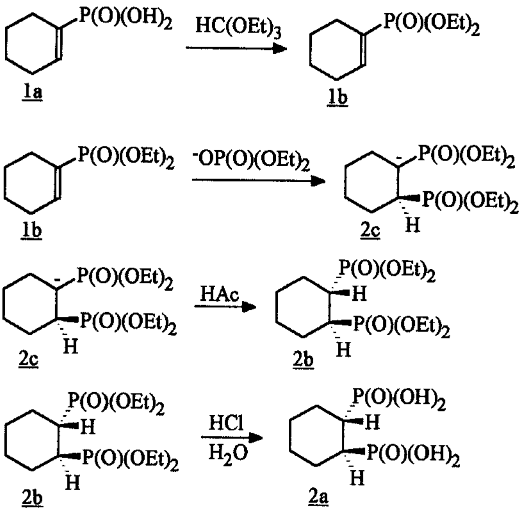
Tavs[6] obtained pure *trans*-cyclohexane-1,2-diphosphonic acid for the first time by a multi-step synthesis involving a Diels-Alder-reaction:



SCHEME 3

The reaction of white phosphorus with cyclohexene in the presence of oxygen,[7] followed by a chlorination of the product with PCl_5, esterification and acidolysis yields in the formation of *trans*-cyclohexane-1,2-diphosphonic acid as side product. Later it was shown[8] that in the course of this reaction the *cis*-cyclohexane-1,2-diphosphonic acid is formed in about twice the yield of the *trans*-isomer.

We found, that the desired model compound can be obtained in high yields using commercially available starting compounds. In a first step cyclohexene-1-phosphonic acid 1a (HOECHST AG, Knapsack) is transferred into the corresponding cyclohexene-1-phosphonic acid diethylester 1b using *ortho* formic acid triethyl ester.[9] In a Pudovik-addition[10] of sodium diethylphosphite on 1b, probably involving a carbanionic intermediate 2c, the tetraethylester 2b of *trans*-cyclohexane-1,2-diphosphonic acid is formed, which is transformed into the acid 2a by means of concentrated HCl.



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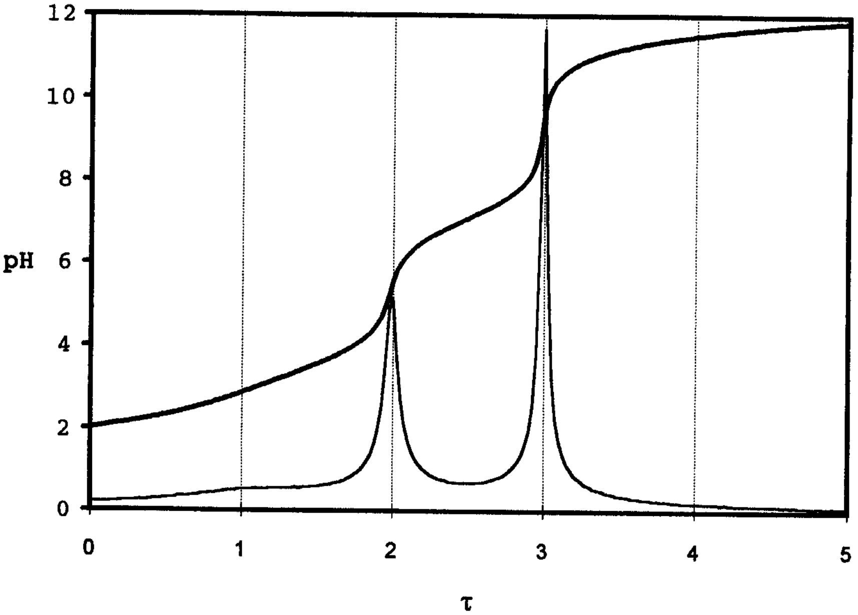


FIGURE 1 Titration curve of *trans*-cyclohexane-1,2-diphosphonic acid with NaOH. Concentration of the titrant: 5 × 10^{-3} mol/l, volume of the titrant: 80 ml, concentration of the NaOH: 0.1 mol/l, temperature: 27°C, —— pH curve, —— 1. deviation.

Potentiometric Titration

For a more detailed discussion of the acid-base properties of *trans*-cyclohexane-1,2-diphosphonic acid a more accurate knowledge of acid constants and of the τ- or pH-dependent distribution of the five species $H_{4-i}L^{i-}$ (i = 0–4) involved in

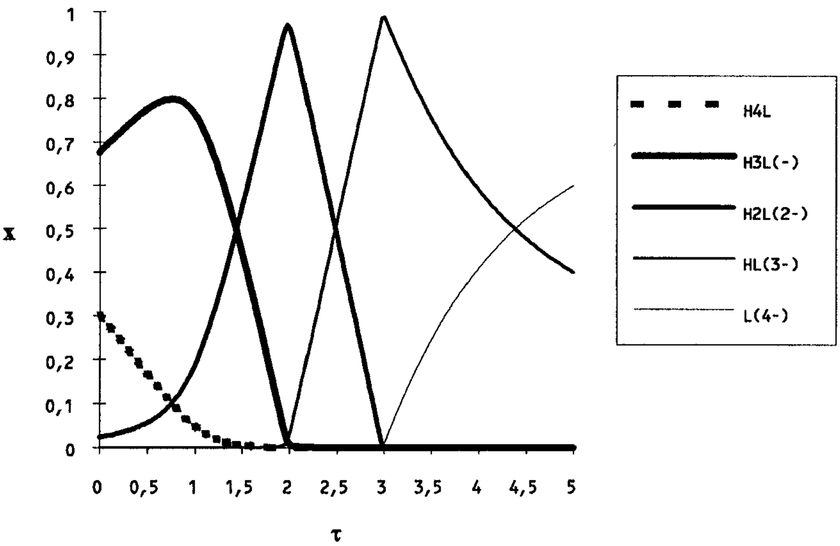


FIGURE 2 Diagram of the distribution of the molar ratios for *trans*-cyclohexane-1,2-diphosphonic acid and its anionic species as function of titration degree τ at $[H_4L]_0 = 5 \times 10^{-3}$ mol/l.

the protolysis equilibrium is required. These distribution diagrams are very important for subsequent discussions of NMR spectroscopic parameters being dependent on the degree of titration. Such a distribution diagram of the different species can be obtained by high-resolved titration followed by analysis of the experimental data and iterative refinement of the pK values. For this purpose three potentiometric titrations were carried out using the titration system MINI-T[11] and applying the program BEST.[12]

Figure 1 presents one of the obtained titration curves. The number of measuring points amounts to 300. This high point density is necessary to determine reliable pK values by means of numerical iteration. The acid constants pK_1–pK_4 were obtained from titration curves as 1.68, 3.48, 7.06 and 11.68, respectively. Using these values and the values of concentration and volume of the titration solution the distribution diagram (Figure 2) was obtained.

Crystal and Molecular Structure

Trans-cyclohexane-1,2-diphosphonic acid crystallizes in the monoclinic space group C2/c. The unit cell consists of four molecules with one-half the molecule per unique volume as an independent unit. The C2/c is a centrosymmetric space group hence the unit cell consists of pairs of molecules with opposite absolute configuration. In consequence, the unit cell can be considered as a racemic mixture of R,R and S,S enantiomers. The molecular structure of *trans*-cyclohexane-1,2-diphosphonic acid is given in Figure 3. As can be seen the carbon skeleton principally corresponds with a chair conformation with bisaxial arrangement of the phosphonate groups, but deviations from the ideal conformation are visible. In Table I bond lengths, bond angles and dihedral angles are compiled. The P—C—C—P′ dihedral angle (ca. 143°) is of special interest, because of its large deviation from the ideal chair

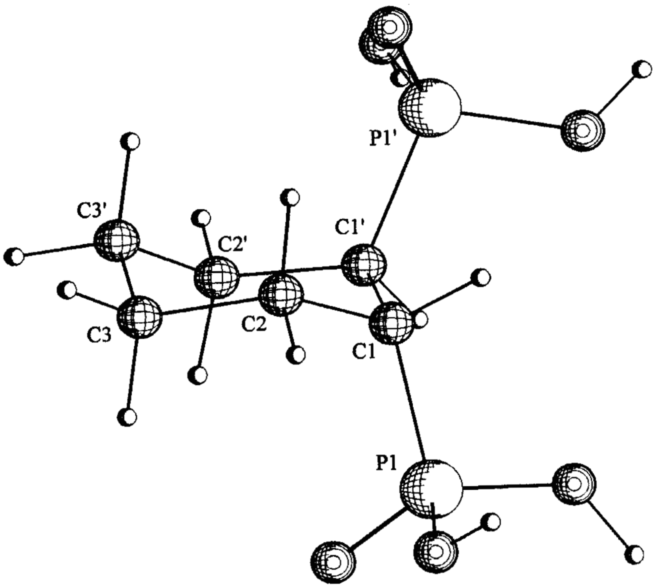


FIGURE 3 Molecular structure of *trans*-cyclohexane-1,2-diphosphonic acid from X-ray diffraction.

(180°). In agreement with this large dihedral angles P—C(1)—C(2)—C(3) (80.0°) and P—C(1)—C(1′)—C(2′) (87.7°) result. Consequently, the cyclohexane ring is flattened and smaller dihedral angles C(2)—C(1)—C(1′)—C(2′) (41.6°) and C(1′)—C(1)—C(2)—C(3) (47.1°) occur. Only the ring side opposite to the both phosphonate groups shows an almost ideal dihedral angle C(2)—C(3)—C(3′)—C(2′) (60.5°). The bond lengths P—C, P═O, C(1)—C(1′) and C(1)—C(2) are 0.01–0.02 Å longer than in ethane-1,2-diphosphonic acid[3] or in the propane-1,3-diphosphonic acid,[13] where the dihedral angles P—C—C—P and P—C—C—C are close to 180°.

Figure 4 shows parts of the solid state structure of *trans*-cyclohexane-1,2-diphosphonic acid along the crystallographic axes *b* and *c*. In both presentations the shaded spheres represent positions of the phosphorus atoms and the spheres marked with a grid the carbon and oxygen atoms. Hydrogen bonds are given by bold dashed lines. The hydrogen atoms of the cyclohexane ring are omitted for better comprehension.

The both enantiomers R,R and S,S are alternately arranged in the lattice. From each phosphonyl group four hydrogen bonds are formed to other molecules. Each P═O oxygen is an acceptor for two hydrogen bonds of different length involving OH groups from two separate molecules. In this way rings of different size are formed: i) a 12-membered ring involving four half molecules connected by two hydrogen bonds with an O—H· · · · · ·O distance of 2.583 Å and further two with an O—H----O distance of 2.618 Å, ii) a 14-membered ring involving two molecules, and iii) a 16-membered ring formed by four half molecules. In this way a spherical network of intramolecular hydrogen bonds is established connecting the acid molecules very strongly. Although, the hydrogen bonds in 2a are 0.06–0.08 Å longer than in ethane-1,2-diphosphonic acid,[3] a high melting point (225°C) and insolubility of this compound in all organic solvents without acidic protons result.

TABLE I

Structure parameters of *trans*-cyclohexane-1,2-diphosphonic acid

Type of parameter	Parameter	X-ray analysis	MNDOC calculation	VAMP[a] calculation
Bond length (Å)	C(1)–C(1')	1.562 (2)	1.541	1.521
	C(1)–C(2)	1.541 (2)	1.542	1.526
	C(2)–C(3)	1.525 (2)	1.538	1.521
	C(3)–C(3')	1.515 (3)	1.535	1.517
	C(1)–P	1.809 (1)	1.849	1.856
	P=O(1)	1.501 (1)	1.503	1.464
	P–O(2)	1.552 (1)	1.613	1.688
	P–O(3)	1.550 (1)	1.613	1.687
Bond angle (°)	C(1')–C(1)–P	110.1 (1)	110.4	112.9
	C(2)–C(1)–P	114.4 (1)	111.1	109.7
	C(1)–P=O(1)	114.1 (1)	120.8	123.6
	C(1)–P–O(2)	109.6(1)	106.5	104.4
	C(1)–P–O(3)	102.0 (1)	106.1	101.4
	O(1)–P–O(2)	108.0 (1)	110.1	110.8
	O(1)–P–O(3)	113.1 (1)	110.1	112.8
	O(2)–P–O(3)	109.9 (1)	101.4	101.2
	C(1)–C(2)–C(3)	113.6 (1)	116.1	114.3
	C(2)–C(1)–C(1')	113.1 (1)	114.8	114.6
	C(2)–C(3)–C(3')	110.2 (1)	111.0	110.4
Dihedral angle (°)	P–C(1)–C(2)–P'	142.9 (1)	146.6	144.6
	P–C(1)–C(2)–C(3)	80.0 (1)	84.4	84.5
	P–C(1)–C(1')–C(2')	87.7 (1)	86.8	88.8
	C(2)–C(1)–C(1')–C(2')	41.6 (1)	39.8	37.7
	C(1')–C(1)–C(2)–C(3)	47.1 (1)	41.8	43.7
	C(1)–C(2)–C(3)–C(3')	56.7 (1)	44.5	54.3
	C(2)–C(3)–C(3')–C(2')	60.5 (1)	45.3	58.7

[a] Results of semi-empirical MNDO calculations with a continuum model for water phase.

Force Field and Semi-Empirical Calculations

NMR investigations of *trans*-cyclohexane-1,2-diphosphonic acid in solution suggest that during titration of this acid conformative equilibria vary. This behaviour should be modulated by calculation of isolated molecules. In order to evaluate the conformative equilibria and the population of the structures involved in these equilibria the differences of their energy levels are required. For the theoretical calculation of the conformers of the acid and anions at first we applied the semi-empirical MNDO methods MNDOC[14] and VAMP-PM3.[15,16]

The geometric data of energy optimization of semi-empirical calculations are included in Table I. Figure 5 shows the superposition of the calculated (MNDOC) and the measured structure of the acid. The spheres marked with a grid represent

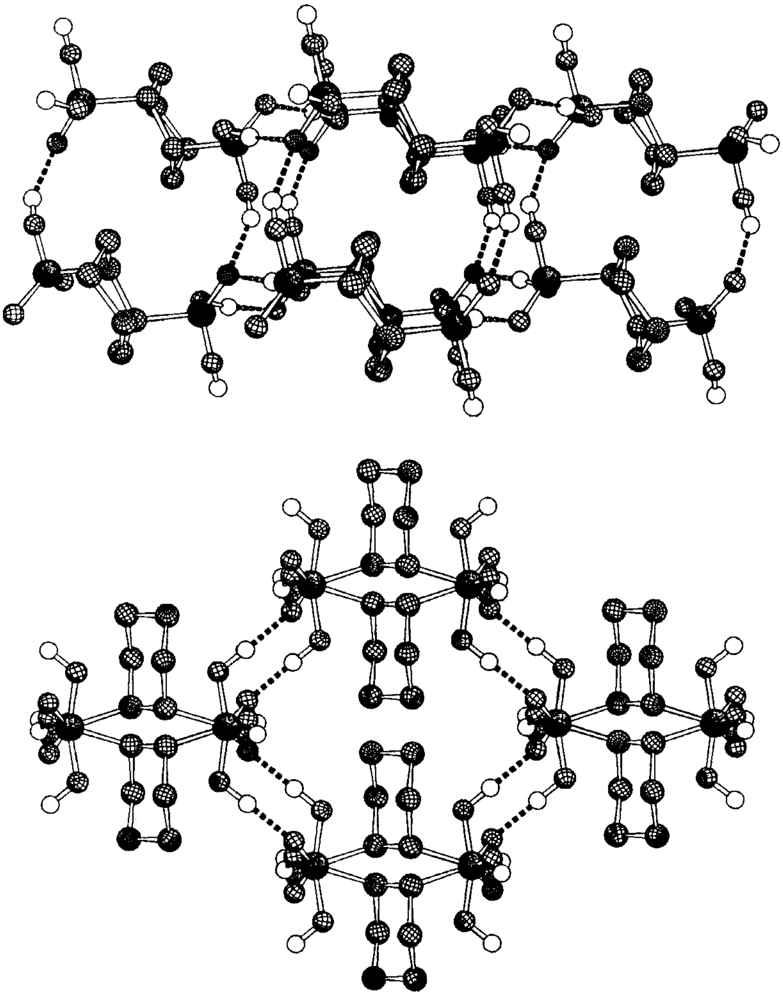
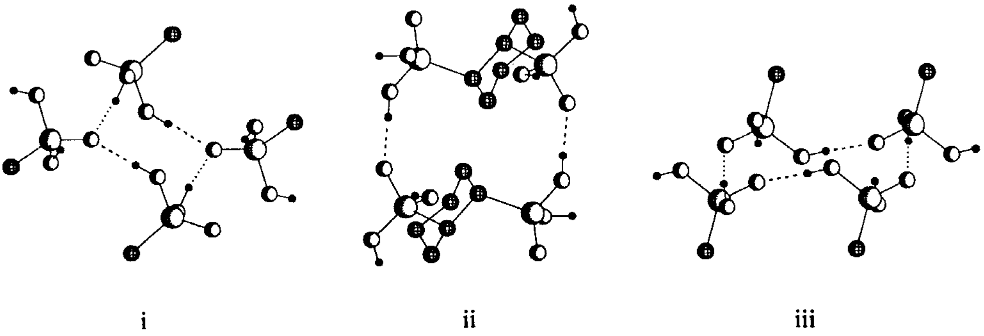


FIGURE 4 Fragment of the solid state structure of *trans*-cyclohexane-1,2-diphosphonic acid. Top: view along the crystallographic axis *b*; bottom: view along the crystallographic axis *c*.



SCHEME 5

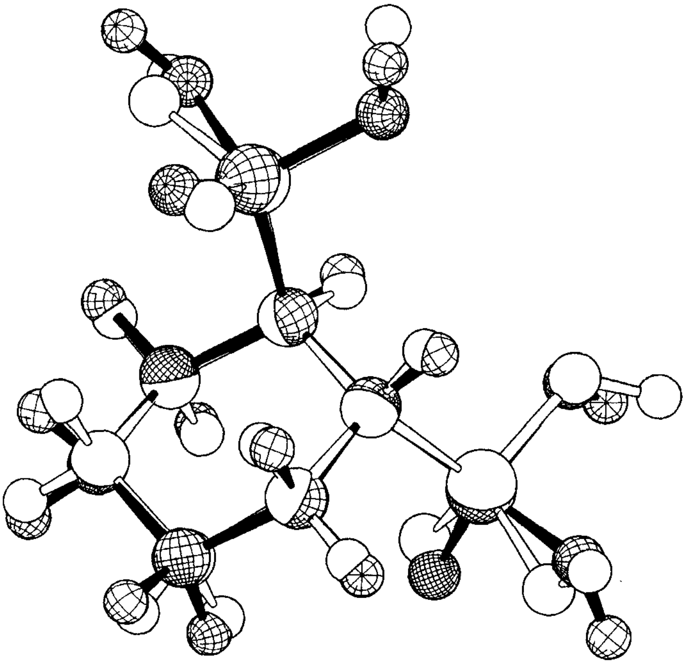


FIGURE 5 Molecular structure of *trans*-cyclohexane-1,2-diphosphonic acid. Spheres covered with a grid: MNDOC calculation; spheres covered without a grid: X-ray diffraction.

the atomic position of the calculated structure. The largest deviations between computed and measured structures are observed in case of the phosphonate groups. Especially the positions of the acid protons are rather different. Here effects of crystal packing become obvious. So the more interesting result consists in the statement that the P—C—C—P′ dihedral angle calculated for an isolated molecule is in a good agreement with the data of the crystal structure. It should be possible to conclude that similar values of the angle also occur in real solution. This dihedral angle is important for the discussion of the NMR experiment.

Acceptable results are obtained by MNDOC calculations concerning the bisaxial conformations of differently charged isolated anions and the bisequatorial conformations of the undissociated acid and of the single charged anion. In Table II bond energies and P—C—C—P′ dihedral angles obtained by geometry optimization are compiled.

Since counter ions are not taken into consideration in these calculations it seems that the anions become more instable with increasing charge. The bisaxial structures are slightly preferred from the energetical point of view, so the existence of these conformers in the crystalline state of the *trans*-cyclohexane-1,2-diphosphonic acid can be understood. Except of the slightly greater value found for the completely deprotonated anion all bisaxial conformers show almost the same dihedral angle.

Even if a bisequatorial starting geometry is used the geometry optimization for the multiply charged anions does not lead to local minima of these conformers but to the transition to a boat-like structure with P—C—C—P′ dihedral angles between 141° and 156°. On attempts to transform the bisequatorial starting geometry into

TABLE II

MNDOC-Calculations of heats of formation (kJ/mol) and of dihedral angles (°) for *trans*-cyclohexane-1,2-diphosphonic acid and its anionic species

Spezies[a]	ΔH°	$\varphi_{P\text{-}C\text{-}C\text{-}P}$
aa00	-299.8	146.8
ee00	-297.1	76.2
aa10	-326.5	147.9
ee10	-322.9	76.2
aa11	-278.1	145.0
aa21	-115.1	146.5
aa22	+124.5	152.7

[a] aa - bisaxial conformation, ee - bisequatorial conformation
xx - number of negative charges at both phosphonate groups

TABLE III

DISCOVER Calculations of total energies (kcal/mol) and dihedral angles (°) for *trans*-cyclohexane-1,2-diphosphonic acid and its anionic species with Na cations

Spezies[a]	E_{total}	$\varphi_{P\text{-}C\text{-}C\text{-}P}$
aa00	-105.3	155.5
ee00	-101.4	53.4
aa10na	-211.5	152.3
ee10na	-216.9	38.1
aa11na	-214.3	126.6
ee11na	-213.1	43.0
aa11na2	-349.3	152.8
ee11na2	-298.7	40.1
aa21na2	-410.8	152.8
ee21na2	-396.2	56.7
aa22na2	-390.0	156.5
ee22na2	-354.1	59.5

[a] aa - bisaxial conformation, ee - bisequatorial conformation
xx - number of negative charges at both phosphonate groups
na - one Na cation, na2 - two Na cations

the bisaxial conformation the calculation leads to a local minimum of the boat-like state. This result shows that especially in the case of higher charged ions the application of the MNDOC method can lead to wrong results since a boat-like structure is improbable in each case. The main reasons are the over-estimation of the repulsion of two similarly charged atoms or atomic groups[17] and the neglect of counter ions and water molecules, which mainly stabilize higher charged ions. For this reason force field calculations using the program DISCOVER[18] were carried out, where sodium ions represent the counter ions and parameters optimized for phosphonic acids[19] were used. The optimizations were carried out under consideration of Morse potentials and cross terms using the va09a method until a gradient of 0.001. It was shown in Table III that for most of the species the bisaxial form is calculated to be more stable while only ee10na and ee21na are energetically preferred. In Figures 6 and 7 the structures obtained after energy minimization are given.

The later discussed results of NMR spectroscopic investigation in aqueous solutions showing a dominance of bisequatorial species in the range of $\tau = 0 \ldots 3$ according to the coupling constant $^3J_{PP}$ are not correctly reflected by DISCOVER calculations of isolated molecules despite a consideration of the counter ions. Obviously, the bisequatorial species are stabilized by interaction with water molecules.

The calculations with respect to a structure optimization of the species described till now do not allow an interpretation of possible dynamic processes leading to a ring inversion. Therefore, molecular dynamics calculations on monosodium systems were carried out. The results are given in Figure 8. First the energy-time diagram is shown, the change of the P—C—C—P′ dihedral angles with the time and the conformation of the anion according to the optimized structure. The molecular dynamics simulations were carried out for a temperature of 600 K and a time of 5 psec. In each case 2500 structures and energy information were stored.

The highest stability of the bisequatorial form in case of anions with one, two and three charges is documented by the shortness of the simulated time till the

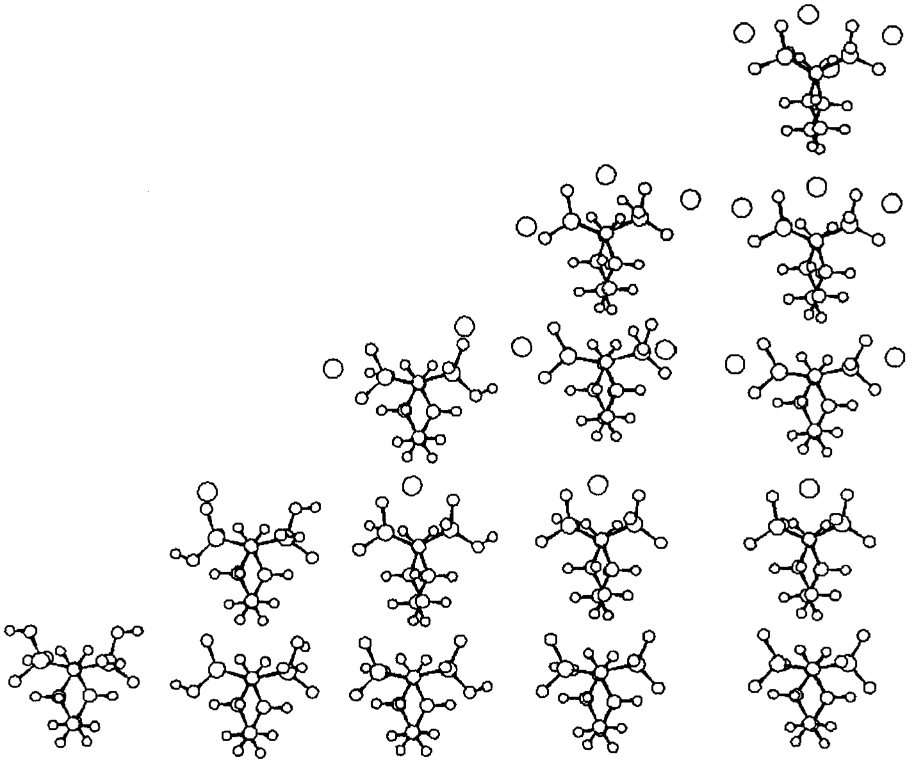


FIGURE 6 Molecular structure from DISCOVER calculations of the bisaxial conformations of *trans*-cyclohexane-1,2-diphosphonic acid and anionic species with Na cations.

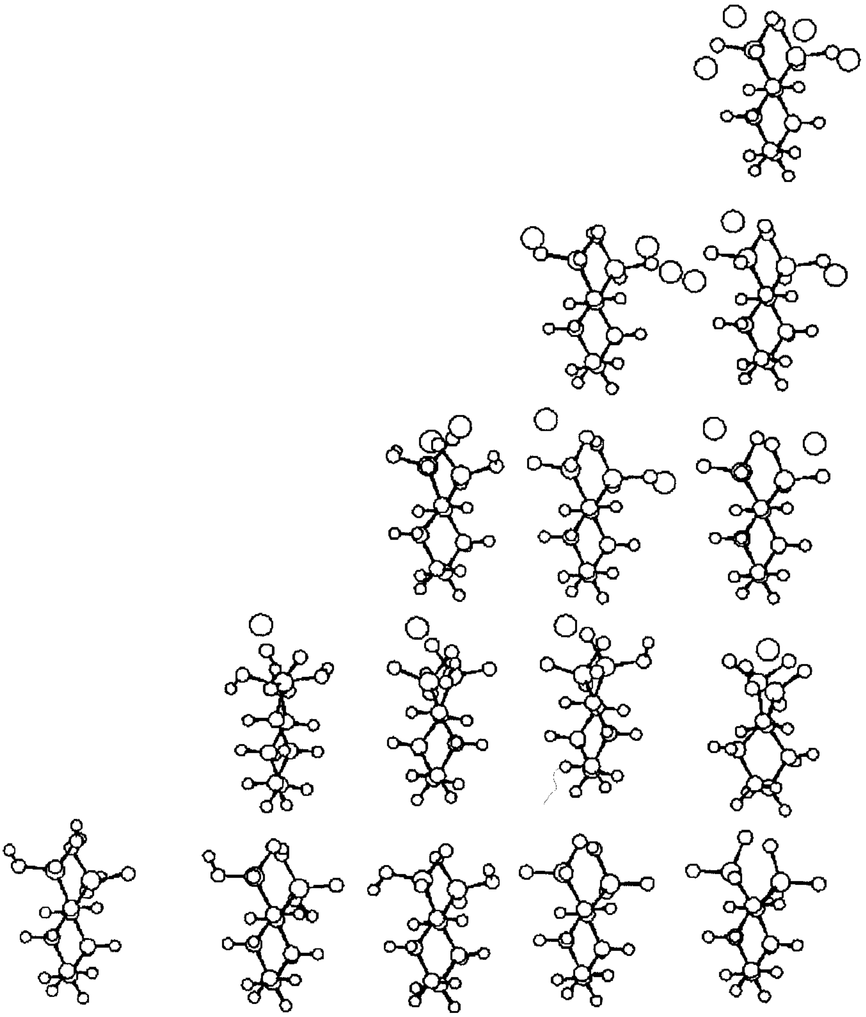


FIGURE 7 Molecular structure from DISCOVER calculations of the bisequatorial conformations of *trans*-cyclohexane-1,2-diphosphonic acid and anionic species with Na cations.

bisaxial structure (in all cases used as starting geometry) is converted into the bisequatorial conformation. These points are characterized by a large decrease in the energy-time graph. This transition is also obvious in the angle-time functions. It seems that the time required till the structural change occurs increases with the number of negative charges. But this should be incidentally since in the case of a single calculation almost at each time inside a certain expected range this change may occur. A more reliable information concerning the speed of changes is only possible on the basis of a statistic evaluation of a large number of analogous calculations, a significant increase of the simulation time or simultaneous calculation of a large number of anion-Na^+ systems. Since all three possibilities require much effort only one careful simulation was carried out. The complex of calculations suggest at least the possibility of inversion of the cyclohexane ring. The method

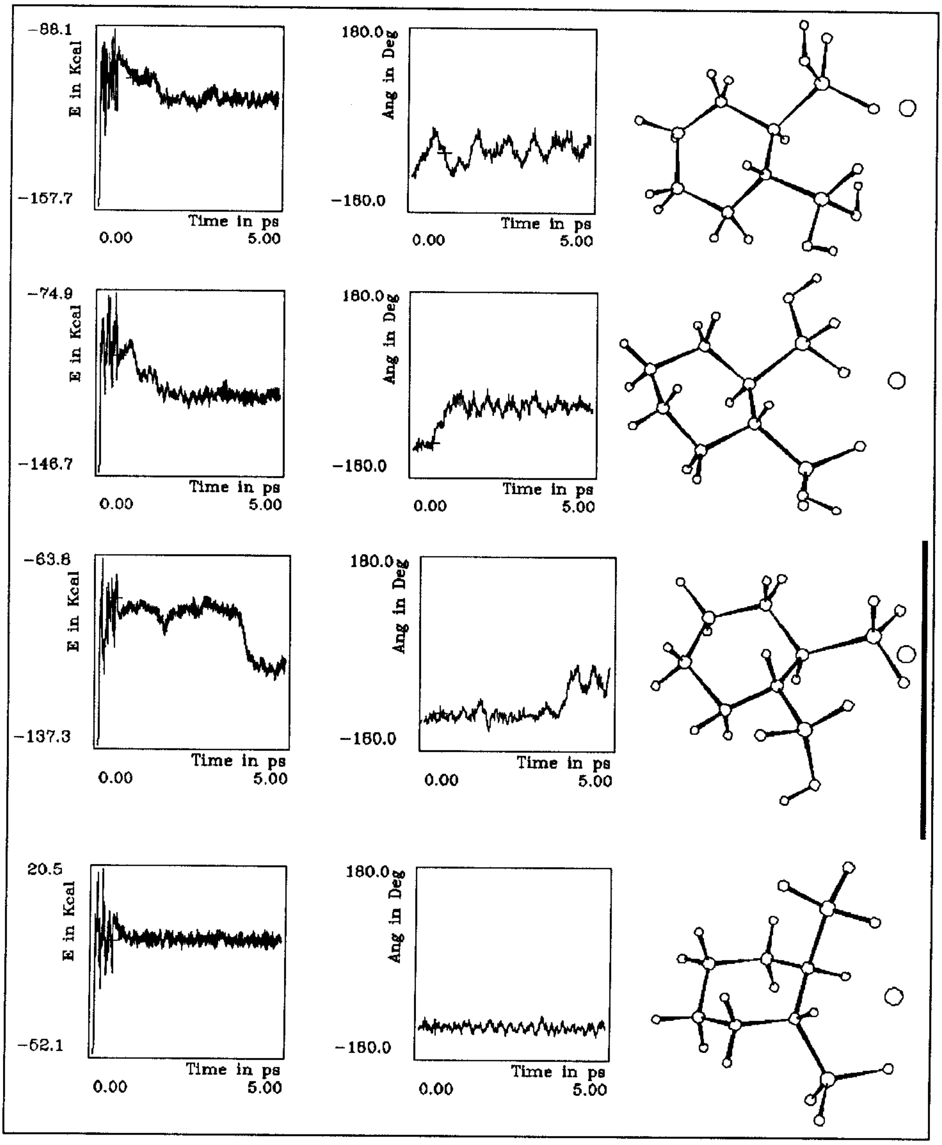


FIGURE 8 MD simulation of the n$^-$ ions of *trans*-cyclohexane-1,2-diphosphonic acid with one Na$^+$ ion. From top to bottom: n = 1, 2, 3, 4; from left to right: energy-time function, P—C—C—P dihedral angle-time function, structure of the optimized conformation.

of molecular dynamics simulation represents a good supplement of the experimental work.

NMR Spectroscopic Investigations

Both ^{31}P nuclei and the ^{13}C nucleus in the single marked isotopomers of *trans*-cyclohexane-1,2-diphosphonates form ABX spin systems due to the isotopy shift of the ^{13}C nucleus. As in the ^{13}C spectra (X part) the splitting of the inner line at δ_C is not visible the spectra can be interpreted like AA′X spectra.

The coupling constant $^3J_{PP}$ usually hidden in the $^{31}P\{^1H\}$ NMR spectrum can be obtained from the ^{13}C spectrum or from the ^{13}C satellites of the $^{31}P\{^1H\}$ spectrum. If all eight ^{13}C satellites are visible in the $^{31}P\{^1H\}$ spectrum (AA′ part) the three coupling constants $^3J_{PP}$, J_{PC} and $J_{P'C}$ can be determined easily. Often is takes less effort to find the four outer satellites, from which $^3J_{PP}$ can be read directly. In such cases J_{PC} and $J_{P'C}$ can be calculated from the ^{13}C spectrum. For a complete mathematical interpretation of the ^{13}C spectrum (X part of an AA′X spin system) the intensities of the 5-line spectrum must be considered. The usual parameters being applied are:

$N = |J_{PC} + J_{P'C}|$, distance of the normal lines,

$4D = [L^2 + 4(^3J_{PP})^2]^{1/2}$, distance between the combination lines,

with $L = |J_{PC} - J_{P'C}|$.

By means of the intensities I_i (inner line at δ_X) and I_0 (sum of the both outer lines) $^3J_{PP}$ and L can be determined[20]:

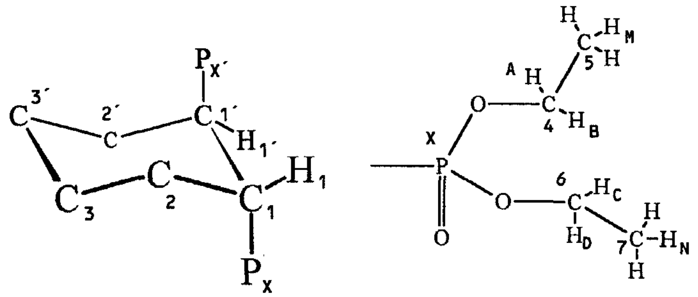
$$|J_{PP'}| = 2D\cdot[I_i/(I_0 + I_i)]^{1/2} \quad \text{and} \quad L = 4D\cdot[I_0/(I_0 + I_i)]^{1/2}.$$

From this the both PC coupling constants can be calculated:

$$J_{PC} = 0.5\cdot(N + L) \quad \text{and} \quad J_{P'C} = 0.5\cdot(N - L).$$

Analysis of these spin systems leads to the relative signs between $^nJ_{PC}$ and $^{n+1}J_{PC}$ of the carbon atoms of the cyclohexane ring ($^{n+3}J_{PC}$ for ester C atoms, respectively) provided that all lines of the AA′X spin system are visible. Since it is known[21] that in phosphonates the absolute sign of $^1J_{PC}$ and $^3J_{PC}$ is positive the absolute sign of $^2J_{PC}$ and $^4J_{PC}$ is obtained during spectra analysis.

The ^{31}P and ^{13}C NMR data of *trans*-cyclohexane-1,2-diphosphonic acid tetraethylester 2b are compiled in Table IV. Considering the known dependence of $^3J_{PP}$ on the dihedral angle[5] from the large value of this coupling constant the conclusion may be drawn that the bisaxial conformation of the phosphonyl groups is strongly preferred. Because of the γ-gauche arrangement P(1)—C(1)—C(2)—C(3) and P(1′)—C(1′)—C(1)—C(2) of this conformation only very small positive values[22,23] of $^3J_{PC}$ are expected. Together with the small negative coupling constants $^2J_{PC}$ and



SCHEME 6

TABLE IV

NMR data of *trans*-cyclohexane-1,2-diphosphonic acid tetraethyl ester

δ_P	$^3J_{PP}$[a]			δ_C $^nJ_{PC}$(n) $^mJ_{PC}$(m)			Temp. K
		1/1'	2/2'	3/3'	OCH_2	CH_3	(Solvent[b])
32.18	82.5	30.49 +139.0(1) -2.6(2)	22.04	22.03	61.96/61.64 6.6/7.1(2)	16.49/16.47 5.9(3)	298 ($CDCl_3$)
31.92	81.5	31.65 +140.5(1) -2.5(2)	23.01	23.00	63.66/63.44 6.9/7.2(2)	16.77/16.74 5.6/6.0(3)	298 (CD_3OD)
31.34	85.8	30.89 +139.7(1) -2.7(2)	22.81	22.52	62.26/61.92 6.2/7.0(2)	16.97/16.98 6.0/6.0(3)	238 (CD_3OCD_3)
31.32	86.1	30.67 +139.6(1) -2.7	22.77	22.44	62.24/61.87 6.5/7.0(2)	16.96/16.88 6.0/6.0	222 (CD_3OCD_3)
31.19	87.2	30.00 +139.5(1) -3.2(2)	22.62	22.16	62.19/61.82 5.8/6.6(2)	16.89/16.79 6.0/6.0(3)	180 (CD_3OCD_3)

[a] Obtained by analysis of the ^{13}C satellites in the ^{31}P spectrum

[b] Concentration: in $CDCl_3$ and in CD_3OD ca. 15 Vol%, in CD_3OCD_3 ca. 10 Vol%

$^4J_{PC}$ small N values result, hence for C(2) and C(3) resolved signals are not observed in the ^{13}C spectrum.

If the temperature is decreased $^3J_{PP}$ (Table IV) increases significantly since the equilibrium of the conformers is shifted further to the bisaxial form. However, the portion of the bisequatorial conformer is so small that the direct observation of the "slow" conformative change at 180 K does not succeed. A forthcoming publication[24] will report special dynamic NMR investigations on cyclohexane-1,2-diphosphonates.

In Table V ^{31}P and ^{13}C NMR data of aqueous solutions of *trans*-cyclohexane-1,2-diphosphonic acid 2a at different concentrations and titration degrees are compiled. Here the change of the ^{31}P chemical shift and the coupling constants $^3J_{PP}$ and $^3J_{PC}$ in dependence on the titration degree τ are of a special interest. For the determination of the τ dependent ^{31}P chemical shift the stopped-flow-method[11] was used in the case of solutions of low concentration, but for the investigation of higher concentrated solutions and the registration of ^{13}C spectra samples of defined concentration were prepared by weighing both components (acid and NaOH). Figure 9 shows the results of the titration obtained with a starting concentration of 0.01 mol/l. The ^{31}P chemical shift decreases till $\tau \approx 3$ and then increases. The same result is obtained if a 0.7 molar solution is investigated. The ^{13}C chemical shifts of all carbon atoms show the opposite behaviour; they attain a maximum at $\tau \approx 3$.

In Figure 9 the function Z(H) computed from the acid constants pK is drawn. This function shows the mean number of protons bound to the anion

TABLE V

NMR data of *trans*-cyclohexane-1,2-diphosphonic acid

Medium	Conc. mol/l	τ	$^3J_{PP}$	P_{ee}[d]	δ_C $^nJ_{PC}$ (n) $^mJ_{PC}$ (m)		
					1/1'	2/2'	3/3'
H_2O/NaOH	0.1	0.0	+20.0[a]	0.82	35.51	26.10	24.43
					+131.4 (1)	−5.2 (2)	+12.7 (3)
					−2.9 (2)	+11.9 (3)	−2.0 (4)
		1.0	+11.7	0.91	37.08	27.61	26.14
					+130.3 (1)	−5.3 (2)	+13.9 (3)
					−2.9 (2)	+13.5 (3)	−2.0 (4)[b]
		2.0	+10.2	0.91	38.04	28.14	26.14
					+130.2 (1)	−5.1 (2)	+13.7 (3)
					−2.9 (2)	+13.5 (3)	−2.0 (4)[b]
		3.0	+8.5	0.93	38.68	28.62	26.63
					+128.2 (1)	−3.9 (2)	+12.8 (3)
					−2.4 (2)	+12.6 (3)	−1.0 (4)[b]
		4.5	+60.5	0.12	35.24	24.56	23.63
					+127.5 (1)	no resolved	no resolved
					−2.4[b]		
		6.0	+63.5[a]	0.05	34.26	23.53	22.60
					+127.4 (1)	no resolved	no resolved
					−1.9 (2)		
H_2O/NAOH/ CD_3OD[c]	0.7	0.0	+25.2[a]	0.76	35.66	26.28	24.78
					+132.8 (1)	−5.1 (2)	+11.6 (3)
					−2.9 (2)	+10.6 (3)	−2.0 (4)
		1.0	+11.1	0.92	36.86	27.39	25.54
					+130.5 (1)	−4.7 (2)	+13.9 (3)
					−2.9 (2)	+13.1 (3)	−2.0 (4)[b]
		2.0	+9.1	0.93	38.00	28.06	26.04
					+130.3 (1)	−5.2 (2)	+13.6 (3)
					−2.9 (2)	+13.5 (3)	−2.0 (4)[b]
		3.05	+10.7[a]	0.89	38.38	28.25	26.30
					+128.5 (1)	−4.1 (2)	+12.3 (3)
					−2.5 (2)	+12.1 (3)	−1.0 (4)
		4.0	+61.5[a]	0.10	34.96	24.34	23.39
					+128.1 (1)	no resolved	no resolved
					−2.5 (2)		
		5.0	+66.6[a]	0.01	34.67	24.03	23.17
					+128.1 (1)	no resolved	no resolved
					−2.4 (2)		
D_2O/KOD/ CD_3OD[c]	0.7	2.0	+9.0	0.93	38.24	28.18	26.12
					+130.4 (1)	−5.2 (2)	+13.6 (3)
					−2.9 (2)	+13.5 (3)	−2.0 (4)[b]

[a] Obtained by analysis of the ^{13}C satellites in the ^{31}P spectrum

[b] Assumed value from analogous results received by analysis of the ^{13}C satellites in the ^{31}P spectrum

[c] Ca. 15 Vol. % CD_3OD

[d] Part of the bisequatorial conformation

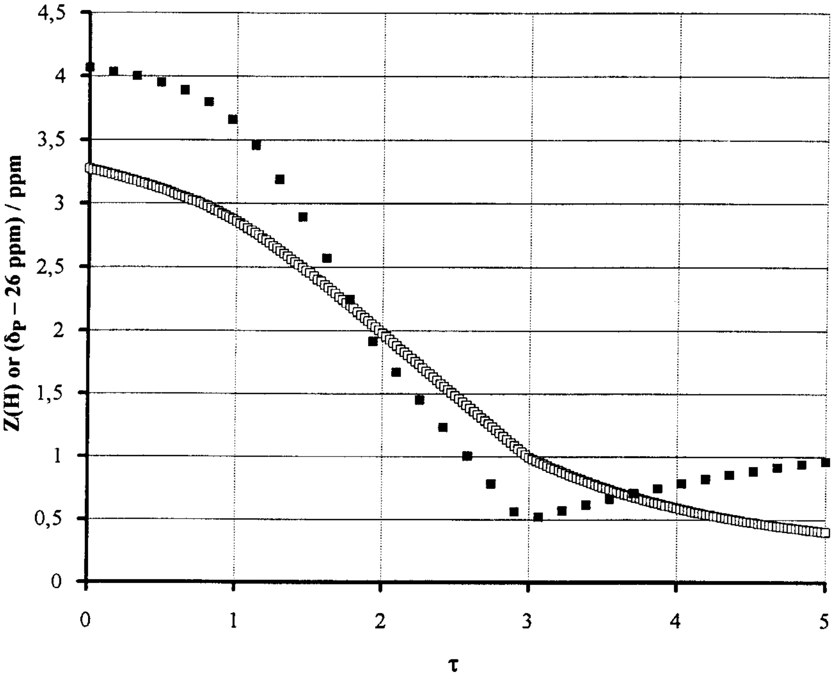


FIGURE 9 ^{31}P NMR titration curve of *trans*-cyclohexane-1,2-diphosphonic acid with NaOH and calculated from the acid constants pK_a the mean number Z(H) of protons bound to the anion $C_6H_{10}O_6P_2^{4-}$. ■—Titration curve; □—Z(H) curve.

$C_6H_{10}O_6P_2^{4-}$ (H_ZL^{Z-4}). From Figures 2 and 9 it becomes obvious that practically at a titration degree of $\tau = 2$ only the anion $C_6H_{12}O_6P_2^{2-}$ occurs and at $\tau = 3$ the triple charged anion $C_6H_{11}O_6P_2^{3-}$ dominates. In the opposite at other titration degrees different species occur simultaneously. The four-negative anion $C_6H_{10}O_6P_2^{4-}$ can be obtained as the main component only if the acid concentration is high enough and a significant excess of sodium hydroxide is present.

The vicinal coupling constants $^3J_{PP}$ compiled in Table V were, if possible, determined from ^{13}C satellites in the ^{31}P{^{1}H} spectra with the accuracy of the point distance of 0.2 Hz. This value was later used for the analysis of the ^{13}C spectra and the calculation of the both $^3J_{PP}$ values. In order to obtain $^3J_{PP}$ values as exact as possible in the case of solutions characterized by relatively broad ^{31}P lines the coupling constant $^4J_{PC}$ of C(3/3′) several times determined to −2.0 Hz from ^{13}C satellites of ^{31}P{^{1}H} spectra was applied for the calculation of $^3J_{PP}$ and $^3J_{PC}$ from the C(3/3′) signal. The hereby computed coupling constant $^3J_{PP}$ was used for the analysis of the C(1/1′) and C(2/2′) signals.

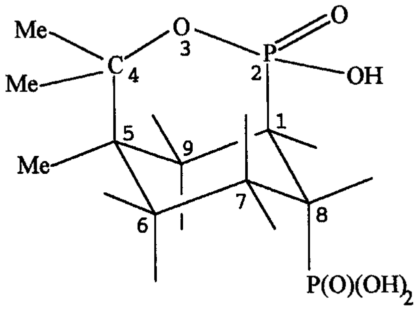
In the opposite to the corresponding tetraethylester 2b *trans*-cyclohexane-1,2-diphosphonic acid 2a shows a coupling constant $^3J_{PP}$ with values reduced to 20–25 Hz. This effect demonstrates a drastic shift of the equilibrium of conformers in direction of the bisequatorial structure. By ^{31}P spin tickling in ^{13}C measurements[5] and ^{31}P—^{13}C shift correlated 2D spectra[25] we confirmed the positive sign of the vicinal coupling constant also by varying the titration degree from $\tau = 0$ to $\tau = 5$.

For a quantitative estimation of the ratio of conformers the change of the coupling constant of a bisaxial conformation $^3J_{aa}$ in dependence on the titration degree had to be studied. For this investigation a conformatively fixed compound like 2-hydroxy-8-dihydroxyphosphoryl-4,4,5-trimethyl-2-oxo-3-oxa-2-phosphabicyclo[3.3.1] nonane is suited which was obtained in the experiment to prepare *cis*-4-*tert*-butylcyclohexane-*trans*-1,2-diphosphonic acid.

From the behaviour of 3 during titration and further investigations[26] the values of $^3J_{aa}$ and $^3J_{ee}$ compiled in Table VI were derived. Presuming that in 3 similar P(1)—C(1)—C(1′)—P(1′) dihedral angles like in 2a occur the portion of the bisequatorial conformer p_{ee} in aqueous solutions of *trans*-cyclohexane-1,2-diphosphonic acid can be estimated:

$$p_{ee} = \frac{^3J_{aa} - {}^3J_{PP}}{^3J_{aa} - {}^3J_{ee}} .$$

In Table V the calculated portions of the bisequatorial conformation are given. Although the dihydroxyphosphonyl group is smaller compared with the dialkoxyphosphonyl group this fact cannot be the reason for the drastic preference of the bisequatorial form of 2a. Probably, the formation of intramolecular hydrogen bonds is responsible for this result (Figure 10). Obviously, the strength of these bonds is highest at $\tau = 3$ although only one acidic proton is present and both phosphonyl groups have one or two negative charges. Only when the last proton has been removed and the formation of hydrogen bonds has become impossible the elec-



SCHEME 7

TABLE VI
Assumed coupling constants for bisaxial and bisequatorial conformations $^3J_{aa}$ and $^3J_{ee}$

τ	$^3J_{aa}$	$^3J_{ee}$
0...1	$86 - 6\tau$	$6 - \tau$
1...2	$80 - 5(\tau - 1)$	$6 - \tau$
2...3	$75 - 4(\tau - 2)$	$6 - \tau$
3...4	$71 - 3(\tau - 3)$	3
4...5	$68 - 1(\tau - 4)$	3
>5	67	3

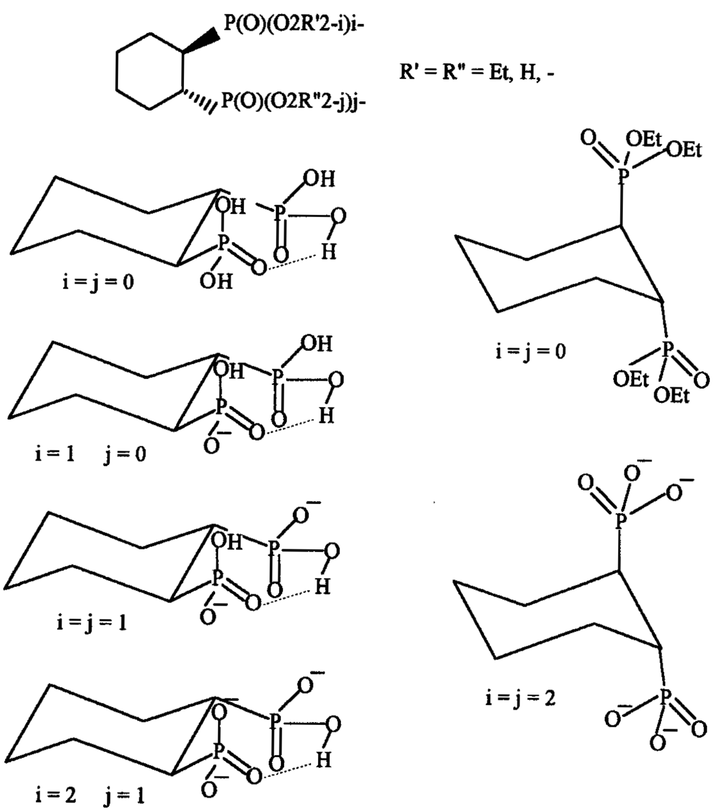


FIGURE 10 Preferred conformations in related species of *trans*-cyclohexane-1,2-diphosphonates.

trostatic repulsion of the both twofold negatively charged phosphonyl groups leads to the bisaxial conformation.

The strong preference of the bisequatorial conformation up to a titration degree of $\tau \approx 3$ is also reflected by the large values of $^3J_{PC}$ between 12–13 Hz, which are characteristic for trans arrangements of P—C—C—C.

^{31}P and ^{1}H solid state NMR spectra are in agreement with results of the crystal structure analysis. The ^{31}P-CP-MAS spectrum shows due to the centrosymmetry of the crystal only *one* sideband system from which the isotropic value and the principal values of the chemical shift tensor can be determined:

$$\delta_{iso} = 35.8 \text{ ppm} \quad \delta_{11} = 66 \text{ ppm} \quad \delta_{22} = 52 \text{ ppm} \quad \delta_{33} = -10 \text{ ppm}.$$

These values are quite similar to those of the ethane-1,2-diphosphonic acid.[27] Because of effects of substituents in β-position higher values are found for δ_{11} and δ_{33}.

In a ^{1}H-CRAMPS-spectrum of crystalline *trans*-cyclohexane-1,2-diphosphonic acid the signal of the acidic protons occurs at 10 ppm confirming the presence of intermolecular hydrogen bonds only. For intramolecular hydrogen bonds Scheler, Haubenreisser and Rosenberger[28] have found in several solid acids values from 16 to 19 ppm.

TABLE VII

Summary of the crystal structure determination for $(HO)_2P(O)C_6H_{10}P(O)(OH)_2$

Crystallographic section		
empirical formula	$C_6H_{14}O_6P_2$	
molecular mass	244.1	
lattice constants	a = 13.377(3) Å	α = 90 °
	b = 7.749(2) Å	β = 100.00(2) °
	c = 9.499(2) Å	γ = 90 °
V (Å^3)	969.7(3)	
Z	4	
d_{calc} (gcm^{-3})	1.668	
crystal system	monoclinic	
space group	C 2/c	
Data collection		
diffractometer	Nicolet R3m/V	
radiation	MoK_α	
monochromator	graphite, $\lambda = 0.71069$	
crystal size (mm)	0.23 x 0.19 x 0.17	
data collection mode	Wyckoff, ω: 0.8°	
2θ range (°)	3 - 60	
no. refl.measd.	1306 ($F_0 \geq 4\sigma(F)$)	
no. unique refl.	1420	
Structural analysis and refinement		
solution by	Direct phase determination Full-Matrix LSQ.Hydrogen positions of riding model with fixed isotropic U	
data-to-parameter ratio	14.2	
R ; R_W	0.029 ; 0.035	
weighting scheme	$w^{-1} = \sigma^2(F_0) + 0.00023(F)^2$	
largest difference peak	0.41 eÅ^3	
largest difference hole	0.30 eÅ^3	
program used	SHELXTL-PLUS	

EXPERIMENTAL

Synthesis

Cyclohexene-1-phosphonic acid diethyl ester 1b*:* To 50 g (0.31 mol) cyclohexene-1-phosphonic acid 1a (HOECHST AG, Knapsack) recrystallized from acetone 500 ml *ortho*-formic acid triethylester were added and refluxed. The ethanol formed during the reaction was continuously removed by distillation. After the ethanol generation stopped excessive *ortho*-formic acid triethylester and formic acid ethylester were removed by vacuum. The slightly yellow oily residue was fractionally distilled under oil rotatory pump vacuum: Clear, colourless liquid, boiling point: 70–72°C/0.01 Torr (Reference: 100–102°C/0.2 Torr[29]). δp: 19.66 ppm (50% in C_6D_6). Yield: 61 g cyclohexene-1-phosphonic acid diethylester 1b (90.2% with respect to 1a).

Elemental analysis: C: 55.03% (54.55), H: 8.8% (9.04), P: 14.2% (13.3) (calculated values in brackets). Data of ^{13}C spectrum (10% in C_6D_6): C1: 129.39 ppm, $^1J_{PC}$ = 180.1 Hz; C2: 141.99 ppm, $^2J_{PC}$ = 9.1 Hz; C3: 26.17 ppm, $^3J_{PC}$ = 18.0 Hz; C4: 21.95 ppm, $^4J_{PC}$ = 1.5 Hz; C5: 22.46 ppm, $^3J_{PC}$ = 9.8 Hz;

C6: 24.73 ppm, $^2J_{PC}$ = 8.6 Hz; C7(OCH_2): 61.07 ppm, $^2J_{PC}$ = 5.5 Hz; C8($OCH_2\underline{C}H_3$): 16.62 ppm, $^2J_{PC}$ = 5.8 Hz. This data are quite similar to those of the cyclohexene-1-phosphonic acid.[30]

trans-Cyclohexane-1,2-diphosphonic acid tetraethylester 2b: 3.4 g NaH (98%, 0.137 mol) were suspended in 50 ml absolute THF in a 250 ml round naked flask with refluxer, dropping funnel and N_2-inlet and cooled down to 0°C. During one hour 18.9 g (0.137 mol) diethylphosphite were added dropwise keeping the temperature of the mixture below 5°C. After adding the diethylphosphite the mixture was stirred at the same temperature until the sodium hydride was dissolved completely and a clear, slightly brown solution was obtained. During three hours under further cooling 30 g (0.137 mol) cyclohexene-1-phosphonic acid diethylester 1b were added, then while stirring the solution was warmed up to ambient temperature and allowed to stay unchanged over night. After an NMR control measurement the reaction mixture was heated to 40°C for several days till the edukt signals in the $^{31}P\{^1H\}$ NMR spectrum disappeared. Only one intensive signal at 32 ppm resulted. Finally, while cooling with ice glacial acetic acid was added dropwise till the solution became neutral (pH-indicator paper). THF and other slightly volatile side products were removed by vacuum. After addition of 50 ml methylenechloride it was washed four times with 20 ml water in order to remove sodium acetate and other water-soluble compounds. After removal of the solvent the residue was fractionated in oil pump vacuum. Boiling point: 130–133°C/0.01 Torr (Reference: 165°C/0.3 Torr[6]). Yield: 36 g 2b (73% with respect to 1b). Colourless and nonsmelling, viscous liquid. δ_P = 32.37 ppm (50% in C_6D_6).

trans-Cyclohexane-1,2-diphosphonic acid 2a: 15 g (0.042 mol) cyclohexane-1,2-diphosphonic acid tetraethylester 2b were refluxed with 200 ml concentrated hydrochloric acid using a round naked flask with refluxer and mercury safety valve. The solution became deeply red coloured, and changed to a pale orange after several hours. At this moment 50 ml of concentrated hydrochloric acid were added and the mixture was heated for four hours. Water and other liquid products were removed by vacuum, the crude acid was obtained as a pale pink precipitate. It was recrystallized from water with considerable loss. Yield: 6 g 2a (58% with respect to 2b). Melting point: 225°C (Reference: 216–219°C[6]). Well soluble in water.
Elemental analysis: C: 29.30% (29.52), H: 5.78% (5.88), P: 25.30% (25.38).

Crystal structure

The experimental conditions of the crystal structure determination are summarized in Table VII. For graphical presentation the programs COSMOS[31] and SCHAKAL[32] were used.

Theoretical calculations

The theoretical calculations were performed at the computer systems Siemens 7.780 S and Silicon Graphics Personal IRIS 4D20G of the Düsseldorf Laboratory.

NMR spectra

The NMR spectra were recorded on the BRUKER instruments MSL 300 or WH 90, both equipped with a ^{13}C-^{31}P-^1H triple resonance probehead, an external synthesizer and a transmitter for ^{31}P in the Dresden Laboratory and on an AC 200 in the Düsseldorf Laboratory.

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