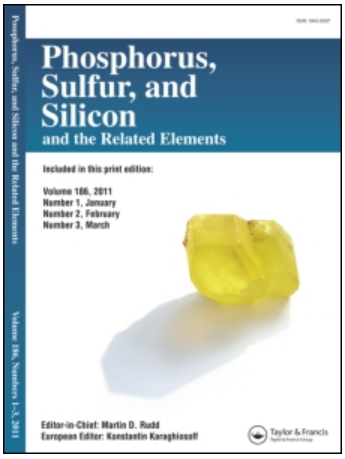

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1-*N*-PHENYLAMINO-1-PHENYL-METHANEPHOSPHONIC ACID DIETHYL ESTER: QUANTUM MECHANICAL AND FORCE FIELD STUDIES

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1-*N*-PHENYLAMINO-1-PHENYL-METHANEPHOSPHONIC ACID DIETHYL ESTER: QUANTUM MECHANICAL AND FORCE FIELD STUDIES

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Using Molecular Modelling methods like Molecular Mechanics (MM), systematic conformational searches and Molecular Dynamics (MD) simulations (QUANTA 3.3.1/CHARMm 22) in combination with semi-empirical methods (MOPAC 6.0 PM3, VAMP 4.4 PM3) the conformational aspects of 1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester were investigated in order to find the most stable conformers. The results of our quantum mechanical structural analysis are in good agreement with the conformations obtained from X-ray diffraction studies. It is shown that PM3 reproduces quite well experimental geometries including phosphorus atoms in α-amino-phosphonic ester derivatives.

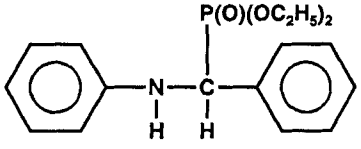
Key words: Molecular Modelling, aminophosphonic acid esters, biorelevance, NMR spectra, conformational search.

INTRODUCTION

α-Aminophosphonic acids, as well as their precursors and derivatives, being the analogues of naturally occurring α-aminoacids, have attracted considerable attention in recent years. First of all, the preparative chemistry of such compounds is extremely interesting, many different reactions have been reported in literature with the aim of improving yields and looking for new and facile synthetic routes.[1]

In search of an improved understanding of the reactivity of such compounds, physicochemical measurements were rationalised in terms of known and accepted theories on electronic distributions and bond formation.[2] However, the majority of hitherto known studies reported on α-aminophosphonic acids and their derivatives, which were and still are related to their biological activities and complexation properties towards biorelevant metal ions such as Ca^{2+}, Mg^{2+}, Zn^{2+}, Cu^{2+}, etc. In fact, some of these compounds were found to be active as enzyme inhibitors, herbicides, fungicides and as modifiers of crucial biological mechanisms in microorganisms.[3] The large number of patents reported for the synthesis of different aminophosphonic derivatives, in conjunction with their use as anti corrosive agents and metal sequestering molecules, indicates the commercial and industrial relevance of such compounds.

It is well known and supported that some chemical properties and modes of action of several compounds may be predicted by theoretical and computer aided studies, i.e. by chemometric methods which are based on the multi variate analyses of different characteristics of classes of molecules investigated.[4] Therefore, in order to contribute to the understanding of the molecular geometry and electronic properties of some α-aminophosphonic acid derivatives we used the molecular mechanics approach to compute the preferred conformations adopted in a hypothetical gas phase and in the solution state of compounds derived from the model system 1:



1

of which solid state geometries and connectivities solved by x-ray structural analyses,[5] where already described in the open literature.[6,11]

In this paper we report on the results of mechanical and semi-empirical calculations to predict conformational properties of 1 with the aim of rationalising some experimental results obtained for α-aminophosphonic acid derivatives.

COMPUTATIONAL PROCEDURES

All the molecular dynamic (MD) simulations and the systematic conformational searches were calculated with the program package QUANTA 3.3.1/CHARMm 22.[7] The atomic partial charges taken into account in the simulations were obtained from calculations with MOPAC 6.0 PM3.[8]

The main dihedral angles responsible for the molecular conformation including rotations around the Ph—N, N—C, C—P and C—Ph axis are investigated by systematic conformational searches (torsion forcings, involving one or two dihedral angles simultaneously) and by MD simulations at two temperatures (300 K, 700 K; simulation period: 50 ps and 90 ps).

After having finished the conformational analyses all following geometrical optimisations were performed using the program MOPAC 6.0 PM3 (keywords: precise nointer bonds localise vectors density graph). PM3 is used since it has the hitherto best parameterisation of phosphorus atoms to optimise the molecular geometry and to calculate the heat of formation.[9] The molecular modelling studies were done using the force field and the semi-empirical software packages running on a Silicon Graphics INDY workstation and a Convex C220 computer.

Additional calculations including solvent effects were made with CHARMm (15 Å sphere, $CHCl_3$) and VAMP 4.0[10] PM3 (SCRF, cavity = 1.0, $CHCl_3$). The resulting structures for the hypothetical gas phase and the $CHCl_3$ solution do not show significant differences. This fact is more or less expected, since 1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester 1 is a non-charged molecule and the solvent $CHCl_3$ has a low dielectric constant. $CHCl_3$ is used for solvent

in simulations since experimental results are obtained from ^1H NMR spectra of 1 in $CDCl_3$ solution.

COMPUTATIONAL RESULTS

The solid state conformation of 1 is reported in Figure 1[6,11]:

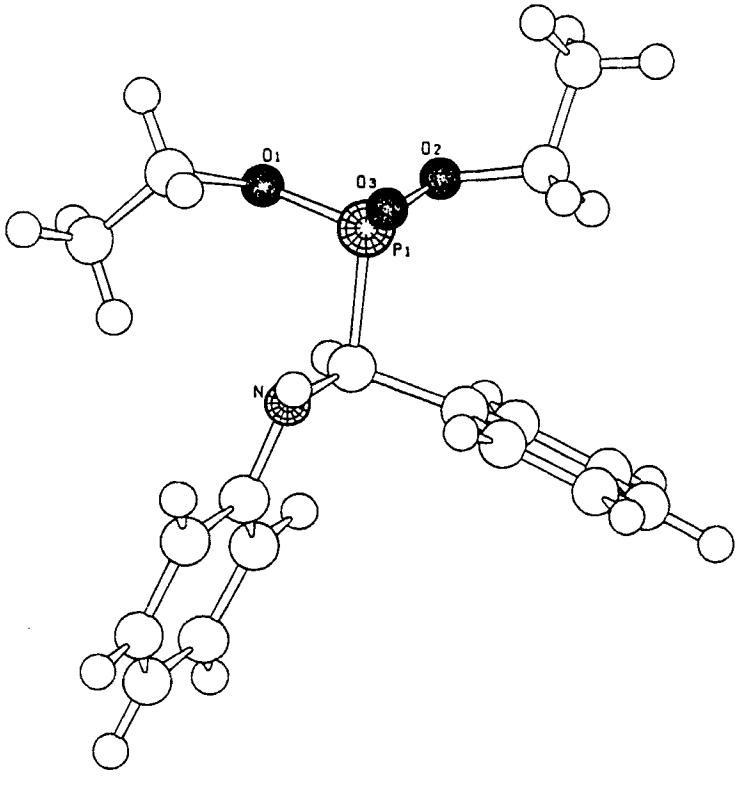


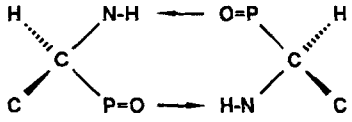
FIGURE 1 Solid state conformation of 1 obtained from X-ray studies.

The following salient structural characteristics were found:

—The hydrogens bonded to the chiral carbon and to the nitrogen in the H—N—C—H moiety are oriented in anti position, while both phenyl rings show syn conformation. Both rings are slightly twisted in order to relieve sterical interactions. The planes of the phenyl rings are practically perpendicular to each other with a dihedral angle of 89.9°.

—The nitrogen atom is considerably flattened with an increased C—N—C bond angle of 121.71°.

—Because of the parallel orientation of the N—H and the P=O bonds, cyclic dimers with N—H ← O=P and P=O → H—N hydrogen bridge bonds are formed.



—The pair of chiral methine carbon atoms give rise to the formation of S,S and R,R enantiomers in the solid state which are tightly bound together by O—H—N bridges.[11,12]

Since the methine carbon of 1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester 1 is chiral, two enantiomeric forms exist in solution. For the sake of simplicity only the S-configuration has been studied by the following conformational analysis.

The most important dihedral angle for the conformation analysis of 1 refers to the rotation around the C—P axis. To obtain rotational barriers torsion forcings were made from 0° to 360° in steps of 10°. Additional geometry optimisations were done for each selected value of the H—C—P=O dihedral angle. The conformation with the trans position of the H—C—P=O group is found as the global structural energy minimum, whereas the gauche conformers represent local minima. The rotation around the C—P axis is hindered by a rotational barrier of 25.9 kcal/mol as calculated from torsion forcing with CHARMm and MOPAC PM3.

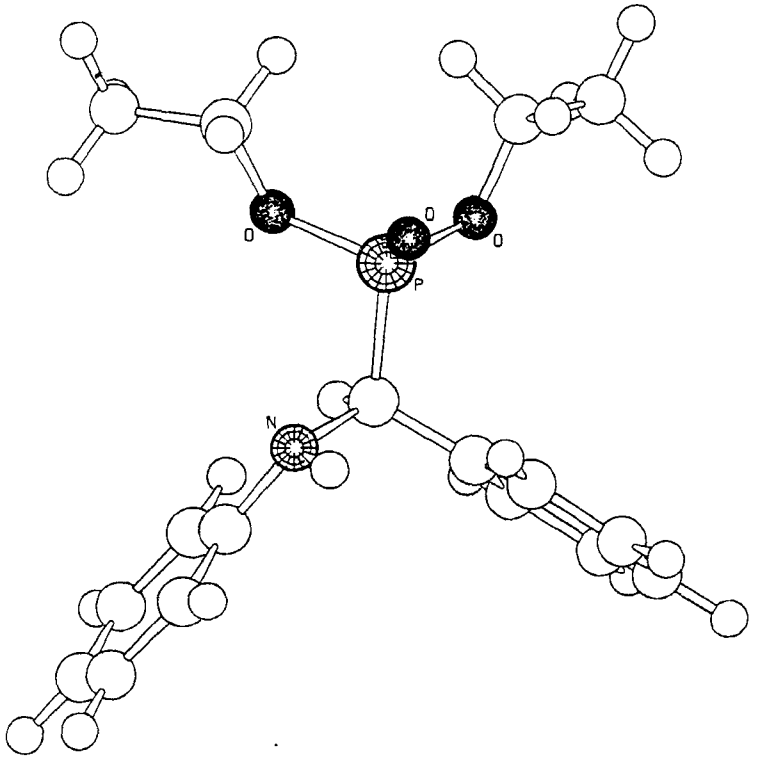


FIGURE 2 Structure of 1 with S configuration, optimised with MOPAC 6.0 PM3.

The optimised most stable conformer obtained from the torsion forcing simulations is used as start geometry for the MD simulations at different temperatures of 300 K and 700 K resp. over simulation periods of 50 ps and 90 ps to investigate the flexibility of the structure.

As result from the systematic search and dynamic simulation the global energy minimum of the structure is shown in Figure 2, which was found to be the most energetic stable conformation of the S-1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester.

A high stability is found for this conformation during the dynamic simulations. The H—C—P=O dihedral angle vary in a range of 20 degree around the anti-position. In opposite to the C—P axis the H—C—N—H dihedral angle vary in a large range of ±40 degree. The H—C—N—H skeleton shows anti conformation where the N—H bond is nearly located in the same plane as the nitrogen bonded phenyl ring (H—N—C_{Ar}—C_{Ar} = 24.9°; N—C_{Ar}—C_{Ar}—H = −5.3°). The dihedral angle between both phenyl ring planes is 98°. This agrees well with experimental observations on the ^{1}H-NMR spectra of 1 and related derivatives. With variable temperature (VT)-^{1}H-NMR measurements from ambient temperature to +100°C no significant conformation changes are observed.

NMR SPECTROSCOPIC EVIDENCE

200 MHz ^{1}H NMR studies at ambient temperature clearly indicate two ethoxy functions characterized by well separated individual signals of individual CH_3—C methyl and C—CH_2—O methylene groups. A corresponding spectrum of 1 in $CDCl_3$ solution is shown in Figure 3.

These strong non-equivalence effects are not necessarily caused solely by restricted rotations around one or several of the P—C, P—O, O—C or C—C bonds. More likely specific orientations of individual P—O—CH_2—CH_3 groups with respect to the aromatic ring planes of both phenyl substituents in 1 will give rise to individual aromatic ring current effects. As a consequence a superposition of two

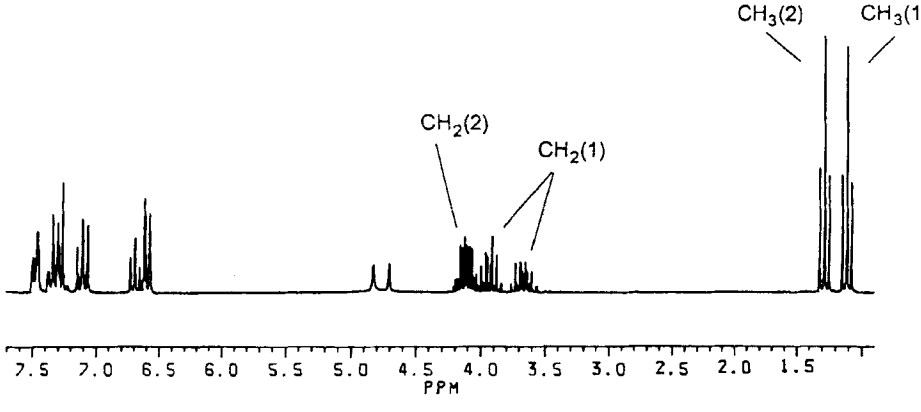
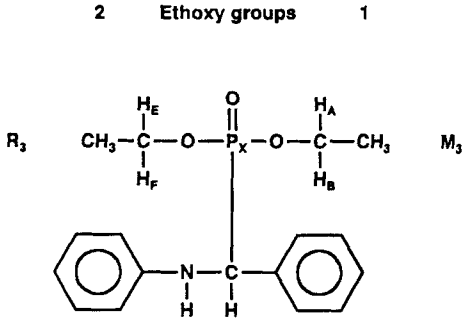


FIGURE 3 200 MHz ^{1}H NMR spectrum of 1 in $CDCl_3$ solution.

individual ABM_3X and EFR_3X spectra are observed in the ethoxy region of the ^1H NMR spectrum:



Analysis and iteration of the ABM_3X and EFR_3X parts of the ^1H NMR spectra using methods and programs described in Reference 13 lead to NMR data for the ethoxy groups as given in Table I:

TABLE I

200 MHz ^1H NMR data of 5% 1 in $CDCl_3$ solution. Chemical shifts δ [ppm], resonance frequencies ν [Hz] and coupling constants $^nJ_{XY}$ [Hz] of methylene and methyl protons

Ethoxy group 1	
Protons	Chemical Shifts δ [ppm]
H_A	3.933
H_B	3.660
CH_3 (M_3)	1.108
	Resonance Frequencies ν [Hz]
H_A	787.1
H_B	732.4
CH_3 (M_3)	221.7
	Coupling Constants $^nJ_{XY}$ [Hz]
J_{AB}	-10.12
J_{AM}	7.12
J_{AX}	7.13
J_{BM}	7.06
J_{BX}	8.24
J_{MX}	0.64

Ethoxy group 2	
Protons	Chemical Shifts δ [ppm]
H_E	4.144
H_F	4.077
CH_3 (R_3)	1.281
	Resonance Frequencies ν [Hz]
H_E	829.4
H_F	816.0
CH_3 (R_3)	256.4
	Coupling Constants $^nJ_{XY}$ [Hz]
J_{EF}	-10.16
J_{ER}	7.11
J_{EX}	7.45
J_{FR}	7.05
J_{FX}	8.18
J_{RX}	0.54

Quantitative calculations of the aromatic ring current effects, based on methods given by Johnson and Bovey[14] as well as Haigh and Mallion,[15] were performed

TABLE II

Calculated total aromatic ring current contributions ARCC [ppm] for methylene and methyl protons of ethoxy groups (1) and (2). Individual contributions from both phenyl ring systems in 1 are summed up. The ring current effect for methyl groups is given as the average value for the 3 singular C—H protons

Protons	HAMA calculated		JOBO calculated		^{1}H-NMR experimental
	ARCC	calc	ARCC	calc	obs
H_A (1)	- 0.03		- 0.07		
		0.10		0.14	0.25
H_B (1)	- 0.13		- 0.21		
H_E (2)	+0.009		+0.004		
		0.02		0.08	0.08
H_F (2)	- 0.01		- 0.09		
CH_3 (M_3) (1)	- 0.08		- 0.20		
		-0.01		0.01	0.18
CH_3 (R_3) (2)	- 0.07		- 0.19		

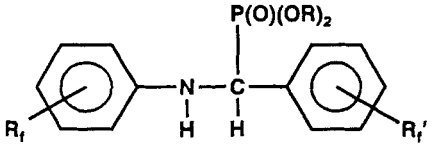
using the programs JOBO and HAMA.[16] The experimental ^{1}H NMR spectrum of Figure 3 was obtained from a $CDCl_3$ solution of 1. Consequently additional solution state structures of 1 were simulated with programs DISCOVER and VAMP including $CHCl_3$ solvent effects.

Using the solvent structure of 1 for ring current effect calculations individual shielding contributions for each individual proton of the methylene groups and the methyl groups were obtained as shown in Table II. Since programs HAMA and JOBO do not predict absolute chemical shifts but only shift contributions due to aromatic ring current effects we will use the differences Δ_{obs} and Δ_{calc} as indicators for the relative positions of protons. Δ_{obs} stands for the difference of observed chemical shifts [ppm] Δ_{calc} implies the difference of calculated ring current contributions [ppm].

It is evident, that the ABM_3X spectrum is governed by specially strong non-equivalence effects. This system corresponds to the $CH_2(1)$ and $CH_3(1)$ protons, mainly influenced by the carbon bonded phenyl ring. Whereas for the $CH_2(2)$ protons, predominantly influenced by the nitrogen bonded phenyl ring system, only small ring current contributions are predicted, which are connected with significantly lower non-equivalence effects in the EFR_3X part. Both programs HAMA and JOBO predict the same order of shift differences allowing for a unique spin assignment. But the Haigh and Mallion approach predicts significantly lower contributions than the Johnson and Bovey model, which comes closer to the still larger experimental shift differences. The simulated Δ_{calc} of current ring effects for the chemical shifts of the methyl groups is as low as 0.01 ppm while the experiment shows 0.18 ppm. This may indicate the higher flexibility of methyl groups in motion and of course further contributions to chemical shifts from the neighbouring substituents and further bond system in 1 which are not fully understood up to now.

The ^{1}H NMR spectrum of 1 shows two $[AB]_2C$ spectra in superposition located between 6.6 ppm and 7.5 ppm. The analysis of such systems is straight forward and of no relevance for the results presented here. But it is interesting to note the striking features of the H—C(P)—N—H skeleton.

A special case occurs for a spin system involving $^{1/2}A^{1/2}B^{1/2}M^{1}X$ where M stands for ^{31}P and X for the quadrupolar ^{14}N with I = 1. The couplings $^{3}J_{PH}$ and $^{3}J_{HH}$ and the resonance of the N—H proton disappear in this special case. Only the doublet of the HCP fragment is visible with data of δ_H = 4.76 ppm and $^{2}J_{PH}$ = 24.6 Hz. We will show in a subsequent paper[17] that this quadrupolar phenomenon is subject to substituent effects in a broad series[18] 2 derived from 1:



2

R_f, R_f' = 2-, 3-, 4-F, CF_3, CF_3O; 3,4-F_2, H

COMPARING THE EXPERIMENTAL SOLID STATE STRUCTURE AND THE SIMULATED GAS PHASE STRUCTURE

The atoms were indicated by numerical subscripts as shown in the following scheme:

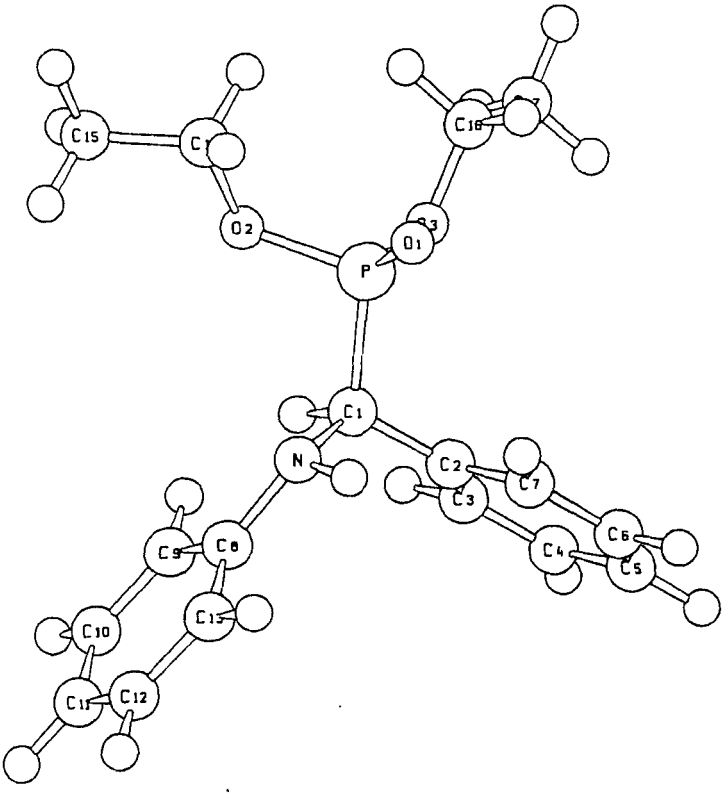


FIGURE 4 Structure of 1 with atomic lables, optimised with MOPAC 6.0 PM3.

In Tables III–V the calculated atomic coordinates, bond angles, bond lengths and dihedral angles for 1 are reported and compared with those obtained from the X-ray structure.

In accordance with the above mentioned solid state structure the computational geometry optimisation leads to a flattened pyramidal coordination of the nitrogen atom. The calculated C—N—C bond angle of 118.1° and the longer N—C_{Ar} bond length of 1.443 Å differ only slightly from values found in the solid state (117.1° and 1.385 Å). Henceforth for this part of the model molecule the computational geometry optimisation leads to corresponding results.

In the superposition the solid state structure is indicated by grid spheres while the atoms of the calculated structure are shadowed.

A strong deviation is found for the orientation of the ethoxy groups indicating high mobility for these functions as may be deduced from the dihedral angles in

TABLE III

Comparing simulated and experimental molecular geometry of S-1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester 1: dihedral angles

Dihedral angle	X-ray	PM3
O1-P-O2-C14	-29.4	20.7
O3-P-O2-C14	-154.4	-103.9
C1-P-O2-C14	95.5	152.6
O1-P-O3-C16	36.5	-37.5
O3-P-O3-C16	161.6	87.83
C1-P-O3-C16	-89.6	-168.6
O1-P-C1-N	55.0	52.4
O1-P-C1-C2	-72.9	-73.4
O2-P-C1-N	-72.2	-77.0
O2-P-C1-C2	159.9	157.2
O3-P-C1-N	-176.9	-179.7
O3-P-C1-C2	55.2	54.5
C8-N-C1-P	162.5	147.9
C8-N-C1-C2	-70.3	-85.6
P-C1-C2-C3	-97.0	-114.1
P-C1-C2-C7	84.7	67.5
N-C1-C2-C3	140.0	125.1
N-C1-C2-C7	-38.2	-53.3
C1-C2-C3-C4	-178.8	-178.7
C1-C2-C7-C6	179.3	178.5
C1-N-C8-C9	-12.9	-31.4
C1-N-C8-C13	168.3	153.8
N-C8-C9-C10	-177.0	-174.5
N-C8-C13-C12	178.1	174.5
P-O2-C14-C15	-114.4	166.4
P-O3-C16-C17	-119.9	175.3

TABLE IV

Comparing simulated and experimental molecular geometry of S-1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester 1: bond angles

Bond angle	X-ray	PM3
O1-P-O2	116.2	116.2
O1-P-O3	115.9	115.1
O2-P-O3	99.2	100.1
O1-P-C1	112.5	120.2
O2-P-C1	105.0	101.2
O3-P-C1	106.6	101.1
P-O2-C14	124.3	119.2
P-O3-C16	120.9	118.6
C1-N-C8	121.7	118.1
P-C1-N	106.0	104.7
P-C1-C2	114.1	114.9
N-C1-C2	115.3	113.9
C1-C2-C3	121.9	119.1
C1-C2-C7	120.2	121.9
N-C8-C9	123.1	121.4
N-C8-C13	118.3	118.9
O2-C14-C15	110.7	108.9
O3-C16-C17	112.2	108.9

TABLE V

Comparing simulated and experimental molecular geometry of S-1-N-phenylamino-1-phenylmethanephosphonic acid diethyl ester 1: bond lengths

Bond length	X-ray	PM3
P-O1	1.456	1.459
P-O2	1.563	1.702
P-O3	1.561	1.703
P-C1	1.815	1.870
O2-C14	1.437	1.404
O3-C16	1.456	1.401
N-C1	1.442	1.481
N-C8	1.385	1.443
C14-C15	1.443	1.521
C16-C17	1.443	1.519

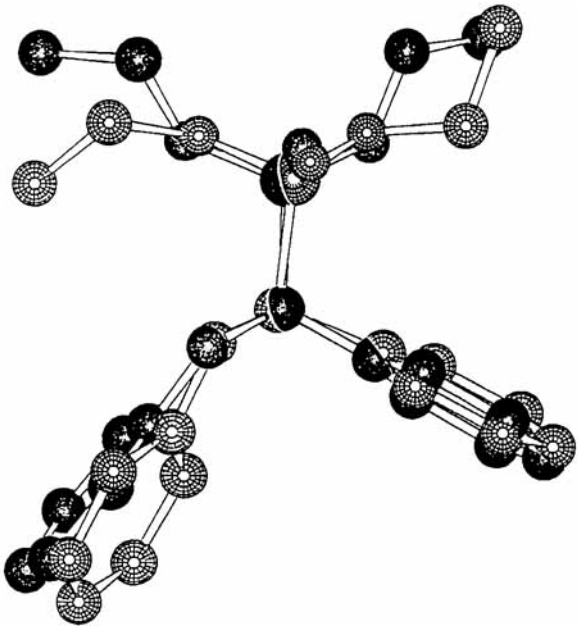


FIGURE 5 Superposition of the X-ray (grid sphered) and with MOPAC 6.0 PM3 optimised (shaded) molecular structure of 1.

Table III. In addition corresponding bond angles involving the fragment C—P—O show higher deviations than all the other data where solid and simulated structure agree satisfactorily (Table IV). Consistent data are obtained for all relevant bond lengths (Table V)

The calculated orientation of the carbon bounded phenyl ring fully agrees with the crystal structure but the nitrogen bounded phenyl ring shows a slight difference. The angle between the representing vectors for both phenyl rings in the geometry optimised conformation is 98° and therefore 8.1° larger than in the solid state structure which yields a value of 89.9°. The latter may be explained by packing effects due to dimer formation in the solid state, an effect which is not taken into account for the computational simulation.

CONCLUSIONS

The quality of structural results obtained from force-field and semi-empirical calculations agrees well with results obtained from x-ray studies and ^{1}H NMR spectra. We wish to point out that the PM3 parameter set in semi-empirical methods leads to good structural and energetic results for compounds including phosphorus atoms like, e.g. α-aminophosphonic ester derivatives. Less reliable results are obtained by using the parameter sets AM1 and MNDO in corresponding calculations.

The combination of systematic search methods with molecular dynamics simulations allows a fast conformational analysis to investigate rotational barriers and preferential conformations. In this case the systematic search procedure is able to detect the global minimum structure with lower potential energy than those found by MD. This fact seems to be a consequence of the high rotational barrier for the C—P axis. On the other hand, the results obtained from the dynamic simulations explain geometric features existing from this compound. Structural flexibilities and conformational changes can be investigated under temperature dependent conditions.

From those results a molecule energy surface is available including all the local and global minima as well as the transitions states to predict the energetic pathway for configuration changes. Information about the molecular flexibility is of great relevance to investigate biochemical problems,[19] especially to predict 3-D electrostatic potential surfaces (CONNOLLY surfaces), e.g. for compound 1, to investigate and describe interactive parts of the molecule.

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