

# *Ab initio* studies on organophosphorus compounds. Part 4.<sup>1-3</sup>

## Intramolecular hydrogen bonding and water interactions of bisphosphonates

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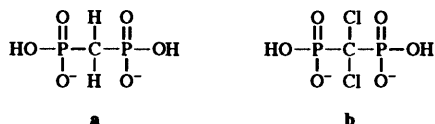
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Molecular properties of two clodronate-type bisphosphonates have been studied in the gas-phase by *ab initio* molecular orbital methods. Both compounds have P–C–P backbone structure and divalent localized negative charge on oxygen atoms. Molecular structures, charge distributions and energetics of the molecules were calculated with the 3-21G(\*) basis set. Internal hydrogen bonds were found between the monophosphonic acid ends of the bisphosphonate molecules. A gas-phase *ab initio* study has also been made of complexes of the bisphosphonate molecule with one to six explicit water molecules. Interactions between the bisphosphonate and water molecules took place through intermolecular hydrogen bonding. Finally, a self-consistent reaction field (SCRF) model was applied to the interaction models to complement the explicit study. The results of the study provide a quantum chemical reference for future experimental and theoretical studies of bisphosphonate compounds.

Molecules characterized by a P–C–P backbone are called bisphosphonates. Included among these compounds are etidronate, clodronate, pamidronate and alendronate, which have intriguing pharmaceutical properties.<sup>4-6</sup> Many bisphosphonate compounds have been used to prevent bone and tooth diseases and as regulators of calcium metabolism.<sup>5</sup> Several mechanisms indicating how bisphosphonates are involved in preventing osteoclastic bone resorption have recently been proposed<sup>4,7</sup> and a number of effective studies *in vivo* and *in vitro* have confirmed that clodronate can inhibit bone resorption.<sup>8-11</sup> The protonation of isopropyl esters of clodronic acid has been studied<sup>12</sup> and the <sup>31</sup>P NMR studies of monoisopropyl and *P,P*-diisopropyl esters have confirmed that a cyclic structure can be formed through intermolecular hydrogen bonding in protonation.<sup>12</sup> Because the precise mechanisms by which bisphosphonates react in the body is still unknown<sup>4,6,8</sup> these compounds are in need of large-scale study using theoretical and experimental methods.

A useful starting point for the study of the activity of bisphosphonates in pharmaceuticals is to obtain geometrical and thermodynamic information about the gas-phase compounds. We studied dianionic methylenebisphosphonate **a** and dichloromethylenebisphosphonate (clodronate) **b** in the gas phase by *ab initio* molecular orbital (MO) methods and present the structural parameters and energetics in this paper. The general structures of the compounds are shown below.



Experimental studies have shown that clodronate is highly soluble in aqueous solutions,<sup>6</sup> and this solubility explains why clodronate can be encapsulated in liposomes in high concentrations.<sup>6</sup> Because clodronate, and also some of its derivatives, are soluble in water, it was of interest to study how bisphosphonate–water complexes are formed. We investigated by *ab initio* molecular orbital methods the interactions between bisphosphonate and water by successively adding one to six water molecules to structure **a**.

The binding sites of the water molecules and the interaction distances between the waters and the bisphosphonate molecule were calculated by an explicit *ab initio* MO method. For further study of the solvent interactions, a self-consistent reaction field (SCRF) model<sup>13</sup> was applied to create an aqueous medium for bisphosphonate. All calculations with *ab initio* molecular orbital methods predicted stable hydrogen-bonded complexes.

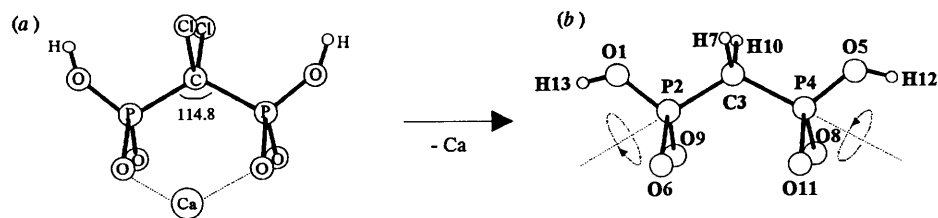
### Computational methods

*Ab initio* Hartree–Fock SCF–MO calculations on bisphosphonates and bisphosphonate–water complexes were performed with Gaussian 90 and 92 programs<sup>13</sup> on SGI 4D/35 and Indigo R4000/Elan computers. Molecular backbone geometries were calculated with the 3-21G(\*) basis set. Use of this basis set for phosphorus compounds has been found to generate geometrical results that are in good agreement with experimental values and with the values of theoretical calculations on higher level basis sets.<sup>1,2,14-21</sup> Correlation corrections were made with calculations by the MP2/3-21G(\*)//3-21G(\*) method.<sup>13</sup> Six explicit water molecules were used for modelling the aqueous solvent around the bisphosphonate molecule in the *ab initio* MO studies. To make the solvent medium complete a self-consistent reaction field (SCRF) model implemented in Gaussian 90 was used to produce water sphere effects ( $\epsilon = 78.54^{22}$ ).<sup>23</sup> The SCRF approach was based on the code of Rivail and Rinaldi and co-workers.<sup>13,24-27</sup> A single-centre multipole expansion up to  $l = 6$  was used to describe the charge distribution of the solute. An ellipsoidal cavity whose dimensions were determined by the solute van der Waals surface was used in the SCRF study. Optimized molecular geometries from the *ab initio* MO studies with 3-21G(\*) basis set were frozen for use in the SCRF calculations. The charges of the atoms were calculated by Mulliken methods.<sup>13</sup> Molecular drawings were processed with Sybyl molecular modelling program routines.<sup>28</sup>

### Results and discussion

#### Studies on free bisphosphonate in the gas phase

Structures of methylenebisphosphonate and dichloromethylenebisphosphonate. The molecular backbone of bisphosphonate



**Fig. 1** (a) Experimentally determined crystal structure of calcium dichloromethylenebisphosphonate pentahydrate.<sup>29</sup> The intermolecular water molecules are not shown. (b) The primary structure of the bisphosphonate studied was formed from the crystal structure in (a).

needed for the *ab initio* MO calculations was constructed with a molecular modelling program from earlier studied and optimized monoanionic  $\text{CH}_3\text{P}(\text{O}_2)\text{OCH}_3$  parts<sup>2</sup> and the P–C–P angle parameters reported for the  $\text{CaCl}_2\text{MBP}\cdot 5\text{H}_2\text{O}$  crystal structure<sup>29</sup> (Fig. 1). The carbon atom in the middle of the bisphosphonate's P–C–P chain has H and Cl substituents in calculated compounds **a** and **b**, respectively. In the initial geometries of the bisphosphonates before geometry optimizations the oxygen atoms of the monophosphonic acid groups were eclipsed and the hydrogens of the OH groups were at the opposite ends of the molecular backbone, as seen in Fig. 1. Application of the geometry optimization procedures showed the eclipsed phosphorus groups to be preferred in the **a1** and **b1** molecules. The *ab initio* MO calculations showed that hydrogen bonds between the monophosphonic acid ends of the bisphosphonate molecules can be formed. One or two internal hydrogen bonds were found in the molecular backbones of structures **a(1–2)** and **b(1–2)**.

Average experimental evaluated values for the lengths of P–O–R and P=O bonds are 156 and 145 pm for the  $(\text{C}_6\text{H}_5\text{CH}_2\text{O})_2\text{PO}_2\text{H}$  and  $\text{Cl}_3\text{P}=\text{O}$  crystal structures, respectively.<sup>30–32</sup> In the  $(\text{CH}_3)_3\text{P}=\text{O}$  crystal the P=O bond lengths were 148 pm.<sup>32</sup> In experimental studies on dimethylammonium phosphate the P–O bond length was found to range from 154 to 158 pm and the P=O bond from 149 to 150 pm.<sup>20,33</sup> Calculated with the 3-21G\* basis set, the dimethyl phosphate anion has P=O and P–O bond values from 147 to 163 pm.<sup>20,30</sup> Almost the same values have been found with the 6-31 + G basis set.<sup>20,30</sup> From calculations with the DZP basis set the  $\text{H}_2\text{P}_2\text{O}_7^{2-}$  dianion has P–O and P–O(H) bond lengths of 148 and 161 pm.<sup>34</sup> Average experimental P=O and P–O(H) bond lengths for the crystal structure of  $\text{CaCl}_2\text{MBP}$  (calcium dichloromethylenebisphosphonate) are 150 and 157 pm, respectively.<sup>29</sup> In the crystal structure of  $\text{Na}_2\text{H}_2\text{hebp}\cdot 4\text{H}_2\text{O}$  (disodium dihydrogen 1-hydroxyethylidene bisphosphonate tetrahydrate), the P=O bond lengths range from 150 to 151 pm and the P–OH bond length is 158 pm.<sup>35</sup> The evaluated value of the P–C–P angle in  $\text{CaCl}_2\text{MBP}$  is 114.8°.<sup>29</sup> Other reported P–C–P angles vary from 113.7° to 117.2°.<sup>29,36</sup> The average value of the P–C–P angle was 115.6°.<sup>29</sup>

Theoretical studies with the 3-21G(\*) basis set have predicted P–O(H) bonds from 163.4 to 167.8 pm for  $\text{PH}_4\text{OH}$ .<sup>21</sup> The corresponding average bond length in the global minimum structure of  $\text{H}_2\text{P}(\text{OH})_2$  calculated with the 6-31G\* basis set is 169.8 pm.<sup>37</sup> The *ab initio* MO calculations at the 6-31G\* level for several pentacoordinated phosphorane compounds predicted that the P–O(H) bond lengths vary in the range 162.0–176.8 pm.<sup>38</sup> The 6-31 + G\* calculations for the  $\text{PO}_3^-(\text{H}_2\text{O})_n$  complex (where  $n = 1, 2, 3$ ) predicted values from 147.1 to 148.0 pm for a single P–O bond.<sup>16</sup>

In our study of bisphosphonate structures, the average values for the P–O and P–O(H) bonds were 149.8 pm and 161.7 pm, respectively (Table 1). Evidently because of the localized dianionic charge character of the bisphosphonates, the lengths of the P–O bonds were between those of the single and double bond. The calculated P–O and P–O(H) bond lengths and P–C–P angles are in good agreement with earlier reported theoretical results.<sup>1–3,16,18,20,21,34,37–39</sup> for phosphonate

and phosphinate compounds. In addition, our results compare well with the results of experimental crystal structure studies.<sup>29,36</sup>

Two different conformations were found for compound **a** (**a1** and **a2**) and two for compound **b** (**b1** and **b2**). The original symmetric molecular geometries (Fig. 1) changed during the geometry optimization and cyclic structures were formed *via* hydrogen bonding (Fig. 2). At least one –O–H group was approached near to the distance of internal hydrogen bonding when the phosphorus groups were rotated around the C–P axis (Fig. 2). Corresponding internal hydrogen bonds have been reported in  $\text{H}_2\text{NO}_4^-$ ,  $\text{H}_2\text{PO}_4^-$  and  $\text{H}_2\text{P}_2\text{O}_7^{2-}$  compounds.<sup>16,34</sup> The existence of attractive intramolecular hydrogen bonding between hydroxy groups on different inositol rings has been reported in both experimental and theoretical studies.<sup>40</sup> The main difference between different conformations [**a(1–2)** and **b(1–2)**] calculated in our study was the number of hydrogen bonds. In the preferred conformations **a1** and **b1**, the eclipsed orientation was predicted for the oxygen atoms of the phosphorus groups, but still the hydroxy groups were not aligned in the same direction (Fig. 2). In **a1** and **b1**, the (H)O–P–O(H) torsional angles were 135 and 123°. In the **a2** and **b2** structures, the (H)O–P–O(H) torsional angles were –79 and –94°, respectively. These smaller values predict that the oxygen atoms of the monophosphonic acid groups are staggered.

One internal hydrogen bond was found in the **a2** and **b2** structures (Fig. 2). The O–H···O angles of the **a2** and **b2** compounds were 156.7 and 155.7° and the corresponding hydrogen bond lengths were 167.9 and 169.1 pm, respectively. Molecular backbones of the **a2** and **b2** compounds had P–C–P angles of 118.6 and 113.8°, respectively. Mulliken charges of 1.44 and 1.46  $e^+$  were calculated for the phosphorus atoms of structure **a2** with the 3-21G(\*) basis set. Similar charges were calculated for the phosphorus atoms of **b2**.

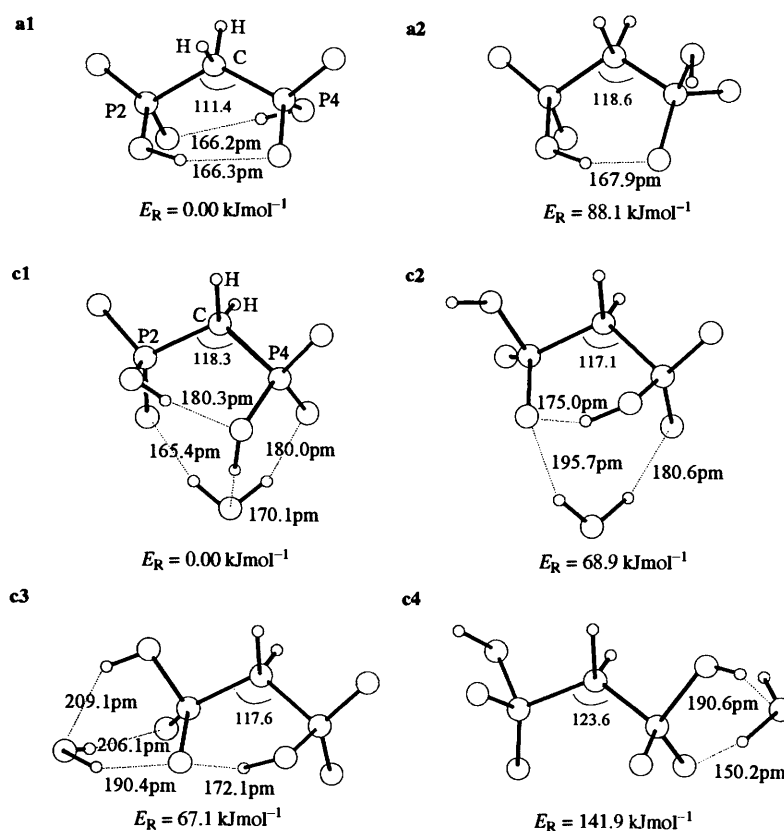
Two very strong internal hydrogen bonds were found in the **a1** and **b1** conformations (Fig. 2). The O–H···O angles of **a1** were 146.2 and 145.7° and the distances H···O were 166.2 and 166.3 pm. The compound **b1** with two chlorine atoms had O–H···O angles of 155.6 and 155.7° and H···O distances were 161.9 and 161.8 pm. The **a1** and **b1** compounds had bisphosphonate backbone angle values of 111.4 and 110.7°, respectively. Relative to **a2** and **b2**, the P–C–P angles were contracted by 7.2 and 3.1° when the second hydrogen bond was formed. The effects of chlorine atoms *versus* hydrogen atoms were seen in the changes in the P–C–P angles. In the chlorine compound the P–C–P backbone angle stays almost unchanged (–3.1°) despite the formation of the second hydrogen bond.

Calculations of the relative energies of the pairs (**a1**, **a2**) and (**b1**, **b2**) at both the HF and the MP2 levels predicted the **a1** and **b1** conformations to be more stable. The **a1** and **b1** structures were energetically stabilized with two internal hydrogen bonds between the monophosphonic acid ends of the molecule. The conformation **a1** was calculated to be 78 and 88  $\text{kJ mol}^{-1}$  more stable than **a2** by the HF and MP2 methods,

†  $e = 1.602 \times 10^{-19} \text{ C}$ .

**Table 1** Selected geometric parameters for the bisphosphonate compounds calculated with 3-21G(\*) basis set

	Bond length/pm							Length/pm	Angle/degrees	$\tau$ /degrees <sup>a</sup>	
	r(P2-O1)	r(P4-O5)	r(P2-O6)	r(P4-O8)	r(P2-O9)	r(P4-O11)	r(P2-C3)				r(P4-C3)
a1	160.4	160.4	151.2	151.1	148.5	148.5	183.3	183.3	302.9	111.4	135.0
a2	161.3	165.9	148.8	148.2	148.9	150.8	185.6	181.5	315.7	118.6	-79.2
b1	158.6	158.6	150.2	150.2	147.3	147.3	188.8	188.8	310.6	110.7	122.5
b2	159.7	162.7	147.7	147.2	147.5	148.9	191.1	187.1	316.8	113.8	-93.8
c1	161.8	163.9	150.3	148.3	148.3	150.3	183.1	183.1	314.4	118.3	37.1
c2	165.2	161.0	150.9	148.4	148.4	149.7	181.2	184.4	311.8	117.1	69.5
c3	163.8	161.3	151.8	148.7	149.5	148.6	179.8	185.8	312.8	117.6	84.1
c4	166.6	163.9	148.9	151.7	148.0	147.7	182.5	181.5	320.9	123.6	38.7
d1	161.4	163.5	152.0	148.1	148.0	150.4	182.6	182.8	321.1	123.0	59.9
d2	162.4	162.5	151.6	149.1	147.6	150.4	182.2	183.6	307.7	114.6	56.1
d3	163.5	162.8	148.7	148.2	150.7	150.0	180.5	183.0	317.1	121.5	-136.0
d4	164.1	161.6	151.4	149.9	148.9	148.1	180.8	184.8	320.8	117.7	76.4
e1	161.1	162.2	152.0	149.0	147.8	151.1	182.9	181.8	319.9	122.6	60.0
e2	162.3	162.3	151.5	150.2	147.4	149.9	182.6	182.7	307.0	114.4	56.0
e3	162.0	160.1	150.5	149.2	150.7	150.3	180.9	183.5	310.5	116.8	70.5
e4	163.8	159.9	150.8	149.2	149.3	149.7	180.1	183.7	307.8	115.6	83.8
f1	161.6	162.3	151.2	148.8	148.9	151.0	182.1	182.1	318.9	122.2	59.8
f2	160.6	162.2	153.3	148.7	148.1	150.4	182.3	183.0	314.3	118.7	66.0
f3	161.6	160.5	150.6	150.2	150.5	149.8	181.2	182.7	308.8	116.1	71.6
f4	161.2	160.3	153.9	149.1	148.6	149.6	180.4	183.8	311.0	117.2	76.3
g1	161.5	162.5	151.3	149.8	148.6	150.5	182.5	181.2	317.5	121.6	58.4
g2	160.7	163.6	151.7	148.9	149.8	149.6	181.2	182.4	317.8	121.8	57.3
g3	160.8	160.9	154.1	149.9	148.0	149.8	181.4	182.5	309.9	116.8	66.9
g4	161.1	160.6	153.0	150.0	149.2	149.7	180.8	182.7	310.3	117.3	69.4
h1	160.3	160.6	153.1	149.7	149.6	149.8	180.5	182.7	309.6	116.9	70.1
h2	160.5	162.5	151.7	149.6	149.5	150.4	181.5	181.6	316.8	121.5	57.3
h3	160.5	162.5	151.7	149.6	149.5	150.4	181.5	181.6	316.8	121.5	52.7
h4	160.3	160.5	152.9	150.0	150.3	149.0	179.6	183.1	309.1	116.9	82.4
i1	158.8	159.3	152.2	148.4	148.3	148.9	185.3	187.7	309.1	111.9	78.9

<sup>a</sup>  $\tau$  = Torsional angle.**Fig. 2** Calculated structures of bisphosphonate (a1 and a2) and bisphosphonate complex with one water molecule (c1 to c4). Hydrogen bonds and relative energies from the MP2/3-21G(\*)/3-21G(\*) basis set calculations are added to the picture. Molecular geometries in a1 and a2 were similar to those calculated for b1 and b2 compounds.

**Table 2** Total and relative energies of the studied compounds calculated with the 3-21G(\*) basis set. The table also includes the formation energies for studied complexes in the model reactions: bisphosphonate + (H<sub>2</sub>O)<sub>n</sub> → bisphosphonate·(H<sub>2</sub>O)<sub>n</sub>, where n = 1–6

	<i>E</i> /au <sup>a</sup>			<i>E</i> <sub>soiv</sub> <sup>b</sup> /kJ mol <sup>-1</sup>	<i>E</i> <sub>Reaction</sub> /kJ mol <sup>-1</sup>			<i>E</i> <sub>R</sub> /kJ mol <sup>-1</sup>		
	3-21G(*)	MP2	SCRF		3-21G(*)	MP2	SCRF	3-21G(*)	MP2	SCRF
<b>a1</b>	-1165.082 926	-1166.073 847	-1165.338 204	-670.2				0.0	0.0	0.0
<b>a2</b>	-1165.053 197	-1166.040 281	-1165.320 491	-701.8				78.1	88.1	46.5
<b>b1</b>	-2078.740 405	-2080.006 518	-2078.979 303	-627.2				0.0	0.0	0.0
<b>b2</b>	-2078.707 125	-2079.972 005	-2078.954 746	-650.1				87.0	90.6	64.5
<b>c1</b>	-1240.711 423	-1241.831 370	-1240.959 938	-652.5	-111.7	-132.8	-87.1	0.0	0.0	0.0
<b>c2</b>	-1240.692 243	-1241.805 130	-1240.951 809	-681.5	-61.3	-63.9	-60.3	50.4	68.9	21.3
<b>c3</b>	-1240.689 590	-1241.805 797	-1240.940 874	-659.7	-54.4	-65.6	-31.6	57.3	67.1	50.1
<b>c4</b>	-1240.664 004	-1241.777 342	-1240.930 892	-700.7	12.8	9.1	-5.4	124.5	141.9	76.3
<b>d1</b>	-1316.340 228	-1317.587 806	-1316.589 595	-654.7	-178.3	-210.3	-137.9	0.0	0.0	0.0
<b>d2</b>	-1316.336 015	-1317.578 518	-1316.572 161	-620.0	-167.2	-185.9	-92.1	11.1	24.4	45.8
<b>d3</b>	-1316.324 454	-1317.567 712	-1316.575 857	-660.1	-136.9	-157.6	-101.8	41.4	52.8	36.1
<b>d4</b>	-1316.323 136	-1317.561 132	-1316.572 386	-654.4	-133.4	-140.3	-92.7	44.9	70.0	45.2
<b>e1</b>	-1391.973 556	-1393.346 078	-1392.213 632	-630.3	-200.3	-221.5	-142.1	0.0	0.0	0.0
<b>e2</b>	-1391.963 237	-1393.329 148	-1392.213 829	-657.9	-173.2	-177.0	-142.6	27.1	44.5	-0.5
<b>e3</b>	-1391.961 576	-1393.326 323	-1392.204 763	-638.5	-168.8	-169.6	-118.8	31.5	51.9	23.3
<b>e4</b>	-1391.958 621	-1393.322 578	-1392.199 614	-632.7	-161.1	-159.8	-105.3	39.2	61.7	36.8
<b>f1</b>	-1467.603 035	-1469.100 673	-1467.831 788	-600.6	-207.0	-225.7	-125.5	0.0	0.0	0.0
<b>f2</b>	-1467.600 224	-1469.096 984	-1467.835 328	-617.3	-199.6	-216.0	-134.8	7.4	9.7	-9.3
<b>f3</b>	-1467.590 554	-1469.080 410	-1467.851 472	-685.0	-174.3	-172.5	-177.2	32.8	53.2	-51.7
<b>f4</b>	-1467.589 290	-1469.081 119	-1467.824 402	-617.3	-170.9	-174.4	-106.1	36.1	51.3	19.4
<b>g1</b>	-1543.227 587	-1544.849 735	-1543.470 627	-638.1	-239.7	-244.8	-180.5	0.0	0.0	0.0
<b>g2</b>	-1543.225 174	-1544.847 921	-1543.454 405	-601.8	-233.3	-240.1	-137.9	6.3	4.8	42.6
<b>g3</b>	-1543.223 969	-1544.842 297	-1543.455 925	-609.0	-230.2	-225.3	-141.9	9.5	19.5	38.6
<b>g4</b>	-1543.223 443	-1544.843 074	-1543.472 325	-653.4	-228.8	-227.3	-185.0	10.9	17.5	-4.5
<b>h1</b>	-1618.857 144	-1620.603 632	-1619.085 103	-598.5	-249.5	-246.4	-151.7	0.0	0.0	0.0
<b>h2</b>	-1618.850 797	-1620.597 698	-1619.098 315	-649.9	-232.9	-230.8	-186.4	16.7	15.6	-34.7
<b>h3</b>	-1618.850 793	-1620.597 681	-1619.098 643	-650.7	-232.9	-230.8	-187.3	16.7	15.6	-35.5
<b>h4</b>	-1618.849 154	-1620.594 518	-1619.096 332	-649.0	-228.6	-222.5	-181.2	21.0	23.9	-29.5
<b>i1</b>	-2532.484 966	-2534.507 923	-2532.712 495	-597.4	-171.7	-171.9	-115.7	0.0	0.0	0.0

<sup>a</sup> 1 au = 4.360 × 10<sup>-18</sup> J. <sup>b</sup> *E*<sub>soiv</sub> = the solvation energy obtained as the difference between the SCRF and SCF(g) energy for isolated molecule.

respectively. Correspondingly, the **b1** conformation, relative to **b2**, was stabilized by 87 and 91 kJ mol<sup>-1</sup> (Table 2). The energy differences between the conformations were clear in both methods used. The effect of the calculated MP2 correlation correction was small relative to the values of the HF level.

Internal hydrogen bonding seems to be important for the molecules in the gas phase, because all four conformations **a**(1–2) and **b**(1–2) formed at least one such bond. The results thus predict the cyclic bisphosphonate structures formed through internal hydrogen bonding interactions. According to <sup>31</sup>P-NMR and potentiometric measurements, the isopropyl esters of clodronic acid also form a cyclic structure in protonation.<sup>12</sup> Internal hydrogen bonding has been theoretically predicted for several pyrophosphate structures.<sup>34</sup> These O–H···O bonds range from 170.0 to 233.0 pm.<sup>34</sup> Two weak intramolecular hydrogen bonds have been calculated with the DZP basis set for an equilibrium geometry of pyrophosphoric acid molecule.<sup>34</sup>

The hydrogen bond lengths of the conformations with two H-bonds were predicted to be shorter than those calculated for the conformations with one internal hydrogen bond interaction. Steric hindrance of chlorine atom substituents on the carbon atom of the bisphosphonate caused a contraction of the P–C–P angle as compared with compounds with a –CH<sub>2</sub>– group. Likewise the P–C bond length was increased by *ca.* 5.5 pm owing to the effect of chlorine substituents. Lengthening of the P–C bonds and changes in the P–C–P angle did not, however, noticeably change the P···P distance of 316 pm in the structure **a2** as compared with the **b2**. The distance was only 1 pm longer in **b2**. Comparison of compounds **a1** and **b1** shows the P···P distance to be *ca.* 8 pm longer in **b1**.

Looking at the differences in the P–C bonds more closely, in conformation **a2** the P–C bond length was 185.6 pm, whereas in conformation **b2**, which contains chlorine atoms, the same

P–C bond increased to 191.1 pm. The P2–C3 bond lengths for bisphosphonates **a1** and **b1** were calculated to be 183.3 and 188.8 pm, respectively. By comparison, crystallographically determined values of the corresponding P–C bonds in the bisphosphonate anion (MBP) in an Na or Ca environment range from 185 to 187 pm.<sup>29</sup> The average P–C bonds in the bisphosphonate crystals vary from 179 to 186 pm.<sup>29</sup>

Theoretical studies with 3-21G(\*), 3-21 + G(\*) and RHF/6-31G\*\*/6-31G\* basis sets predicted P–C bonds from 183.8 to 190.4 pm in several phosphorus compounds.<sup>21,38</sup> The value of 188.8 pm for a single P–C bond in H<sub>3</sub>CPCO compound has been obtained in MP2/6-31G\*\* calculations.<sup>41</sup> In our study, the values calculated for the P–C bond lengths ranged from 179.6 to 191.1 pm with an average value of 182.9 pm. The values are in good agreement with published results.<sup>21,29,38,41</sup> Mulliken charges for the Cl atoms of our phosphonates ranged from –0.16 to –0.17 *e* and by natural population analysis the charges of chlorine were predicted to be in the range –0.11 to –0.12 *e*.

It was found that the two effective internal hydrogen bonds in the **a1** and **b1** bisphosphonates make the P–C–P and hydrogen bond angles more compact than the one internal hydrogen bond in the **a2** and **b2** compounds. Energetics and selected geometrical parameters of optimized structures are reported in Tables 1 and 2. As can be seen, as the degree of intramolecular hydrogen bonding increased, the P–C–P angle decreased and the conformation became energetically more stable.

#### Studies on bisphosphonate–water complexes

In the next set of studies, the methylenebisphosphonate **a** molecule was used as a base in hydrogen bond interaction studies of water clusters with one to six water molecules. The symmetric bisphosphonate backbone was used as the starting point in the calculations and optimizations were carried out with the 3-21G(\*) basis set (Fig. 1).

Interaction systems with double-donor double-acceptor hydrogen bonds were formed as one to six water molecules were successively added to the dianionic bisphosphonate. As the model for the binding of water to the phosphorus groups, we took the double donor–double acceptor interactions which are reported to be preferred for the anionic  $\text{PO}_3^-$  and  $\text{H}_2\text{PO}_4^-$  systems.<sup>14–16</sup>

**Interaction of compound a with one water molecule.** The first water molecule was added to the backbone of the anion **a** as a double proton donor. Four different binding positions of water molecules in the complex were tested at the outset and four different bisphosphonate–water complexes were found. Those conformations were labelled **c1**, **c2**, **c3** and **c4** (Fig. 2). The preferred complex was **c1** (Fig. 2), where the water molecule acted as a bridge between the monophosphonic acid ends of the methylenebisphosphonate. The bridging water molecule was simultaneously a single proton acceptor and double proton donor. In other words, there were three hydrogen bonds to connect a single water molecule to the bisphosphonate. The calculated O–H...O hydrogen bond lengths were 170, 165 and 180 pm and the corresponding angles were 154, 163 and 149°. In complexes of *N*-methylacetamide and water the C–O...H and N–H...O hydrogen bond lengths ranged from 188 to 197 pm when the 6-31G basis set was used for calculations.<sup>42</sup> In recent theoretical *ab initio* molecular orbital studies of  $\text{PO}_3^-\cdot(\text{H}_2\text{O})_n$  and  $\text{H}_2\text{PO}_4^-\cdot(\text{H}_2\text{O})_{n-1}$  clusters ( $n = 1, 2$  and  $3$ ) were found to form double-donor double-acceptor hydrogen bonds with water molecules.<sup>14–16</sup>

The bridging water molecule in the bisphosphonate complex was strongly hydrogen bonded because both of the anionic phosphorus ends take part in the binding process. The fourth hydrogen bond in the structure was of an internal type, connecting the monophosphonic acid ends of the bisphosphonate together, with O...H and  $\angle \text{O}\cdots\text{H}-\text{O}$  values of 180 pm and 147°. The P–O and P–O(H) bond lengths for the **c1** compound ranged from 148.3 to 150.3 pm and from 161.8 to 163.9 pm, respectively. The phosphorus–phosphorus distance was 314 pm and the P–C–P angle was 118.3°. A (H)O–P–P–O(H) torsional angle of 37.1° was calculated for the **c1** compound. The second conformation, **c2**, was similar to **c1**, but the bridging water molecule now acted as a pure double donor, forming only two hydrogen bonds to the phosphorus groups. The hydrogen bond lengths between the bisphosphonate and the water molecules were 181 and 196 pm. In addition, the straight internal hydrogen bond between the phosphorus ends was found in the complex, but the length was decreased by 0.05 pm relative to the **c1** conformation.

In the **c3** and **c4** complexes, the water molecule was interacting with the monophosphonic acid group of the bisphosphonate (Fig. 2). In the **c3** conformation the water molecule simultaneously acted as a single proton acceptor and double proton donor. Interaction distances between the water and the bisphosphonate molecules were 209, 190 and 206 pm. These values agree with the hydrogen bond lengths from 210 to 220 pm calculated for symmetric  $\text{PO}_3^-$ –water clusters.<sup>15</sup> One water molecule binds to the  $\text{H}_2\text{PO}_4^-$  anion with bond lengths ranging from 215 to 225 pm.<sup>14</sup> As in **c2**, an intramolecular hydrogen bond was found also in the **c3** conformation. The hydrogen bond lengths for the water binding in the **c** conformation were considerably longer than those calculated for **c1**, evidently because the water molecule had a dianionic binding position in **c1** and monoanionic position in **c3**. In the fourth complex, **c4**, the water molecule was acting as a proton acceptor and donor, forming two hydrogen bonds to the phosphorus group. The bond lengths were 191 and 150 pm. The latter distance was considerably shorter than the other hydrogen bonds calculated. No internal hydrogen bond was found in the **c4** structure and the P–C–P backbone angle was accordingly increased up to 123.6°, as compared with angles ranging from 117.1 to 118.3° in the **c1**, **c2** and **c3** structures.

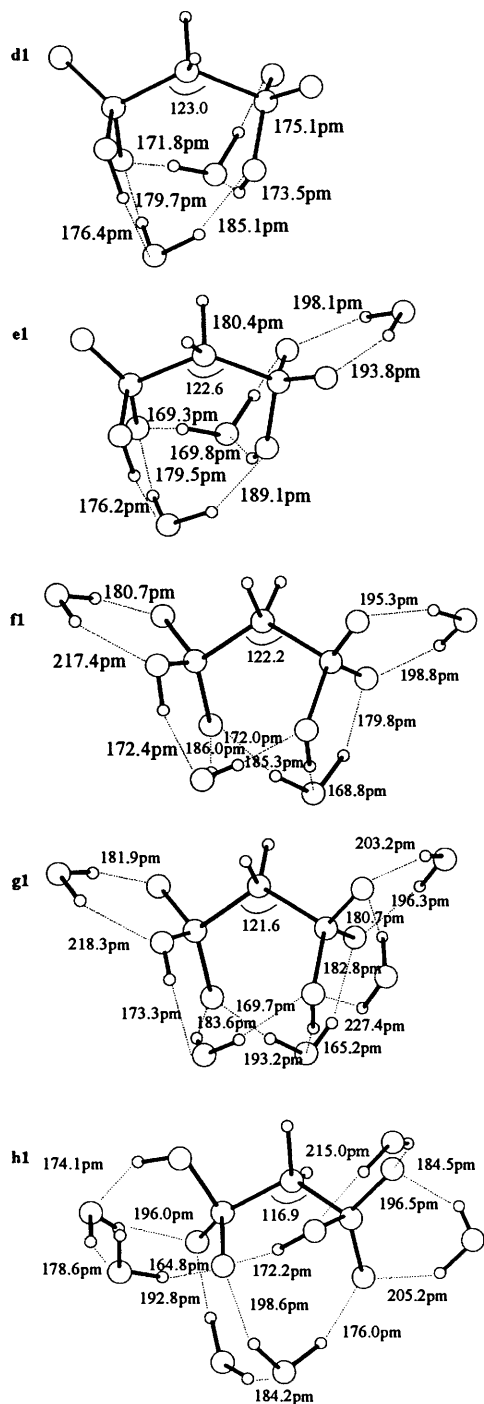
The HF/3-21G(\*) and MP2/3-21G(\*)//3-21G(\*) basis sets were used for energy studies. Relative energies for the **c1**, **c2**, **c3** and **c4** complexes at the HF level were 0, 50, 57 and 125 kJ mol<sup>-1</sup> and at the MP2 level 0, 69, 67 and 142 kJ mol<sup>-1</sup>, respectively.

**Interaction of compound a with two water molecules.** When two water molecules were added to the bisphosphonate structure and the structure was optimized, the preferred conformation was **d1** (Fig. 3). Both water molecules had double donor character and formed a water bridge between the phosphorus groups of the bisphosphonate. At the same time the oxygens of the water molecules acted as a single proton acceptor, forming extra hydrogen bonds to the hydroxy groups of the bisphosphonate. Altogether, then, there were six effective intermolecular hydrogen bonds in the structure **d1**, varying in length from 172 to 185 pm. Similar bisphosphonate–water binding orientations were found in the **d1** and **d3** complexes, though in the **d3** system there were only five intermolecular hydrogen bonds since the second water molecule did not have single proton acceptor character. Water binding geometries were different in the **d2** and **d4** complexes. In the **d2** structure, the first water molecule formed a bridge between the two monophosphonic acid ends of the bisphosphonate, while the second water molecule interacted directly with the one monophosphonic acid group. In the **d4** structure the water molecules were at the opposite ends of the methylenebisphosphonate. The double donor–double acceptor interactions between water and bisphosphonate molecules were still found in **d2** and **d4** complexes. The water binding O–H...O bond lengths in **d4** ranged from 177 to 212 pm.

By way of comparison, hydrogen bonds ranging from 219 to 227 pm in length were calculated for two water molecules connected to the  $\text{H}_2\text{PO}_4^-$  species when calculations were made at the DZP + diff SCF theoretical level.<sup>14</sup> In both the **d2** and **d4** structures the phosphorus groups were connected *via* an internal hydrogen bond and the effect of the internal hydrogen bonding was clearly seen in the contracted P–C–P angles 114.6 and 117.7°. The calculated angles were in good agreement with experimental studies.<sup>29,36</sup> In the **d1** and **d3** complexes, a lack of straight internal hydrogen bonding between the phosphorus groups caused the P–C–P angles to open up to 123.0 and 121.5°, respectively. The same effect was found in the backbone angle of the **c4** complex.

**Interaction of compound a with three water molecules.** With three water molecules added to the bisphosphonate structure and optimization made with the 3-21G(\*) basis set, the preferred calculated complex structure was **e1** (Fig. 3). This structure was the same as that of the **d1** complex, but with a third water molecule was bound as a double proton donor to the monophosphonic acid end of the bisphosphonate. A value of 122.6° was calculated for the P–C–P angle of the methylenebisphosphonate, because there was no internal hydrogen bond between the phosphorus groups. In the **e2**, **e3** and **e4** structures, phosphorus groups were connected by internal hydrogen bonds and the effects of the H-bonding were seen in the P–C–P values (Table 1). The main geometries of the bisphosphonate backbones in the **d2** and **e2** species were alike up to the system with two water molecules. In **e2** the third water molecule was bound to the monoanionic phosphorus group.

**Interaction of compound a with four water molecules.** When four water molecules were added to the bisphosphonate structure, four different complexes were calculated, with **f1** the preferred structure (Fig. 3). The main geometry of the methylenebisphosphonate backbone was similar to that found for **d1** and **e1**. One water was placed at the monophosphonic acid end of the methylenebisphosphonate and the three other water molecules were bound as in the preferred model **e1** calculated for the complexes. The P–C–P angle was 122.2° and the contraction was 0.4° relative to **e1**. Internal hydrogen bonds were found in the **e2**, **e3** and **e4** complexes. The effects of those



**Fig. 3** The energetically preferred conformations for the studied bisphosphonate–water complexes from **d1** to **h1**. The P–C–P angles and the hydrogen bond lengths are presented in the picture.

hydrogen bonds were seen in the values 119, 116 and 117° calculated for the P–C–P angles.

**Interaction of compound a with five water molecules.** When five water molecules were added to the bisphosphonate structure, the four conformations **g1**, **g2**, **g3** and **g4** were calculated for the bisphosphonate–water complexes. In the preferred bisphosphonate–water molecule **g1** (Fig. 3) there were two water molecule bridges linking the phosphorus groups together. These two water molecules simultaneously acted as single proton acceptors and double proton donors. Corresponding interactions were found in the **d1**, **e1** and **f1** complexes. Three more water molecules acting as double proton donors were placed around the methylenebisphosphonate. The P–C–P angle was contracted to 121.6°. The **g1** and **g2** complexes correspondingly had three hydrogen bond based water bridges

between the monophosphonic acid ends of the methylenebisphosphonate. The (H)O–P–O(H) torsional angles were 59.9, 60.0, 59.8 and 58.4° for **d1**, **e1**, **f1** and **g1**, respectively.

**Interaction of compound a with six water molecules.** Four complexes were again generated when six water molecules were added to the bisphosphonate structure. In the preferred system **h1** (Fig. 3), the P–O bond lengths ranged from 149.6 to 153.1 pm and the P–OH bond lengths were 160.5 pm. The crystal structures of sodium dichloromethylenebisphosphonate tetrahydrate and the calcium dichloromethylenebisphosphonate pentahydrate have P–O bond lengths ranging from 148.4 to 150.1 pm and P–O(H) bond lengths ranging from 156.6 to 157.7 pm.<sup>29</sup> Besides these our calculated values agree well with the experimental bond lengths of 147.0 and 164.2 pm for the dimethyl phosphonate anion.<sup>20</sup> In the bisphosphonate **h1** backbone, the calculated anionic  $\angle$  O–P–O angles ranged from 115 to 118° and the  $\angle$  O–P–O(H) angles from 107 to 110°. The results agree well with the  $\angle$  O–P–O bond angles from 117.3 to 120.0° and the  $\angle$  O–P–O(H) bond angles from 107.8 to 111.5° measured in the crystal structures of NaCl<sub>2</sub>MBP and CaCl<sub>2</sub>MBP salts.<sup>29</sup> The average values of the calculated  $\angle$  C–P–O and  $\angle$  C–P–O(H) angles were 110.4 and 101.7°, while the corresponding experimental values were 106.9° and 104.4°, respectively.<sup>29</sup> Schaefer and co-workers have reported anionic O–P–O angles of 122° for the H<sub>2</sub>PO<sub>4</sub><sup>−</sup>·(H<sub>2</sub>O)<sub>n</sub> (n = 1, 2) complex.<sup>14</sup> Yliniemelä *et al.* reported O···H hydrogen bond distances less than 210 pm in a complex of dianionic oxyphosphorane with six interacting water molecules.<sup>43</sup>

There were, simultaneously, one internal hydrogen bond and one water bridge connecting the phosphorus groups of the bisphosphonate in the **h1** structure (Figs. 3 and 4). The bridging water molecule acted as a double proton donor to bisphosphonate, but at the same time it had single proton acceptor character through hydrogen bonding with another water molecule. The hydrogen bonds lengths in conformation **h1** varied from 165 to 215 pm. The methylenebisphosphonate in the **h1** complex was replaced with the dichloromethylenebisphosphonate backbone and the **il** complex structure was optimized. The molecular geometries including internal hydrogen bonds and the water binding sites in the **h1** and **il** complexes were similar. In the chlorine compound the P–C–P angle was contracted to the value of 111.9°. The hydrogen bond lengths in conformation **il** varied from 170 to 216 pm.

By way of comparison, the distances between the hydroxide oxygen atom and hydrogens of water molecules range from 157 to 177 pm.<sup>44</sup> These distances are shorter than the characteristic hydrogen bonds between water molecules and it has been suggested that hydrogen bonds are stronger when formed with negatively charged ions than with neutral molecules.<sup>44</sup> The oxygen–hydrogen distance of the water molecules in the **h1** complex was lengthened upon formation of hydrogen bonds with the dianionic bisphosphonate. The same effect has been reported by Rivail and co-workers.<sup>44</sup> The P–C–P bond angle of the **h1** bisphosphonate was contracted to the value 116.9°, which corresponds reasonably well with the experimental values<sup>29,36</sup> The water molecules were placed around the bisphosphonate. The interatomic (H)O–P–O(H) torsional angle in **h1** was 70.1° and the P···P distance was 310 pm.

The **h2** and **h3** complexes had no internal hydrogen bonds between the phosphorus groups and therefore the P–C–P angles increased to 121.5°. The main structures of the **h2** and **h3** complexes were alike. Increasing water media around the bisphosphonate caused a contraction of the P–C–P bond in the **h2** as in the **d1**, **e1**, **f1** and **g1** complexes. The **h2** and **h3** conformations had two bridging water molecules between the monophosphonic acid ends of the bisphosphonates, and the single proton acceptor character and double proton donor character were found for both (Fig. 4). A corresponding interaction between the methylenebisphosphonate and water molecules in the **d1**, **e1**, **f1** and **g1** clusters was found. The

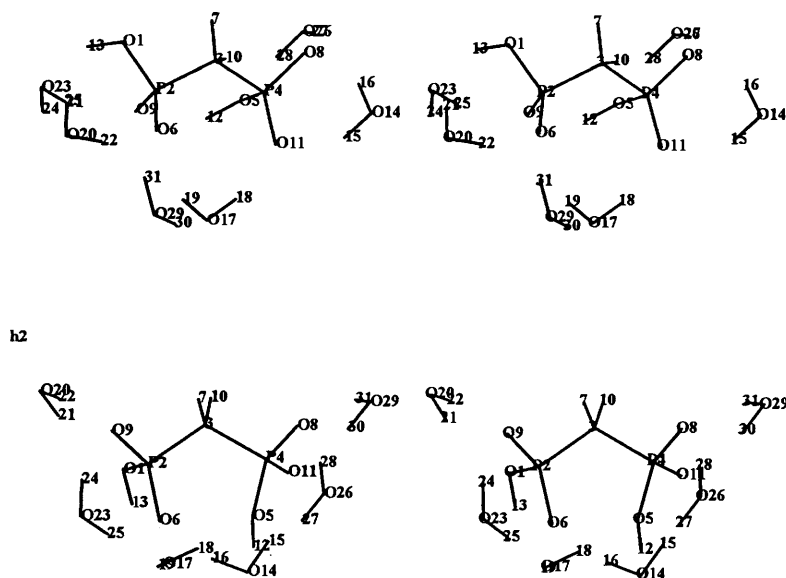


Fig. 4 **h1** and **h2** complexes are presented as stereo pairs [3-21G(\*)]

(H)O–P–P–O(H) torsional angles were 57.3, 52.7 and 82.4° for the **h2**, **h3** and **h4** structures, respectively. In **h4**, there was one internal hydrogen bond and a water dimer bridge between the phosphorus groups.

The effects of the internal hydrogen bonding were clearly seen in the P–C–P angles of the bisphosphonates. In complexes where internal hydrogen bonds connected the monophasphonic acid groups, the P–C–P angles ranged from 110.7 to 118.7°. When these bonds were replaced by water bridges, however, the P–C–P angles increased to values between 121.5 and 123.6°.

The Mulliken charges of the phosphorus atoms were 1.46 *e* for the **a1** bisphosphonate (Table 3). As the number of water molecules increased, the phosphorus charges increased, with a value of 1.55 *e* reached in the **h1** complex. The average phosphorus charges were 1.46 and 1.47 *e* in the **a** type complexes calculated with the HF/3-21G(\*) basis set and SCRF studies, respectively. With both these methods an average charge of 1.54 *e* was calculated for the phosphorus atoms in the **h** complex. It can tentatively be concluded that the HF and SCRF models predict the same average charges for the phosphorus atoms of the bisphosphonate.

The total gas phase charge of the bisphosphonate was –2 *e* in the **a1** compound. However as more water molecules were added to the complex, the charge of the bisphosphonate decreased. Evidently the anionic charge was fluxed to the water media. At the HF/3-21G(\*) level and with the SCRF studies, the average charges of the bisphosphonate **h** complexes were calculated to be –1.62 and –1.59 *e*, respectively. In general, for the calculated series **a** to **h** the improvement of the SCRF model over the SCF results was quite small for the bisphosphonate charges.

The oxygen atoms of the bisphosphonate were grouped, according to their character in the hydrogen bonds, into single donor, single donor–single acceptor, single donor–double acceptor, single acceptor, double acceptor and triple acceptor. Within these groups the average P–O bond lengths all decreased a little as the size of the complex increased. The same trend was found in the oxygen charges of the bisphosphonate.

#### Model reactions for the formation of the bisphosphonate–water complexes

Model reactions between the bisphosphonate and water cluster reactants were produced by calculating energies at the HF/3-21G(\*) and MP2/3-21G(\*)//3-21G(\*) levels. Hydrogen bonded

water clusters were used as the solvent model and the products were bisphosphonate–water complexes with one to six water molecules. The different sized water clusters were separately calculated to obtain *ab initio* MO energies for water cluster reactants for model reaction paths. The pure water clusters that were calculated were based on the geometries reported by Xantheas and Dunning<sup>45</sup> and Kim *et al.*<sup>46</sup> The formation of the preferred bisphosphonate–[H<sub>2</sub>O]<sub>6</sub> complex released energy of 250 kJ mol<sup>–1</sup> when the 3-21G(\*) basis set was used for calculations and 246 kJ mol<sup>–1</sup> with the MP2/3-21G(\*)//3-21G(\*) level.

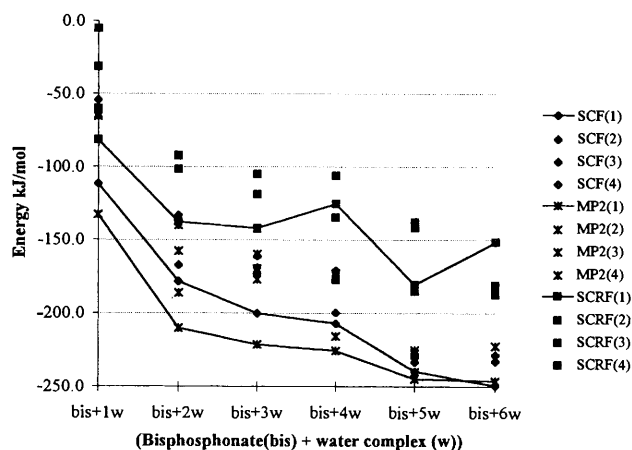
The SCRF model with ellipsoidal cavity was used to produce water media around the bisphosphonate and the bisphosphonate–water complexes. However the multiple expansions that were used exhibited serious convergence problems, especially for the large bisphosphonate–water complexes. The origin of the problem was probably an underestimation of the cavity surfaces of the compounds. To solve the cavity problem, all X, Y and Z dimensions of the ellipsoidal cavities were accordingly increased by 0.5 Å. The expansions of the cavities were successful and, as a result, reasonably converged series were obtained in the multiple expansions. The cavity expansions were in accordance with the method discussed in the review by Tomasi and Persico.<sup>47</sup>

The total solvation energy was obtained as the difference between the SCRF and SCF gas-phase energies.<sup>48</sup> Normally, the total solvation energy should include at least cavitation and dispersion corrections, but neither term was taken into account in our calculations because the effects were not expected to change significantly the geometry of the stationary points in the free energy surface.<sup>49</sup>

In the calculation of solvation effects for *o*-phosphorylcholine with approximate solvation models in molecular dynamics studies,<sup>50</sup> the presence of 20 explicit water molecules around the polar group was sufficient to stabilize the *trans* conformation and to model qualitatively the behaviour in bulk water.<sup>50</sup> Because our methylenebisphosphonate molecule is of considerably smaller steric size than phosphorylcholine we felt justified in placing only six explicit water molecules around it in our *ab initio* MO study. The total calculated solvation energies for the isolated **a1** and **a2** gas-phase molecules were –670 and –702 kJ mol<sup>–1</sup> in aqueous media (Table 2). The total solvation energies for the **c** group complexes compared fairly well with those calculated for the **a** group complexes. As the size of the complex

**Table 3** Mulliken charges for selected atoms with 3-21G(\*) basis set

	O1	O5	O6	O8	O9	O11	P2	P4	O14	O17	O20	O23	O26	O29
<b>a1</b>	-0.87	-0.87	-0.82	-0.82	-0.77	-0.77	1.46	1.46						
<b>c1</b>	-0.85	-0.88	-0.81	-0.76	-0.77	-0.81	1.49	1.47	-0.90					
<b>d1</b>	-0.85	-0.86	-0.83	-0.76	-0.76	-0.82	1.51	1.48	-0.89	-0.86				
<b>e1</b>	-0.85	-0.85	-0.83	-0.77	-0.75	-0.82	1.51	1.51	-0.88	-0.85	-0.87			
<b>f1</b>	-0.86	-0.85	-0.81	-0.76	-0.76	-0.81	1.54	1.51	-0.87	-0.84	-0.87	-0.86		
<b>g1</b>	-0.85	-0.86	-0.81	-0.77	-0.75	-0.79	1.55	1.53	-0.87	-0.84	-0.86	-0.86	-0.85	
<b>h1</b>	-0.83	-0.84	-0.82	-0.78	-0.75	-0.77	1.52	1.55	-0.86	-0.85	-0.81	-0.85	-0.86	-0.89
<b>i1</b>	-0.82	-0.83	-0.81	-0.74	-0.71	-0.75	1.55	1.60	-0.84	-0.84	-0.81	-0.83	-0.85	-0.88



**Fig. 5** Model reaction energies for the formation of the different-sized bisphosphonate-water complexes calculated with SCF/3-21G(\*), MP2/3-21G(\*)/3-21G(\*) and SCRF/3-21G(\*) basis sets, respectively. The number of conformations calculated is shown in parentheses. (bis = bisphosphonate and w = water molecule). Reaction: bisphosphonate + (H<sub>2</sub>O)<sub>n</sub> → bisphosphonate-(H<sub>2</sub>O)<sub>n</sub> (n = 1–6).

increased, however, the solid energy difference relative to the energy of the **a** complex increased. When the complex included six water molecules, the values for the solvation energies of the **h** complexes were between  $-599$  and  $-651$  kJ mol<sup>-1</sup>. The results indicate that explicit water molecules near bisphosphonate are essential to the energy model of solvation and SCRF media usefully complement the solvation model.

In addition, model reactions were used to predict the theoretical solvation effects for the studied molecules. Energies of  $-111$  and  $-82$  kJ mol<sup>-1</sup> were calculated with the SCF and SCRF methods when the **c1** complex (the bisphosphonate and one water molecule) was formed from the reactants. An upward trend in the energies was found with increasing cluster size. When the energies of the six water molecules were individually added to the reaction path, the averages  $-665$  and  $-558$  kJ mol<sup>-1</sup> for **h** compounds were calculated with the HF and SCRF models, respectively. If the reactant water molecules were hydrogen bonded clusters, the average SCRF energy was  $-177$  kJ mol<sup>-1</sup> in the bisphosphonate cluster with six water molecules (Fig. 5 and Table 2). Energies of  $-171$  and  $-116$  kJ mol<sup>-1</sup> were calculated with the SCF and SCRF methods when the **i1** complex was formed from the reactants.

## Conclusions

Two different bisphosphonate structures, methylenebisphosphonate **a** and dichloromethylenebisphosphonate **b**, were calculated in the gas phase by theoretical *ab initio* molecular orbital methods. One or two internal hydrogen bonds were found between the monophosphonic acid ends of the molecule. The conformations of the **a** and **b** compounds with two internal hydrogen bonds were energetically favoured and had similar optimized molecular structures. To study the effect of

surrounding water molecules on methylenebisphosphonate compounds, one to six explicit water molecules were successively added to molecule **a**. Calculated bond lengths, angles and torsional angles of the free molecules and the bisphosphonate-water clusters agree with the corresponding experimental and theoretical studies of related compounds.

The bisphosphonate-water complex and the free bisphosphonate in the gas phase had similar bond lengths and angles. The added water molecules stabilized the charges of the dianionic bisphosphonate. There was a tendency to form water bridges between the monophosphonic acid ends of the bisphosphonates through the series of the complexes from **c** to **i**. Conformations with internal hydrogen bonds between the monophosphonic acid ends were also found through the series. The existence of the internal hydrogen bonds in the bisphosphonate backbone stay unchanged in aqueous media. Cluster formation occurred through hydrogen bonding between water and bisphosphonate molecules. The preferred type of water binding to the bisphosphonate was double donor-double acceptor hydrogen bonding. The interaction in complexation was the strongest when the water molecule was bound as a bridge between the anionic phosphorus ends of the bisphosphonate. Part of the anionic charge of the bisphosphonate shifted to the water molecules during complexation. The *ab initio* MO model with explicit water molecules and the SCRF model for solvent sphere were applied to the studied species. Evidently the SCRF model that was used cannot alone present the solvation of the bisphosphonate molecules. To predict intermolecular interactions near bisphosphonate in a reasonable way requires the inclusion of explicit water molecules in the study. For energy studies, the explicit calculated water complexes were complemented with the SCRF model. Optimized geometries and energetics for the free bisphosphonates and the bisphosphonate-water complexes can provide a qualitative reference for further theoretical solvation studies.

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Paper 5/03949E  
 Received 19th June 1995  
 Accepted 10th July 1995