Coordination of Water to Magnesium Cations

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The stereochemistry of binding of ligands by divalent metals and the propensity of these ligands to be water were investigated. Structural data of crystal structures in the Cambridge Structural Database (CSD) that contain divalent magnesium were examined with respect to the coordination of water molecules and other groups around a magnesium ion and any possible variability in the coordination number of magnesium. The analysis highlighted the stability of the hexaaquated magnesium ion, $Mg[H_2O]_6^{2+}$, which is found in the presence of various anions or chelating groups; this implies that the magnesium ion often prefers to bind directly to water rather than to anions. In the absence of a polycyclic complexing agent such as porphyrins or crown ethers, the coordination number of magnesium in crystal structures tends to be six. The orientation of water molecules around a magnesium ion is found to be such as to bring the $Mg^{2+}\cdots O–H$ angle as near as possible to 120–127° (Mg···H near 2.6–2.7 Å). *Ab initio* molecular orbital studies of the structures of hydrated Mg^{2+} ions with up to seven water molecules partitioned between the first and second coordination shells were also carried out. The lowest energy configuration of hydrated Mg^{2+} has six water molecules packed into the inner coordination shell, although structures with five water molecules in the first shell and one in the second or four in the first shell and two in the second are less than 5 and 10 kcal/mol, respectively, higher in energy. No stable configuration with seven water molecules arranged in the inner coordination shell could be found; the stable structure has six water molecules in the first shell and one in the second coordination shell, hydrogen bonded to two water molecules in the first shell. There appears to be less covalency in $Mg^{2+}\cdots O$ than in $Be^{2+}\cdots O$ interactions, water molecules are less affected by the presence of Mg^{2+} than by that of Be^{2+}, and hydrogen bonding between the first and second coordination shell is weaker for magnesium than for beryllium complexes.

Introduction

The divalent magnesium cation Mg^{2+} has an ionic radius of 0.65 Å, approximately two-thirds that of Ca^{2+} or Na^+ and half that of K^+, the other cations that are abundant in biological systems.[1] Because of its small size and relatively large charge, Mg^{2+} is the hardest of these four ions. Highly electronegative donor atoms such as the oxygen atoms in phosphate or carboxylate anions (i.e. hard ligands) form stable complexes with magnesium.[2] The occurrence of active-site magnesium ions has been established for several enzymes such as D-xylose isomerase,[3] glutamine synthetase,[4] ribonuclease H,[5] ribulose bisphosphate carboxylase,[6] and ras p21.[7] As the magnesium ion has only one valence state, +2, it cannot play a direct role in any redox-mediated enzymatic reactions. The general mode of action of magnesium cations in such enzymes appears to be to bind portions of the active site together by means of six metal–ligand bonds arranged in an octahedral manner with all O···Mg···O angles near 90°. This role of magnesium may depend on the rigidity of its coordination sphere, so that its function is structural, in contrast to the role of zinc which has a very flexible coordination sphere and is generally directly involved in the catalytic mechanism. Several molecular orbital studies have been reported in the literature on magnesium ion coordination,[8–11] and these show the strong propensity of magnesium cations to assume sixfold coordination and to bind strongly to water molecules.[9,12–14]

In order to investigate the general role of magnesium we have examined its coordination from two points of view: (1) analyses of the crystal structures of small molecules containing this cation, as found in the Cambridge Structural Database and (2) *ab initio* molecular orbital calculations on aquated structures of the form $Mg[H_2O]_n^{2+}\cdot mH_2O$, with *n* water molecules in the first coordination shell and *m* water molecules in the second coordination shell (see Chart 1). Such calculations allow comparisons of the energies of various hexaaquated structures such as $Mg[H_2O]_4^{2+}\cdot 2H_2O$, $Mg[H_2O]_5^{2+}\cdot H_2O$, and $Mg[H_2O]_6^{2+}$. Comparisons are also made with our previous study on $Be[H_2O]_n^{2+}\cdot mH_2O$ structures.[15] In this paper we specifically investigate the manner

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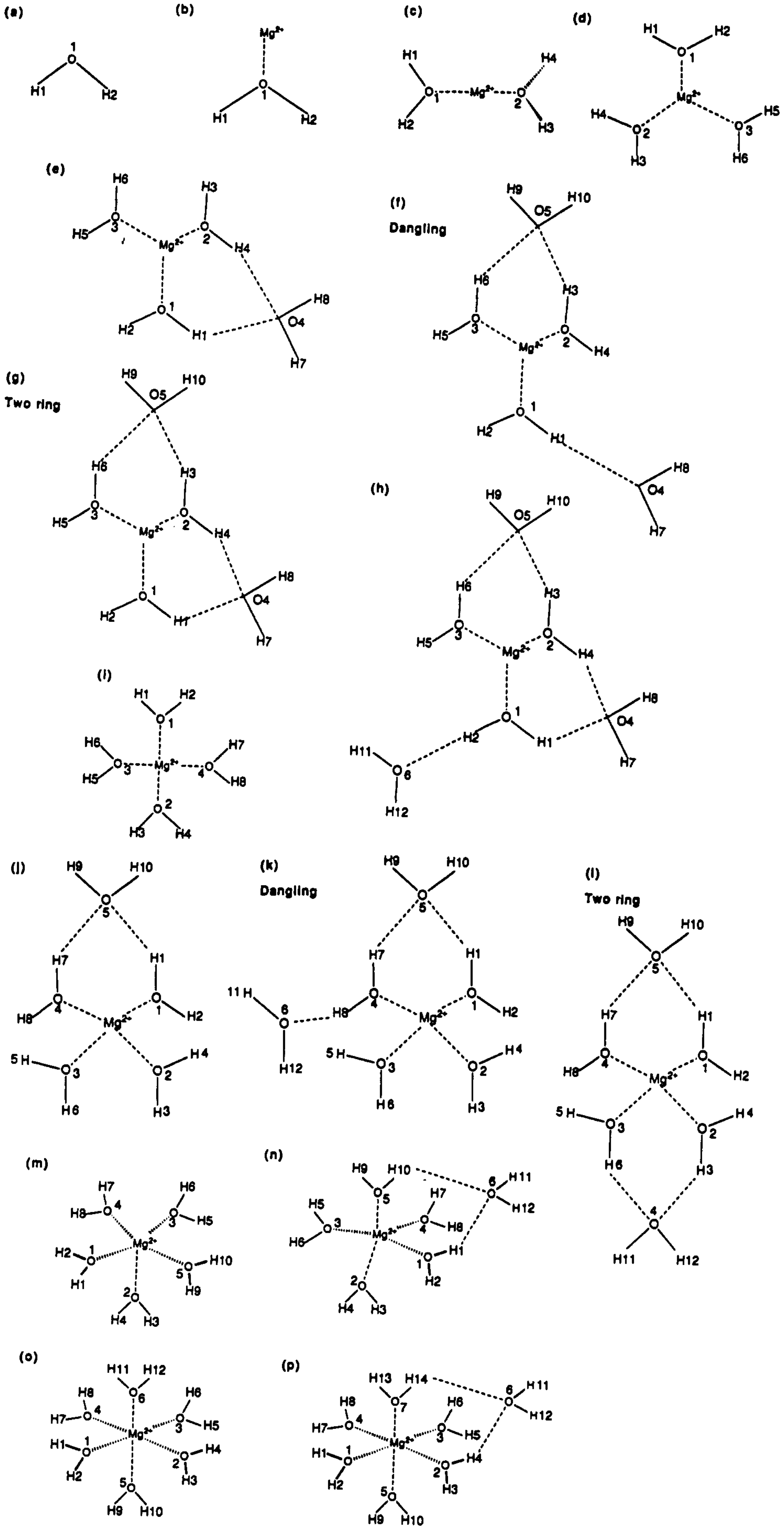
Chart I



in which water molecules are arranged around a divalent magnesium ion, the relationships between water molecules in the first and second coordination spheres, and any variation in coordination number as a function of the nature of the coordinating ligands.

Methods

(a) Structural Data from Crystal Structure Analyses in the CSD. The three-dimensional data on crystal structure determinations contained in the Cambridge Structural Database (CSD) (1992 version) were used as the basis for the structural analyses reported here.[16] The aim was to determine the most common mode of magnesium binding and to investigate the role of water in such binding. Initially data on compounds containing magnesium were extracted from the CSD database by use of the program QUEST and a master file was created. Only those compounds with magnesium bound to the elements O, N, Cl, Br, or S were considered since we were interested in crystal structures relevant to magnesium–protein and magnesium–nucleic acid interactions in an aqueous environment. As a result, 83 entries with magnesium bound to a variety of other chemical elements (mainly carbon) were eliminated from this analysis. Only one case was found in which a magnesium cation is directly coordinated to sulfur (refcode SIDNAU).[17] Ten crystal structures were not used because of disorder in the metal site, unusually long Mg···O distances, or high *R* values (greater than 0.10).

The master file of crystallographic parameters was then broken down into smaller files, each containing a specific magnesium coordination number. The method used was to create a *.GEO file which specified particular magnesium fragments. For example, starting with magnesium with a coordination number of 6 and surrounded only by oxygen atoms, we ran the computer program GSTAT and extracted from the magnesium master file those entries containing this fragment. This program also gave information on the molecular geometry of the fragment. Crystal structures with coordination numbers 3–8 were found to exist in the present CSD data file, so that six individual coordination files (one for each coordination number) were set up and each was studied separately. In many cases the coordination number had to be checked by an inspection of the structure from the atomic coordinates. In other cases the coordination number was evident from the chemical formula drawn by the software of the CSD program system. A list of magnesium compounds so selected are given in Table 1. The percentages of the total entries in each magnesium coordination file are listed in Table 2. A review of cation coordination numbers in crystal structures by Brown[18] lists 6.0 as the average coordination number for magnesium ions in inorganic crystal structures. The present analysis of organic crystal structures provides the same information.

(b) Computational Methods. All molecular-orbital calculations were carried out on the CRAY Y-MP computer at the National Cancer Institute, using the GAUSSIAN 90 and GAUSSIAN 92 series of programs.[19,20] RHF calculations with gradient optimizations were employed throughout using the 6-31G* basis set.[21] The effects of electron correlation were included by performing single-point Møller-Plesset (MP) perturbation calculations, in some cases up to the MP4SDTQ/6-31G*//RHF/6-31G* level.[22–24] Vibrational frequencies were obtained from analytical second derivatives calculated at the RHF/6-31G*//RHF/6-31G* level in order to verify that the computed structures were stable states and not transition states[25–27] and to correct reaction energies for zero point vibrational energy differences. Many of the structures were also reoptimized at the MP2/6-31G*//MP2/6-31G* level, with all orbitals active, in order to assess the effects of electron correlation on the geometrical parameters. For a few of the smaller hydrates, further optimizations were performed at the MP2 level, employing basis sets with multiple polarization functions, in order to test the sensitivity of the calculated geometries to the use of more complete basis sets. Finally, generalized second-order densities were computed at the MP2/6-31G*//MP2/6-31G* level in order to study the transfer of charge between magnesium ions and water in a few selected cases[28] and to compare the results with those for the analogous beryllium hydrates.

Results and Discussion

(a) Structural Studies. We selected for analysis those crystal structures in which divalent magnesium is coordinated to oxygen, nitrogen, sulfur, chlorine and/or bromine, since these are the ligands expected in a protein or nucleic acid environment. Most crystal structures in the CSD were studied for a variety of different reasons and therefore it seemed reasonable to study the statistics of the results with respect to coordination number and the nature of the liganding atoms. The coordination numbers found in these crystal structures are listed in Table 1.

Details of the nature of liganding atoms in the crystal structures so selected are also given in Table 1. The single structure with coordination number 3 contained a square Mg–O–Mg–O– structural motif.

A. Crystal Structures with Four-Coordinate Magnesium Ions. The 16 crystal structures with a magnesium coordination number of 4 consist of nine structures containing ethers in which the oxygen atom is coordinated to the magnesium ion. These ethers include diethyl ether, dioxane, and tetrahydrofurane. In five of these crystal structures the magnesium is bound to complexes containing nitrogen. Remaining are two structures—diethyl phosphate and a structure in which magnesium is bonded to four chlorine atoms. No cases were found in which four-coordinate magnesium is bound to water.

B. Crystal Structures with Five-Coordinate Magnesium Ions. Of the 14 magnesium pentacoordinate complexes, 10 are porphyrin or porphyrin-like polycyclic ring systems with one additional axially bound group which is generally water, tetrahydrofuran or, in one case, perchlorate. Other complexes involve O=As groups in one case, O—P bonds, phenol, and a nitrogen-containing heterocycle. An example of a pentacoordinate complex, a tetraphenylporphyrin derivative (refcode BOYFAW), is shown in Figure 1a.[29]

C. Crystal Structures with Seven-Coordinate Magnesium Ions. Crystal structures in which the magnesium ion has a coordination number of 7 are generally crown ether complexes or their analogues. The magnesium binds to five ether oxygen atoms of the crown ether (even when six are available), and binds axially to two other atoms from the solvent or from another complexing agent.[30] In the 18-crown-6 ether complexes one oxygen of the crown ether is extended away from the metal ion as shown in Figure 1b.

D. One Crystal Structure with an Eight-Coordinate Magnesium Ion. The one crystal structure containing octacoordinate magnesium ions (refcode BUGWEF)[31] is a complex of magnesium

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Table 1. Refcodes and Metal Coordination of Crystal Structures Containing Mg^{2+}–O, Mg^{2+}–N, Mg^{2+}–Cl, Mg^{2+}–Br or Mg^{2+}–S in the CSD

		Coordination Number 3			
GAGLIJ	O, O, O	MgOMgO square			
		Coordination Number 4			
BALMGT	N, N, N, O	cube N, THF	FOFLAN	N, N, N, O	THF, complex N structure
BUMGDE10	O, O, O, Br	ether, O- -Bu	JAJYIC	O, O, N, N	THF, cube N
CAVCIL	N, N, Cl, Cl	heterocycle N, Cl	KIKCEM	N, N, N, Cl	Cl, complex N structure
CIPVAY	Br, Br, N, N	heterocycle N, Br	MGALMO	O, O, O, O	dioxane
DAZKOE	O, O, O, O	THF, O═Re with bulky ligands	MGBEET	O, O, Br, Br	ether, Br
DEYVUY	N, N, N, O	ether, complex N structure	MGDETP	O, O, O, O	diethyl phosphate
DILPUJ	O, O, O, Br	ether, Br, O- -C═	NTBHMG	N, N, N, N	complex structure of N
DUPCOG	Cl, Cl, Cl, Cl	4 Cl	SIDNAU	N, N, S, S	bulky N,S chelate
16 entries 4 with THF, 4 with ether, but none with water					
		Coordination Number 5			
AECLPA01,10	4N, O	chlorphyllide + water	GIKCOS	4N, O	polycycle + THF
BOYFAW	4N, O	porphyrin + perchlorate	MCLPHD10	4N, O	chlorophyllide + water
DUJKUO	4N, O	porphyrin + water	MGPCPH	4N, O	plithalocyanine + water
ECPHBH	4N, O	chlorophyllide + water	MPCHLM10	4N, O	chlorophyllide + water
FUJBIV	3O, Br, N	THF + N heterocycle, Br	PPOSMG	5O	4O–P + water
GEPBUY	4N, O	porphyrin + water	SINDAU	5O	THF + phenol
GIKCIM	2N, 3O	polycycle	TMASOM	5O	O═As with bulky groups
14 different entries 11 with porphyrins or closed polycycles, 3 with THF, 9 with water					
		Coordination Number 7			
BZMGIC	5O, 2N	5O of crown, 2N	KASTUT	5O, 2N	4O, 2N of complex, 1 water
FIYXUG	5O, 2Cl	5O of crown, 2Cl	KEGXOJ	5O, 2Cl	5O of crown, 2Cl
FUYCOR	5O, 2N	5O of crown, 2N of NCS	MGEDTA01,10	5O, 2N	4O, 2N of complex, 1 water; also Mg $(H_2O)_6^{2+}$
GECZAP10	7O	4O of crown, 3 water	NAMGED	5O, 2N	4O, 2N of complex, 1 water
8 different entries, all are crown ethers or portions of such, 4 bound to water					
		Coordination Number 8			
BUGWEF	7O	7O of complicated complex, 1 water			

Coordination number 6 with 6 water molecules directly coordinated to Mg^{2+}

	species present but not directly bonded to Mg^{2+}		species present but not directly bonded to Mg^{2+}
ANAPHS	aniline derivative	GIJVEA	$Fe(CN)_6$, hexamethylenetetramine
AQMEDA	EDTA	HMTMGC10	dichromate, hexamethylenetetramine
BAWGOV	N heterocycle	JAPFOV	phthalate
BADTEX01,10	purine	JAPFUB	phthalate
BIKPUG	purine	KAVBUE	Mn EDTA complex
CAWTID	Ga complex	KIMNID	aminophosphonate
CDEDTA11	Cd EDTA complex	MGABES	benzenesulfonate
CIRVAA,01	maleate	MGCITD	also a Mg^{2+} citrate chelate
DECDIY	nucleoside	MGEDTA01,10	EDTA, water
DIPNUL	pyridine	MGHBZA10,20	*p*-hydroxybenzoate
DXMGHC10	dioxane	MGNTSP	nitrosophenolate
FAHSAI	phenoxide	SIMZUJ	orotate
FAPFOR	Mo EDTA complex	TAKZEK	dodecyl sulfate
FOJWOQ	thorium phenolate complex	THIAMG10	thiamine
GATLUI	phosphonate	TOXDMG	crown ether
GAYLUN	ZnATP, pyridine	31 different entries	

with a macrocyclic polyether that had been designed to accommodate small cations such as Mg^{2+} and Li^+, but to exclude larger cations. In this complex, illustrated in Figure 1c, one Mg–O distance is long (Mg···O(12) = 2.49, 2.58 Å for the two molecules on the asymmetric unit compared to an average of 2.2 Å for other Mg···O distances). Seven oxygen atoms of the macrocycle and one water molecule are bound to the magnesium ion. The coordination can be considered octahedral with five equatorial substituents (O1, O16, O23, O26, O29), a pair of axial substituents (O5 and O12) on one side, and a water molecule on the other side. In view, however, of the long Mg···O(12) distance, it might be questioned whether this complex has a magnesium coordination number of 7, or 8.

E. Crystal Structures with Six-Coordinate Magnesium Ions. The majority of structures with magnesium bound to oxygen, nitrogen, chlorine, bromine, or sulfur are hexacoordinate. Of these, there are 31 crystal structures that contain hexaaquated magnesium. These are found in the presence of carboxyl groups, sulfonates, phosphonates, and other anions that would have been expected to bind to the magnesium ion (see Table 1). On the other hand there are 118 different crystal structures in which magnesium binds various complexing groups, but among these, water is often found, as are tetrahydrofuran and diethyl ether. Other common complexing groups are carbonyl, carboxyl, phosphate, and chloride. These structural results are summarized in Table 3.

F. Geometry of Magnesium Coordination. The geometry of the Mg^{2+} coordination sphere was investigated in order to establish its flexibility in this large variety of crystal structures. An example, from a neutron-diffraction study of magnesium hydrogen maleate (refcode CIRVAA01),[12] is shown in Figure 1d. Since all angles in a regular octahedron are 90°, we examined the average values of Mg···O distances and O···Mg···O angles for various coordination numbers. The results are given in Table 4. Note that the average value for a coordination number of 6 is 90.0° and that the standard deviation is low for this coordination number. The narrow distribution of angles is evident. It is clear from Table 2 that oxygen is the preferred ligand of magnesium, that six ligands

Table 2. Chemical Identities of Ligands to Divalent Magnesium[a]

coord no.	% O	%N	% Cl	% Br	% S	no. of entries	%
3	100	0	0	0	0	1	0.5
4	39	38	11	9	3	16	8.5
5	43	56	0	1	0	14	7.4
6[b]	82	9	7	2	0	149	78.8
7	75	18	7	0	0	8	4.2
8	100	0	0	0	0	1	0.5
all ligands	77	14	7	2	0.2	189[c]	

[a] Data for organic crystal structures, extracted from the CSD (1992 version). Remeasurements of the same crystal structure are not included in the count. [b] Includes 31 structures containing $Mg(H_2O)_6^{2+}$. [c] Total number of entries for all elements attached to Mg^{2+} = 272. Of the 83 entries not included in this table, 71 involve at least one Mg–C bond. Other elements bonded to Mg (with number of entries in parentheses) are Si (4), Co (2), Mo (1), Ge (1), H (1), P (1), borane (1) and I (1). In addition, 10 entries (not included in the numbers quoted above) were eliminated because they showed disorder, questionable metal ion identity, or other crystallographic problems (BASLIQ, DASNEQ, DENGEI, EGFEMG, GIMNIZ, KAJYOJ, MGMECL, MGPTOX, MGPOPMG, TFMGHB).

Table 3. Six-Coordinate Mg^{2+} Complexes (Refcodes)[a]

1 water molecule: MPOMGM

2 water molecules: FSALCM, MGPICD, MGBTHF, BEWFOY, CEXWUX, DACAMG, DACAMH, FARCAC, GEYSUY, GEYTAF, MGFORD, MGHMAL, THFMGB, PPOSMG, SAWYUK, URMGBH

3 water molecules: GEYTEJ, BAYJOA, DOMSAZ, VAXJEJ, BOPPOL

4 water molecules: MGEDCU, AQFVMG, INSMGC, MGPHCU, BAWZII, BAYJIU, DIRBUB, DOMSAZ, DURSAK, FELGUY, FUYCAD, JAYPEE, KABRAG, KINMAV, MGMALA, MGMLTE, SEBMIV, VAXHUX, VAXJAF, ZNEDTA, INICMG, MGFORD

5 water molecules: KELDAG, MGSACA

THF (no.): DAZKIY (4), KANHUC (5), KANHOW (5), DIYLAY (6), DUHKOG (4), CIRGOZ (4), MGBTHF (4), MGBTHF (4), MGBTHF (2), CIPXOO (3), COGBUV (3), DIHFIJ (3), DIYLEC (3), DOCFOQ (4), DOMSAZ (3), DOMSAZ (2), DOVGAW (4), GEDFOK (4), JEBNAF (2), JESRII (3), JIGMAN (3), JIGMER (3), KEGNIT (3), KEHBOO (3), OXYWNG (4), SICMOG (2), SICMOG (3), THFMGB (4)

pyridine (no.): BAYJIU (2), BAYJOA (3), CULXEM (2), INICMG (1), MGPICD (2), MGPPYD (4), OEPORM (2), PEPTMG (4), PXMGPY (2), VAXJEJ (1), ZZZAVG (4)

diethyl ether (no.): JIGZUU (2), JIHBAD (2)

carboxylate (no.): GEYTEJ (2), FSALCM (2), BUMREG (1), MGPICD (2), MGPHCU (2), BAWZII (2), BEWFOY, DIRBUB (2), DUJWOU (2), FARCAC (3), FELGUY (2), GAWMIA (6), GEYSUY (4), GEYTAF (4), KABRAG (2), MGHMAL (4), MGMLTE (1), VAXHUX (2), VAXJEJ (2), VAXJAF (2), ZNEDTA, INICMG (1), KIKRIF (6), KIKROL (6), MGEDCU (2), MGFORD (2), MGFORD (6), MGMALA (1), SAWYUK (2), SEBMIV (1)

Methanol (no.): GEPBIM (2), GEPBOS (2), JABHID (6), JABHOJ (6), KAWWIO (6), MGBRME (6)

Ethanol (no.) JADJED (6)

[a] For more details see deposited Table 10S.

Table 4. Average O–Mg–O Bond Angles (in deg) as a Function of Coordination Number (CN) for Crystal Structures in the CSD

	CN = 4	CN = 5	CN = 6	CN = 7
av O–Mg–O angle from the CSD	103.1	94.1	90.0	83.5
std dev	2.5	2.1	0.5	4.3
values from RHF-level MO calcns	109.6	100.3	89.7	

bind around magnesium ions, and that crystal structures containing the hexaaquated cation $Mg[H_2O]_6^{2+}$ are common.

(b) Molecular Orbital Studies. The RHF/6-31G*//RHF/6-31G* and, where available, the MP2/6-31G*//MP2/6-31G* structures of many divalent magnesium cations surrounded by

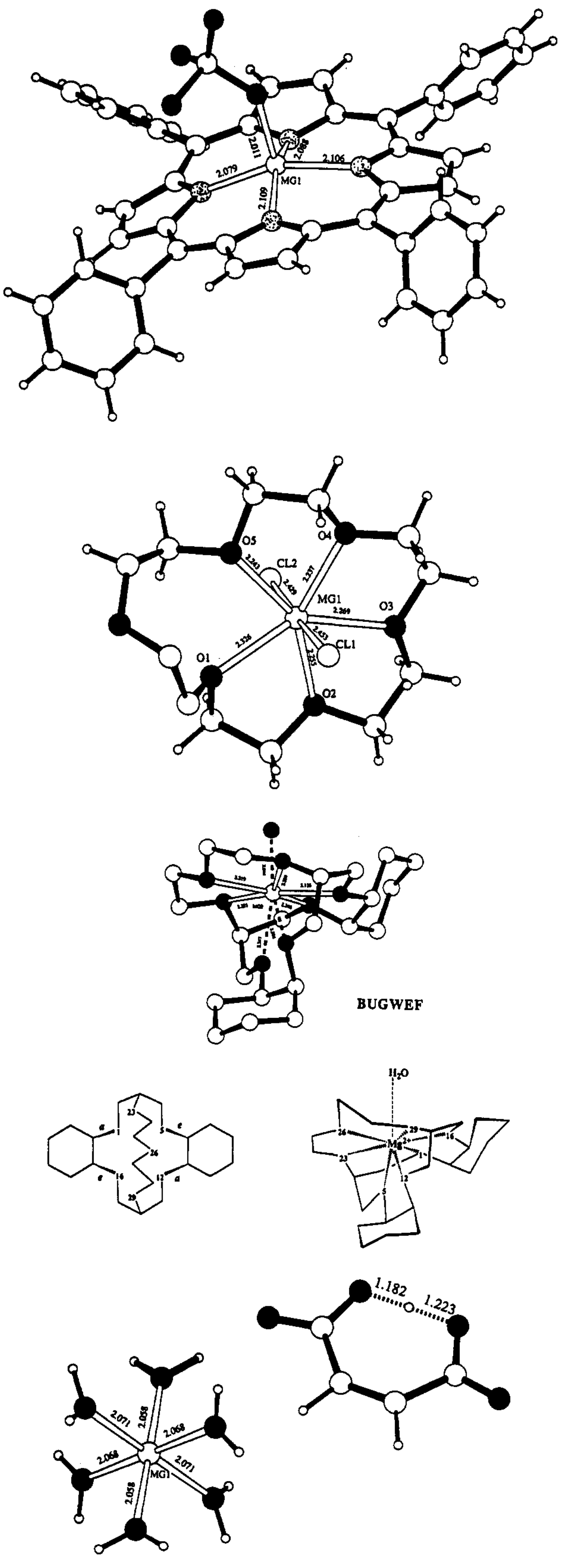

Figure 1. Some structures from the CSD (top to bottom): (a) Porphyrin which contains 5-coordinate Mg^{2+} (BOYFAW); (b) Crown ether (KEGXOJ) showing that only five oxygen atoms are selected and two axial chlorine atoms make up the seven-coordination (note that the sixth oxygen of the crown ether lies distant from the metal ion); (c) Only eight-coordinate magnesium compound (BUGWEF) found in the CSD, shown as view of the molecule and two diagrams of the molecular formula; (d) CIRVAAO1, a neutron diffraction study, showing an $Mg[H_2O]_6^{2+}$ unit which lies independent of the hydrogen maleate anion.

Table 5. Hydration Energies (kcal/mol)[a]

n	m	RHF/6-31G*// RHF/6-31G*	MP2/6-31G*// RHF/6-31G* (FC)[b]	MP3/6-316*// RHF/6-31G* (FC)[b]	MP4SDQ/6-31G*// RHF/6-31G* (FC)[b]	MP4SDTQ/6-31G*// RHF/6-31G* (FC)[b]	MP2/6-31G*// MP2/6-31G* (FULL)[c]
(A) Reaction Energies for $Mg[H_2O]_n^{2+} + H_2O \rightarrow Mg[H_2O]_{n+1}^{2+}$							
0		−82.25	−85.62	−84.54	−84.81	−85.18	−86.18
1		−73.57	−77.22	−76.39	−76.58	−76.96	−77.69
2		−60.78	−63.59	−63.06	−63.16	−63.52	−64.41
3		−49.52	−52.49	−52.12	−52.16	−52.58	−53.34
4		−32.28	−35.77	−35.44	−35.41		−36.83
5		−29.77	−33.21	−32.95	−32.92		−33.78
(B) $Mg[H_2O]_n^{2+}\cdot mH_2O + H_2O \rightarrow Mg[H_2O]_n^{2+}\cdot(m + 1)H_2O$							
3	0	−27.59	−32.27	−31.16	−31.22	−31.82	−32.87
3	1	−25.32	−28.96	−27.94	−27.95		
4	0	−25.34	−29.87	−28.80	−28.84		−30.58
4	1	−24.62	−28.84				
5	0	−24.17	−28.49				
6	0	−19.68	−23.81				

[a] Corrected for zero point vibrational energy differences at the RHF/6-31G*//RHF/6-31G* level. [b] FC = Frozen core, valence orbitals active. [c] FULL = all orbitals active.

up to seven water molecules are shown in deposited Figure 1S (with bond distances and angles) and are diagrammed in Chart 1. Atomic coordinates are listed in the form of Z-matrices in Table 1S of the Supplementary Materials. All the structures shown in deposited Figure 1S have been verified to be local minima by frequency analyses at the RHF/6-31G*//RHF/6-31G* level. The total molecular energies of the structures in deposited Figure 1S at a variety of computational levels are given in deposited Table 2S, and the thermodynamics of various hydration processes are summarized in Table 5. It is clear from Table 5 that including correlation effects are important when these hydration processes are described. It appears, however, that the MP2/6-31G*// RHF/6-31G* level is adequate for estimating the relative reaction energies. Some details of the Mg–O distances and water geometry are given in deposited Table 3S.

It is important to establish the degree to which RHF and MP2 calculations using the 6-31G* basis set adequately describes such structures. Thus, in the case of H_2O, $Mg[H_2O]_n^{2+}$, and $Mg[H_2O]_2^{2+}$, we carried out RHF and MP2 level optimizations using both the 6-31G* basis set and the more complete 6-31G** basis set; see deposited Figure 1S. Although the O–H and Mg–O bond lengths can vary by as much as approximately 0.025 Å at these computational levels, the predicted *changes* in these bond lengths in going from H_2O to $Mg[H_2O]^{2+}$ to $Mg[H_2O]_2^{2+}$ are consistent to approximately ±0.003 Å. Thus, RHF/6-31G* optimizations should be adequate for understanding most of the structural changes that occur as the degree of hydration is varied.

In the case of $Mg[H_2O]^{2+}$ we also carried out MP2/6-31G-(2d,2p), MP2/6-31G(2df,2p), and MP2/6-311G(3df,2p) optimizations to establish a better absolute Mg–O bond length for this molecule. The computed Mg–O bond lengths are 1.9301, 1.9297, and 1.9152 Å, respectively. These results suggest that MP2/6-31G* optimizations yield Mg–O bond lengths which are too long by approximately 0.03 Å. As might be expected, additional d-functions play a more substantial role in determining the length of the Mg–O bond in $Mg[H_2O]^{2+}$ than the length of the Be–O bond in $Be[H_2O]^{2+}$.[15]

A. $Mg[H_2O]_n^{2+}$ (n = 1–6). We consider first hydrated magnesium ions with water constrained to the inner coordination shell. Stable structures were found for $Mg[H_2O]_n^{2+}$ with n = 1–6 as shown in deposited Figure 1Sb,c,d,i,m,o. Attempts to find a stable structure with seven water molecules in the first coordination shell failed; the optimizations led to structures with six water molecules in the first coordination shell and one water molecule in the second coordination shell, hydrogen bonded to two water molecules in the first shell; see deposited Figure 1Sp. An analogous situation was found when we attempted to add five water molecules in the first shell of a divalent beryllium ion;[15] the optimizations led to structures with four water molecules in the first shell and one in the second shell.

Optimizations at the MP2/6-31G* computational level find the Mg–O bond lengths increase in the $Mg[H_2O]_n^{2+}$ structures from 1.948 to 2.097 Å as n increases from 1 to 6, while the O–H bond lengths decrease from 0.989 to 0.975 Å; this latter value is only slightly larger than the optimized O–H bond length in an isolated water molecule, 0.968 Å, at the same computational level. The H–O–H bond angle opens slightly in these structures as n increases. Interestingly, the $Mg[H_2O]_5^{2+}$ structure approximates a trigonal bipyramid as indicated by the bond lengths (2.043–2.053 Å equatorially; 2.092–2.097 Å axially) and the interbond angles (six near 90°, three near 120°, and one near 180°); see deposited Figure 1Sm.

The hydration energies for the addition of another water molecule to the first coordination shell of $Mg[H_2O]_n^{2+}$ (n = 0–5), given in Table 5a, show a monotonic, although not uniform, decrease as n increases. For $n \leq 2$ these energies are significantly less negative than the corresponding values for $Be[H_2O]_n^{2+}$, while the hydration energies for $Mg[H_2O]_3^{2+}$ and $Be[H_2O]_3^{2+}$ are nearly the same. Since we were unable to find a stable structure for $Be[H_2O]_5^{2+}$, we cannot directly compare hydration energies for n = 4 or 5. However, the reaction $X[H_2O]_4^{2+} + 2H_2O \rightarrow X[H_2O]_6^{2+}$ (X = Be, Mg) is more negative for X = Mg. In Figure 2, we plot the hydration energy per water molecule, defined as

$$E_{per} = [E(Mg^{2+}) + nE(H_2O) - E(Mg[H_2O]_n^{2+})]/n \quad (1)$$

computed at the MP4SDQ/6-31G*//RHF/6-31G* level, and corrected for zero point vibrational energy differences computed at the RHF/6-31G*//RHF/6-31G* level. E_{per} drops by nearly a factor of 2 in going from n = 1 to n = 6.

In Figure 3, the net charge on the central magnesium atom, computed from the generalized charge density at MP2/6-31G*//MP2/6-31G* level with all orbitals active, is plotted as a function of n. It is clear that a significant amount of charge is transferred from the surrounding water to the central magnesium ion for all the hydrates, $Mg[H_2O]_n^{2+}$ (n = 1–6). The net positive charge on the central magnesium ion decreases monotonically, but not uniformly, from +1.76 at n = 1 to +1.18 at n = 6. This trend is different from that found in the analogous beryllium calculations in which the net positive charge decreases from +1.40 at n = 1 to +0.77 at n = 4, but then *increases* to +0.98 at n = 6. Furthermore, it should be noted that less charge is transferred in the magnesium hydrates than in the corresponding beryllium hydrates, which suggests that the dative bond component of the Mg^{2+}–O interaction is smaller than the corresponding dative bond component of the $Be^{2+}\cdots O$ interaction.[32]

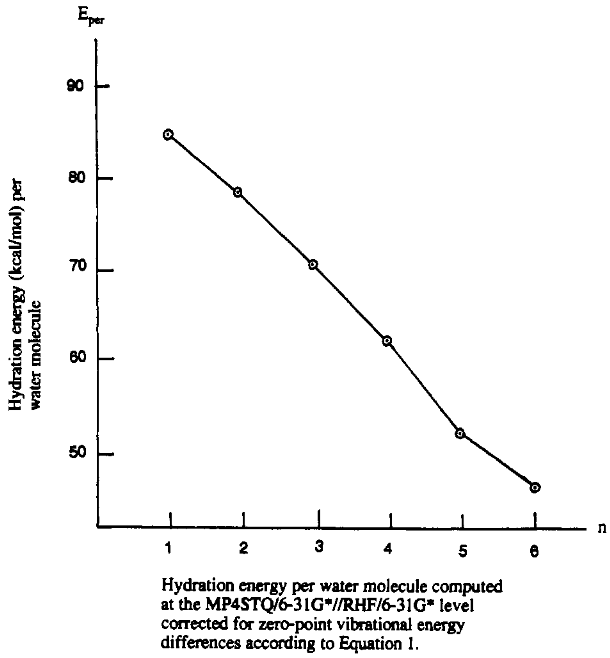

Figure 2. Hydration energy per water molecule computed at the MP4SDQ/6-31G*//RHF/6-31G* level and corrected for zero-point vibrational energy differences, according to eq 1.

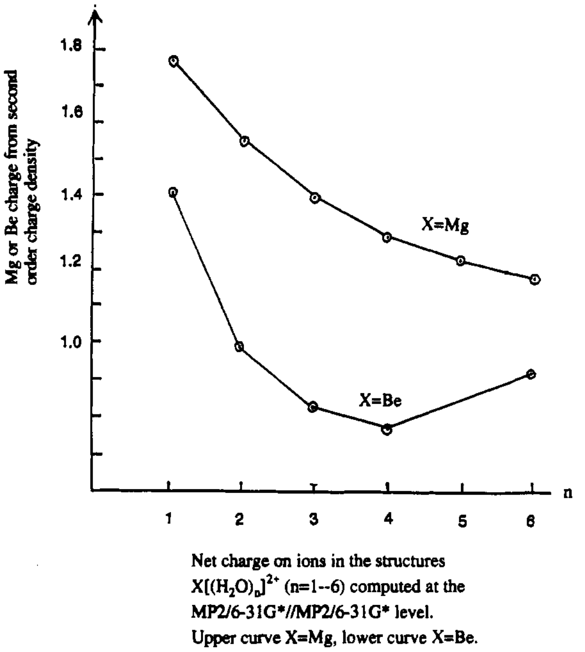

Figure 3. Net charge on the magnesium cations in the structures Mg-$[(H_2O)_n]^{2+}$ ($n = 1$–6), computed from the MP2/6-31G*//MP2/6-31G* charge density, compared with analogous data for beryllium cations.

B. $Mg[H_2O]_n^{2+}\cdot mH_2O$ ($n = 3$–6; $1 \le m \le 3$; $4 \le n + m \le 7$). Several structures of the form $Mg[H_2O]_n^{2+}\cdot mH_2O$, with n water molecules in the first coordination shell and m water molecules in the second coordination shell, were found to be stable, see Deposited Figure 1Se–h,j–l,n,p. In these calculations no symmetry was imposed *a priori* to lessen the chance of optimizing to transition states. We cannot, of course, rule out the possible existence of other stable conformations of these structures. We did not search for stable species of this form for $n = 1$ or 2.

$Mg[H_2O]_3^{2+}\cdot H_2O$, $Mg[H_2O]_4^{2+}\cdot H_2O$, $Mg[H_2O]_5^{2+}\cdot H_2O$ and $Mg[H_2O]_6^{2+}\cdot H_2O$. Stable structures were found with three, four, five, and six water molecules bound to a divalent magnesium ion in the first coordination shell and with a single water molecule in the second coordination shell, hydrogen-bonded to two water molecules in the first shell; see deposited Figure 1Se,j,n,p. In the case of both $Mg[H_2O]_3^{2+}\cdot H_2O$ and $Mg[H_2O]_4^{2+}\cdot H_2O$, the single water molecule in the second coordination shell becomes a part of a symmetrical six-membered ring, similar to the structures found for $Be[H_2O]_3^{2+}\cdot H_2O$ and $Be[H_2O]_4^{2+}\cdot H_2O$.[15] However, at the MP2/6-31G*//MP2/6-31G* computational level the $O_{outer\ shell}\cdots H_{inner\ shell}$ distances are found to be 0.064 and 0.039 Å longer in the magnesium compounds than in the corresponding beryllium compounds, suggesting the formation of somewhat weaker hydrogen bonds between the first and second coordination shells for magnesium. Indeed, the computed exothermicities for adding a single water molecule in the outer coordination shell of Mg-$[H_2O]_3^{2+}$ and $Mg[H_2O]_4^{2+}$ are 6.7 and 3.8 kcal/mol less than those for $Be[H_2O]_3^{2+}$ and $Be[H_2O]_4^{2+}$ at the MP2/6-31G*//MP2/6-31G* level.

In the case of both $Mg[H_2O]_5^{2+}\cdot H_2O$ and $Mg[H_2O]_6^{2+}\cdot H_2O$ the six-membered hydrogen-bonded rings are *not* symmetrical; the two $O_{outer\ shell}\cdots H_{inner\ shell}$ bond lengths differ by 0.011 and 0.014 Å, respectively, at the RHF/6-31G*//RHF/6-31G* computational level. Although the two distinct $O_{outer\ shell}\cdots H_{inner\ shell}$ bond lengths for $Mg[H_2O]_5^{2+}\cdot H_2O$ are similar to those for $Mg[H_2O]_3^{2+}\cdot H_2O$ and $Mg[H_2O]_4^{2+}\cdot H_2O$, the $O_{outer\ shell}\cdots H_{inner\ shell}$ shell bond lengths for $Mg[H_2O]_6^{2+}$ are ~0.03–0.04 Å longer. The hydration energy to put a water molecule in the outer shell of $Mg[H_2O]_6^{2+}$ is some 4.7, 6.1, and 8.5 kcal/mol less exothermic than for $Mg[H_2O]_5^{2+}$, $Mg[H_2O]_4^{2+}$ and $Mg[H_2O]_3^{2+}$, respectively.

In all these molecules, in accord with expectations,[33] the O–H bonds of the water molecules in the inner shell that participate in the hydrogen bonding lengthen, the Mg–O bonds which become part of the ring shorten, and the O–Mg–O angles which become interior angles in the ring are significantly reduced, compared to their corresponding values in $Mg[H_2O]_n^{2+}$.

Comparing the total molecular energies of $Mg[H_2O]_3^{2+}\cdot H_2O$ and $Mg[H_2O]_4^{2+}$, we find $Mg[H_2O]_4^{2+}$ to be 19.7 kcal/mol (19.4 kcal/mol) lower in energy than $Mg[H_2O]_3^{2+}\cdot H_2O$ at the MP4SDTQ/6-31G*//RHF/6-31G* (MP2/6-31G*//MP2/6-31G*) level. Although the corresponding result for beryllium is somewhat smaller, 16.5 kcal/mol (15.4 kcal/mol), it is clear that there is a significant lowering of the energy when four waters are directly bound to either a divalent magnesium or beryllium ion, compared to the case in which only three water molecules are directly bound to the ion and one water is hydrogen bonded to two water molecules in the inner shell.

Comparing the total molecular energies of $Mg[H_2O]_5^{2+}\cdot H_2O$ and $Mg[H_2O]_6^{2+}$, we find $Mg[H_2O]_6^{2+}$ to be only 4.1 kcal/mol more stable at the MP2/6-31G*//RHF/6-31G* level. Thus, while there is an energetic advantage to having six water molecules in the inner shell compared to five water molecules in the inner shell and one water molecule hydrogen bound in the outer shell, the advantage is relatively small. However, structurally the trigonal bipyramidal arrangement of ligands has so many angles near 90° that hexacoordination appears, from an analysis of the CSD, to be preferred.

$Mg[H_2O]_3^{2+}\cdot 2H_2O$ and $Mg[H_2O]_4^{2+}\cdot 2H_2O$. Another water molecule can be added to the outer coordination shell of Mg-$[H_2O]_3^{2+}\cdot H_2O$ to produce $Mg[H_2O]_3^{2+}\cdot 2H_2O$, in at least two ways. In the most stable form, the second water molecule forms a "dangling" hydrogen bond with the unique water molecule in the inner shell of $Mg[H_2O]_3^{2+}\cdot[H_2O]$, which is not part of the symmetrical six-membered hydrogen-bonded ring. The $O_{outer\ shell}\cdots H_{inner\ shell}$ distance of the second water molecule is quite short, 1.632 Å, at the RHF/6-31G*//RHF/6-31G*. The bond lengths, angles and symmetry of the six-membered ring are perturbed only to a small extent by the second water molecule; see deposited

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(33) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991.

Table 6. Average Values of Water Angles (deg) from *ab Initio* Molecular Orbital Calculations

	Be^{2+} hydrates	Mg^{2+} hydrates
no H bond no metal binding	105.4	105.3
no H bond bound to metal	108.7	106.3
one H bond bound to metal	111.4	108.6
two H bonds bound to metal	113.8	111.4

Figure 1Se,f. In the less stable structure, two asymmetrical, but identical, hydrogen-bonded, six-membered rings are formed. As might be expected $Mg[H_2O]_5^{2+}$ is substantially lower in energy, 27.7 kcal/mol, than the most stable form of $Mg[H_2O]_3^{2+}\cdot 2H_2O$ at the MP4SDQ/6-31G*//RHF/6-31G* level.

A second water molecule can be added to the outer coordination shell of $Mg[H_2O]_4^{2+}\cdot H_2O$ in at least two distinct ways to form $Mg[H_2O]_4^{2+}\cdot 2H_2O$. In one form, two symmetrical, hydrogen-bonded, six-membered rings are formed with no bonds in common, and the computed geometrical parameters in the ring are very similar to those in the symmetrical ring in $Mg[H_2O]_4^{2+}\cdot H_2O$; see deposited Figure 1Sj. In the second form one water in the outer shell forms an unsymmetrical six-membered ring, while the other hydrogen bonds to only a single water in the inner shell ("dangling" configuration).

It is interesting to note that the most stable form of $Mg[H_2O]_4^{2+}\cdot 2H_2O$ is only 8.7 kcal/mol *higher* in energy than $Mg[H_2O]_6^{2+}$. In the analogous beryllium compounds, all the $Mg[H_2O]_4^{2+}\cdot 2H_2O$ conformers were more than 20 kcal/mol *lower* in energy than $Be[H_2O]_6^{2+}$.

$Mg[H_2O]_3^{2+}\cdot 3H_2O$. An initial attempt was made to find a stable structure with three identical symmetrical, six-membered, hydrogen-bonded rings, i.e. the so-called "tile" structure of $Be[H_2O]_3^{2+}\cdot 3H_2O$, which was found to be some 10 kcal/mol *lower* in energy than $Be[H_2O]_6^{2+}$.[15] A frequency analysis of the corresponding magnesium structure, however, showed it to be a third-order transition state, some 37.1 kcal/mol *higher* in energy than $Mg[H_2O]_6^{2+}$ at the RHF/6-31G*//RHF/6-31G* computational level. A stable structure of the form $Mg[H_2O]_3^{2+}[H_2O]_3$ was found (see deposited Figure 1Sh), with two distinct unsymmetrical hydrogen-bonded six-membered rings, and one water molecule hydrogen-bonded to a single water of the first shell ("dangling" configuration). The energy of this structure is over 34 kcal/mol less stable than $Mg[H_2O]_6^{2+}$.

We show in Table 6 that as a water molecule is bound to a metal ion the H–O–H angle increases and that, when it forms hydrogen bonds, this angle increases further. This is in line with our results for beryllium hydrates although this effect is more pronounced for beryllium than for magnesium. The hydrogen bonding to outer shell water molecules is found to lie at H···O distances that span a similar numerical range as that found experimentally.[12] The *ab initio* values in the present study lie in the range 1.839–2.145 Å with one additional value of 1.693 Å; experimental values from a neutron diffraction analysis[12] lie in the range 1.815–2.008 Å.

Framework Energies. Some insight into the factors that determine the relative energies of the various configurations of water around a divalent magnesium cation can be obtained by studying the water framework with the central Mg^{2+} ion removed, with no reoptimization of the structure. Consider first the two cases with four water molecules surrounding the magnesium ion, e.g. $Mg[H_2O]_4^{2+}$ and $Mg[H_2O]_3^{2+}[H_2O]$. At the MP2/6-31G*//RHF/6-31G* level with only the valence orbitals active, the framework $[H_2O]_3\cdot H_2O$ is 11.0 kcal/mol *lower* in energy than the more compact $[H_2O]_4$ framework, see deposited Table 4S. Next, *neutral* magnesium atoms were inserted into the two frameworks, which incorporate the appropriate nuclear repulsion energies into the calculations, but reduce the transfer of charge from the surrounding water. $Mg[H_2O]_3^0\cdot H_2O$ is computed to be only 2.0 kcal/mol *lower* in energy than $Mg[H_2O]_4^0$. Finally, if we replace the neutral magnesium atom with a divalent magnesium cation, $Mg[H_2O]_3^{2+}\cdot H_2O$ is 19.1 kcal/mol *higher* in energy than $Mg[H_2O]_4^{2+}$, a net turnaround from the framework energies of 30.2 kcal/mol. Interestingly, in analogous beryllium calculations, the net turnaround was quite comparable, 29.7 kcal/mol.

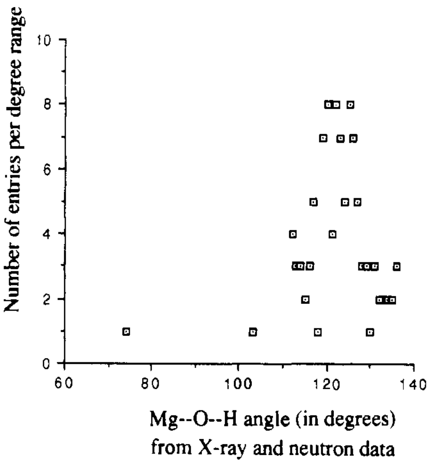

Figure 4. Mg···O–H angles in crystal structures of $Mg(H_2O)_6^{2+}$ complexes.

Consider next the case with divalent magnesium surrounded by six water molecules. As expected, the framework energies decrease as the number of water molecules in the outer shell increases, e.g. $[H_2O]_6$ is 10.9 kcal/mol higher in energy than $[H_2O]_5[H_2O]$, which is 12.9 kcal/mol higher in energy than $[H_2O]_4[H_2O]_2$, which is 5.0 kcal/mol higher in energy than $[H_2O]_3[H_2O]_3$; see deposited Table 4S. If neutral magnesium atoms are now inserted into the frameworks, $Mg[H_2O]_6^0$ is only 0.4 kcal/mol higher in energy than $Mg[H_2O]_5^0\cdot H_2O$, which is 1.5 kcal/mol *lower* in energy than $Mg[H_2O]_4^0\cdot 2H_2O$, which is 3.6 kcal/mol lower than $Mg[H_2O]_3^0\cdot 3H_2O$. Finally, if Mg^0 is replaced by Mg^{2+}, $Mg[H_2O]_6^{2+}$ is now 4.1 kcal/mol lower in energy than $Mg[H_2O]_5^{2+}\cdot H_2O$, which is 4.6 kcal/mol lower in energy than $Mg[H_2O]_4^{2+}\cdot 2H_2O$, which is 25.7 kcal/mol lower in energy than $Mg[H_2O]_3^{2+}\cdot 3H_2O$.

These calculations show clearly that the transfer of charge to the central magnesium cation from the surrounding water molecules is more important in stabilizing $Mg[H_2O]_4^{2+}$ relative to $Mg[H_2O]_3^{2+}\cdot H_2O$ than in stabilizing $Mg[H_2O]_6^{2+}$ relative to $Mg[H_2O]_5^{2+}\cdot H_2O$. This is in agreement with the fact that the rate of change of charge transfer to the magnesium decreases as the number of water molecules in the inner coordination shell increases; see Figure 3.

(C) Orientation of Water Molecules. The orientation of water molecules on the coordination octahedron of Mg^{2+} was investigated by use of crystal structures from the CSD and the results of the *ab initio* molecular orbital calculations. In X-ray diffraction results we eliminated crystal structures containing elements heavier than sulfur, those with *R* values greater than 0.08, and those with no reported hydrogen atom positions. The results are shown in Figure 4 and deposited Tables 5S and 6S, which indicates that the optimal Mg···O–H angle lies in the range 120–128°. The average Mg···H distance is 2.61 Å, and the average Mg···O distance is 2.07 Å. In spite of the problem of locating hydrogen atoms in such crystal structures, the O–H vector is usually well defined even if the O–H bond is apparently short. In the neutron diffraction study of $Mg[H_2O]_6^{2+}$ in a hydrogen maleate salt,[12] the average Mg···O distance is 2.066 Å (minimum 2.058 Å; maximum 2.071 Å), the average Mg···O–H angle is 125.2° (minimum 122.9°, maximum 126.6°), and the average Mg···H value is 2.70 Å. These compare well with average *ab initio* values of 2.097 Å for Mg···O at the MP2/6-31G*//MP2/6-31G* level (approximately 0.03 Å longer than the experimental value, as expected, see earlier), 126.2° for the Mg···O–H angle and 2.70 Å for Mg···H.

These experimental and computational results indicate that there is no likelihood of hydrogen bonding between two adjacent oxygen atoms on the coordination polyhedron of Mg^{2+} (which would give Mg···O–H angles near 45°). The geometrical results suggested that the slight positive charges on the hydrogen atoms are repelled by that on the magnesium cation. In addition, the experimentally found arrangement of water molecules favors the buildup of an additional layer of water molecules or of anions.

The magnesium ion gathers six oxygen atoms (the first coordination sphere) around it at a distance of 2.0–2.1 Å. We have shown that water molecules lie on this coordination sphere with Mg–O–H angles of approximately 127°. The second coordination sphere of oxygen atoms has a radius of approximately 4.3 Å (with magnesium in the center), enough to accommodate about 30 close-packed oxygen atoms. This distance is verified in, for example, the crystal structure of magnesium citrate decahydrate[34] in which distances between Mg^{2+} and oxygen atoms hydrogen bonded to water molecules in an $Mg(H_2O)_6{}^{2+}$ unit are 4.30, 4.25, 4.31, 4.62, 4.11, and 4.27 Å apart. When there is steric strain, of course, these distances may be decreased or increased slightly (as shown by the experimental values just quoted).

Conclusions

We have shown by *ab initio* molecular orbital calculations that there exist a variety of stable structures with four, five and six water molecules partitioned between the first and second coordination shells of divalent magnesium cations. In all these cases, however, the lowest energy structure is such that it has the maximum number of water molecules (six) packed into the first coordination shell. Of considerable interest is the weaker hydrogen bonding to the second coordination sphere, compared to values reported for the aquation of beryllium.[15] The overall conclusion is that magnesium accommodates well a coordination number of 6, but this arrangement is energetically not much more favorable than one with five water molecules in the first coordination shell and one in the second or one with four in the first and two in the second. No case of seven water molecules in the first coordination shell could be found, even though results from X-ray crystallographic studies were used to generate starting coordinates. This tendency for a magnesium ion in an aqueous environment to coordinate six groups, preferably oxygen ligands, is also shown by an analysis of crystal structures of organic compounds. The coordination number found ranges from 3 to 8 (with one entry in each 3 and 8). By far the largest number of crystal structures show a coordination number of 6, as already reported for inorganic structures.[18] Those crystal structures with coordination numbers 5 and 7 mostly contain polycyclic chelating agents such as porphyrins or crown ethers. In these four or five ligand atoms, respectively, are constrained in position by the polycyclic system. For those crystal structures with coordination numbers of 6 the hexaaquated magnesium ion is common. Other crystal structures with varying numbers of bound water exit, so that 50.3% of six-coordinate structures with bound O, N, Cl, and Br (43.9% of all such crystal structures) have at least one water molecule bound to the magnesium ion. In addition, other binding groups commonly found include ethers such as diethyl ether and the cyclic ethers tetrahydrofuran and dioxane.

The main feature in the packing of water molecules around a magnesium ion appears to be the Mg···O–H angle, which tends to lie near 120–128°. This serves to orient groups in the second coordination sphere that receive hydrogen bonds from Mg-bound water molecules. The 6-fold coordination of magnesium ions, established here as most likely in an aqueous environment, is found in several protein crystal structures.[3–7] Side chain carboxyl groups are the most common ligands of magnesium ions in native proteins, and the remaining coordination sites are filled with water molecules. Some or all of these water molecules are replaced by groups such as carbonyl, carboxyl, or hydroxyl groups on ligands when they bind to the enzyme.

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Supplementary Material Available: Table 1S, giving atomic coordinates (Z matrices) of results of *ab initio* molecular orbital calculations, Table 2S, giving total molecular energies (au) and zero point vibrational energies (kcal/mol) of hydrated magnesium cations, Table 3S, giving details of molecular geometry at the RHF/6-31G*//RHF/6-31G* level for $Mg(H_2O)_n{\cdot}mH_2O^{2+}$, Table 4S, giving framework effects, Table 5S, giving Mg···O···H angles, Table 6S, giving the geometry of water molecules at the RHF/6-31G*//RHF/6-31G* level, Table 7S, giving charges on oxygen atoms. Table 8S, giving charge on magnesium ion. Table 9S, giving changes in geometry on addition of a second sphere water molecule, Table 10S, listing a bibliography of crystal structures discussed in this study (from the CSD), and Figure 1S, showing diagrams of the molecular geometry of the results of *ab initio* molecular orbital calculations. (54 pages). Ordering information is given on any current masthead page.

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