A Comprehensive Energy Component Analysis of the Interaction of Hard and Soft Dications with Biological Ligands

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Abstract: The interactions of the ions Zn^{2+}, Mg^{2+}, Ca^{2+}, and Cd^{2+} with biological ligand models are analyzed with an energy decomposition method giving the contributions of electrostatics, exchange repulsion, ligand polarization, ligand-to-cation charge transfer, and the electronic correlation effect. The last two energy terms best correlate with the selectivity of ligands between group IIA and IIB ions and are therefore associated with chemical hardness and softness. The charge transfer is inhibited in a complete ligand shell and so the correlation effect, primarily a ligand–cation dispersion-like interaction, may be a more important factor in solution selectivity. The components associated with ionic binding are very similar for group IIA and IIB ions of similar size, suggesting no special stabilization for hard–hard ligand–cation pairs. Soft ligands are more selective for soft cations and hard ligands are simply non-selective with water being the least selective ligand. Other selectivity effects are discussed and the charge transfer is also analyzed in terms of physical atomic partial charges derived from dipole gradients.

Introduction

This work reports investigations of the interaction properties of the ions Zn^{2+}, Mg^{2+}, Ca^{2+}, and Cd^{2+} with model ligands containing functional groups commonly found in biomolecules. Electronic issues regulating selectivity are explored by comparing the binding of one ligand versus a water molecule. We also briefly show that the major distinctions found for the dication properties still hold with a completed first shell of ligands. The analysis suggests that a sensible theoretical model of the electronic interaction qualities can be constructed from an energy component decomposition of *ab initio* quantum chemical calculations.

The role of electronic effects in cation–ligand selectivity is the assumed basis of the theory of hard-and-soft acids-and-bases (HSAB).[1,2] However, the detailed nature of HSAB effects has only been the subject of theoretical speculation[1,2] while authors concentrated on developing hardness scales[1,3] and empirical models of interaction strengths.[4] The absence of a direct view of the interactions has allowed criticism of the HSAB theory because of observations of presumed violations, i.e. strong hard–soft interactions in biomolecules.[5] The results presented here appear to satisfactorily explain electronic factors relating these mismatched interactions to hard–hard and soft–soft complexes. The result is an accurate formulation focusing on the purely comparative nature of the HSAB concept.

An energy decomposition analysis, as pioneered by Morokuma and other quantum chemists,[6] is suitable for this analysis purpose. The simplified version used here[7] breaks down an interaction into components of electrostatics and exchange repulsion plus polarization and charge transfer. The first two components describe purely ionic bonding associated with the unperturbed ion and ligand charge distributions. The last two represent electronic relaxation effects primarily associated with the polarizable ligand electrons. All of this relaxation contributes to bonding, but in molecular orbital terms most of the charge transfer and some of the polarization effect must come from modifications of a ligand lone pair orbital in forming a dative covalent bond with the cation.

The decomposition can therefore indicate specific physical origins for phenomena of energetics and structure that might be observed in the *ab initio* results. A notable success of this sort involved analyses of *ab initio* calculations on neutral hydrogen bonds. These studies indicated that the electrostatic component of the interaction correlated with the total energy for variations of angular coordinates.[8] Concurrently it was shown that energy minimization of a simplified electrostatics model based on atomic multipoles with hard-wall atomic distance restraints could closely reproduce the observed structures of hydrogen-bonded complexes.[9]

The situation is more complicated for the dication complexes considered in this work because the strong electrostatic fields induce very significant electronic relaxation effects in the ligands. The Morokuma energy decomposition produces significant numerical values for most of its terms, including the remainder term, E_{MIX}.[10] Early theoretical studies of biological ligand interactions with Zn^{2+} by Pullman and co-workers[11] therefore only reported the total effect of electronic relaxation as a delocalization energy and relied on Mulliken-style charge density breakdowns and density deformation plots for further analysis.

The strength of the relaxation effects requires that we use a basis set of near-Hartree-Fock-limit quality as described and verified below. Good consistency in the numerical quality of the results is very much required for the comparisons presented here. A recently proposed Hartree–Fock supermolecule energy decomposition called the reduced variational space (RVS) scheme[7]

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provides for a simple and elegant analysis. This has fewer terms than the popular Morokuma scheme and all have a distinct putative physical meaning. These capabilities allow for a significant expansion over the scope of previous studies in that electronic factors including electronic correlation can be related to observable selectivity effects for a variety of ligand and dication types.

The methods of this study are similar to those that Bagus and coworkers have applied successfully to studies of the interaction of neutral metal clusters with ligands.[12] The important π orbital metal-to-ligand donation they often found is excluded in this work because the ligands are all poor electron acceptors. The other energy terms are also of such large magnitudes that electronic relaxation of the cations plays a relatively minor role.

It is expected that binding energies and selectivities for ions can only be fully analyzed through a realistic simulation of the ligands. A future report[13] will describe explicit functional representations of the RVS energy terms developed from physical principles and then fitted to numerical results such as given here. A representation in this form updates the Sibfa molecular mechanics force field[14] for general calculations on biomolecules that might bind various cations. The use of an accurate force field model with electronic effects built in can add to the correlative analysis of this work with reliable studies of specific molecules.

A more complete view of electronic redistribution is provided by supplementing the energetic analysis with a measure of the final charge density distribution. This is usually reported in the form of integrated atomic partial charges. However, distribution differences between related structures are usually quite small and can be obscured by basis set effects in the Mulliken analysis. The method described next instead uses a physical property, the dipole moment derivative,[15] to estimate the amount of ligand to cation charge transfer. The results agree with major expected trends but also show interesting distinctions from the energetic measure of charge transfer in the RVS analysis.

Methods

Dinur and Hagler[15] noted that when one atom in a planar molecule is infinitesimally displaced in a perpendicular direction an atomic partial charge can be defined as

$$q_i = \mu_\perp / \Delta x_i \qquad (1)$$

from the normal dipole moment component linear in Δx. A physical argument supporting this starts from the proposition that the dominant charge movement accompanying atomic displacement consists of the movement of the charge naturally associated with the atom plus a flow of charge between atoms. For a small normal displacement, the flow of charge between atoms must have only a quadratic dependence on the displacement. The normal dipole moment then results exclusively from the atomic charge of the displaced atom. The assembly of these atomic charges also has the desirable property of reproducing the molecular dipole moment.[15]

We note that this physical argument also allows for a partial charge generation for atoms lying on a reflection plane in a nonplanar molecule. A perpendicular displacement produces charge flows from atoms on one side of the plane which are counterbalanced by charge flows from the other side and so eq 1 should still be valid. The optimized structures of the complexes examined here are either planar or have the dication located on a reflection plane. We are therefore able to report a measure of the amount of charge transfer from a ligand to a dication from cation partial charges based on a calculated physical property rather than some integration scheme.

Table 1. Brief Description of the RVS Analysis As Used in This Work[a]

MO basis set				HF energy breakdown
Cat$_{occ}$	Lig$_{occ}$	[Cat$_{vac}$]	[Lig$_{vac}$]	$E_C + E_L + C + EX$
Cat$_{occ}$	[Lig$_{occ}$]	Cat$_{vac}$	Lig$_{vac}$	$E_C + E_L + C + EX + POL_C + CT_{C\rightarrow L} + BSSE_{C\rightarrow L}$
[Cat$_{occ}$]	Lig$_{occ}$	Lig$_{vac}$	[Cat$_{vac}$]	$E_C + E_L + C + EX + POL_L$
[Cat$_{occ}$]	Lig$_{occ}$	Lig$_{vac}$	Cat$_{vac}$	$E_C + E_L + C + EX + POL_L + CT_{L\rightarrow C} + BSSE_{L\rightarrow C}$
Cat$_{occ}$	Cat$_{vac}$	*Lig*$_{occ}$	*Lig*$_{vac}$	$E_C + BSSE_{C\rightarrow L}$
Lig$_{occ}$	Lig$_{vac}$	*Cat*$_{occ}$	*Cat*$_{vac}$	$E_L + BSSE_{L\rightarrow C}$

[a] The component orbital sets are listed in the order used for an initial guess. The brackets indicate that the orbital set was constrained during an HF calculation. Italics designate that only the basis functions were included as in a counterpoise calculation.

These calculations were performed by displacing the dication by 0.02 Å perpendicular to a reflection plane. This step size is a compromise between smaller values amplifying numerical error and larger values suffering from nonlinearity of the dipole moment. The changes in the perpendicular dipole components were noted and estimated to give consistent precision of at least 0.01 electron for the charges from eq 1. Dipole moment differences are computed with respect to a fixed point in the ligand structure. The results are therefore well-defined for the charged species while the individual dipole moments are origin-dependent.

In the case of the water and formate ligands there are always two reflection planes in the optimized structures and charges were computed from both possible perpendiculars. Average values of the charge transfer amounts are reported for these ligands in Table 8. The two results differed by approximately 0.03 electron on average in the eight specific cases. This suggests that intrinsic charges are associated with the cations with useful accuracy according to the rationalization discussed above.

The RVS energy analysis has been implemented in a version of the Hondo code.[16] The required calculations and decomposition are described in Table 1 using the notation of Stevens and Fink.[7] Electrostatic (C for Coulomb) and exchange (EX) energies are computed from the unperturbed cation and ligand wave functions. Polarization (POL_L) and charge transfer ($CT_{L\rightarrow C}$) terms are reported for relaxation of ligand electronic structures. Only the total of the polarization and charge transfer is reported for the relaxation of the dication electron density because these terms are always comparatively small. The difference of the Hartree–Fock and MP2 interactions after basis set superposition error (BSSE) correction is additionally reported as the CORR term.

The origins of the correlation effects in these interactions can be elucidated. The occupied canonical Hartree–Fock orbitals for the ion–ligand complexes were found to be separable into groups associated with the ionic core or with the strongly perturbed ligand valence space. For example, 1s, 2s, and 2p core orbitals for magnesium and 1s, 2s, 2p, 3s, 3p, and 3d orbitals for zinc were easily identifiable. In these orbitals, the contaminating coefficients of the ligand basis functions were usually smaller than 0.01 au in magnitude. The MP2 correlation energy is a sum of pair energies associated with excitations from two occupied spin orbitals. The effect of correlation within the ion core or within the ligand valence space can be calculated by summing the appropriate pair energies which are printed by the Hondo code. These sums may be compared with the correlation energy of the isolated ion or ligand, and the resulting interaction terms give contributions to selectivities. The pair energies involving simultaneous excitation of an ion core orbital and a ligand valence orbital given a distinct interaction term representing dispersion between the core and the relaxed ligand.[17] This decomposition of the CORR interaction is reported below in Figure 2 to show that the role of this term in selectivity for Zn^{2+} versus Mg^{2+} is primarily due to the dispersion-like interaction.

One other modification of the basic RVS scheme was to use the complete counterpoise correction for reported total interaction energies. This was adopted primarily to allow the use of the Gaussian[18] code direct methods for the largest calculations. These could not accommodate the virtual

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counterpoise correction used in the original RVS paper.[7] The BSSE component inherent in the CT terms was subtracted out also as indicated in Table 1.

The definitions in the RVS analysis do not necessarily result in the sum of the individual terms being equal to the total interaction energy. The reasonableness and completeness of the decomposition was originally verified for application to hydrogen-bonded systems by summing the terms and noting that the remainder was comparatively negligible.[7] The same test can be applied to the entries in Tables 7 and 9 which validates the method for this application to much stronger interactions. The major neglected factor in the RVS analysis format compared with the full Hartree–Fock treatment appears to be the lack of self-consistent relaxation effects in the analysis terms. This is probably not a major factor in the class of interactions studied here because the primary relaxation of the cation electrons in response to the presence of the ligands appears to be minimal. The self-consistent or mutual polarization response is then also expected to be negligible.

In addition to calculations with various single ligands, complete water shells of six ligands with group T_h symmetry were also examined for each dication. The water shell was considered as one component in the RVS analysis. The partial charge calculation described above was also carried out for these complexes. This provides detailed information on changes in going to a complete ligand shell. This is important for estimating whether selectivity factors examined for individual ligands can apply in a condensed phase.

The RVS energy decomposition includes a sizable charge transfer term resulting from relaxation of electron density of the ligand into the virtual orbitals of the cation. The ligand polarization energy conversely has only relaxation into the ligand virtual orbitals. There is some ambiguity in these definitions because the virtual orbitals of the ligand and cation will have extensive overlap. A change in the diffuse components of the cation or ligand basis set can therefore redistribute some of the relaxation between the virtual sets of the ligand and cation. Part of the energy lowering is then redistributed between the charge transfer term and the polarization term.

We wish to minimize the differences between the analysis terms and the physical concepts of charge transfer and polarization. This might be accomplished by using basis sets optimized to represent the corresponding charge density components so that the overlap of the basis functions of another species could only have a minor effect. This starts with basis sets which are energy-optimized for the valence spaces. Added diffuse basis set components are optimal to represent the polarization of a ligand in an electric field. The polarization component of the ligand might thus adequately represent that electronic relaxation which is independent of the particular virtual orbital structure of a given cation. The cation basis sets are energy-optimized for valence states and have the flexibility to represent various charge states. This allows for a description of the dication valence charge distribution with various amounts of charge transfer from ligands.

Core-effective-potential (CEP) basis sets in 31 contractions[19] were used for the ligand atom valence representation. The outer shells are somewhat more diffuse than the comparable all-electron 6-31G basis set which may aid in representing concentrations of negative charge in the anionic ligands. This was supplemented by approximately energy-optimized d polarization functions for non-hydrogen atoms. These improve the quality of the charge distribution as reflected in the electrostatic moments and reduce BSSE effects for the interaction energies. A more diffuse set of d polarization functions was also included to represent electronic polarization in an external field. The particular exponents are approximately optimal for this purpose as measured by the quality of computed dipole polarizabilities.[20] These shells should also be important in reproducing dispersion interactions affecting the CORR term. All of the polarization exponents are listed in Table 2. Further extensions such as diffuse valence functions and polarization functions on hydrogen atoms were found to have comparatively minor effects on the interaction properties of the ligands at the Hartree–Fock level.

Table 2. Polarization Functions Used in This Work

carbon	d (0.75) and d (0.15)
nitrogen	d (0.77) and d (0.15)
oxygen	d (0.80) and d (0.20)
sulfur	d (0.70) and d (0.13)
magnesium	0.15 × d (1.93) + 1.0 × d (0.41)
calcium	0.41 × d (1.78) + 1.0 × d (0.38)
zinc	f (0.90)
cadmium	f (0.63)

Table 3. HF Binding Energies with Constrained Water Structure and No BSSE Correction[a]

	Mg^{2+}–water		Ca^{2+}–water	
basis	R_{Mg-O}, Å	BE, kcal/mol	R_{Ca-O}, Å	BE, kcal/mol
cation CEP	1.98	–75.7	2.24	–55.2
CEP + 2 d shells	1.94	–79.0	2.01	–64.5
cation X31G	1.94	–78.3	2.36	–50.2
X31G + d shell	1.94	–81.0	2.31	–53.2
X31G + 2 d shells	1.92	–81.3	2.29	–54.5
X31G + 2d contraction	1.92	–81.1	2.29	–54.4
large basis of ref 22	1.90	–81.9	2.26	–54.3

[a] The ligand basis is CEP-31G(2d) excepting the literature result.

Table 4. A 6-6631G Calcium Basis Set

	α_{sp}	C_s	C_p
1s	31 417.566 039	0.002 081	
	4 726.370 923	0.015 950	
	1 079.891 806	0.076 391	
	312.896815	0.246741	
	102.813706	0.478478	
	35.556407	0.321348	
2sp	532.379177	–0.004296	0.005 705
	128.224113	–0.051288	0.040 564
	42.834752	–0.130341	0.147 609
	17.055291	0.126415	0.304056
	7.419820	0.595750	0.364988
	3.223513	0.443072	0.188166
3sp	16.685172	–0.005801	–0.008449
	5.262959	–0.211384	–0.014585
	2.254210	–0.059027	0.148494
	0.975785	0.604765	0.346782
	0.466207	0.517351	0.255526
	0.252132	0.128245	0.106897
4sp	0.359751	–0.209427	–0.037784
	0.119347	0.140887	0.185896
	0.052489	0.831324	0.559205
5sp	0.022463	1.000000	1.000000

The proper basis set selection for the dications was a more complex issue. CEP basis sets of the same class as for C, N, O, S exist for magnesium[19] and calcium[21] in which all of the electrons except for the outer valence pair are replaced by effective potential operators. These give Hartree–Fock optimized structures and binding energies for a water molecule binding to the dications reported in Table 3. The Mg^{2+} results did not agree well with previous large basis all-electron calculations of Bartolotti et al.[22] We also tried adding d polarization shells to the dications which shortened and strengthened each interaction. The magnesium results are then reasonable if it is assumed that the magnesium core polarization would contribute a small amount to the binding strength. However, the particularly strong and short contact with calcium is a likely indicator that the effective potential approximation as applied in ref 21 is breaking down. This pattern of good results with magnesium and too strong binding with calcium has also been reported for another type of effective core potential.[23]

We therefore chose to use roughly equivalent all-electron basis sets instead of the CEP types for group IIA. The 6-631G basis set for magnesium[24] should be of comparable valence quality to the CEP-31G. A 6-6631G basis reported in Table 4 was generated for calcium by a sequence of optimizations like those for Mg described in ref 24. These basis sets were tested by comparison to runs with extensive decontraction

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Table 5. Binding Characteristics for Constrained Water with BSSE Correction after HF Optimization

cation basis	R_{M-O}, Å	BE_{HF}, kcal/mol	BE_{MP2}, kcal/mol
Zn CEP	1.90	−87.4	−90.4
Zn CEP + f	1.89	−88.7	−95.7
Cd CEP	2.15	−66.0	−68.2
Cd CEP + f	2.13	−67.4	−74.0

plus extra diffuse sp shells. These showed only small deviations in the interaction properties.

The role of polarization functions for the all-electron basis sets was examined. The results warranted the addition of a contracted d shell for each. The exponents for one or two extra d shells were optimized by minimizing the interaction energy of the dication with water. This is approximately a variational procedure because only the $x^2 + y^2 + z^2$ component of each d shell contributes to lowering the dication HF energy and this turns out to be numerically insignificant. Similar cation d-exponent trials with hydroxyl and ammonia ligands suggested that the optimal exponents were essentially transferable.

Results for the water interactions are given in Table 3 without BSSE correction to compare with the results from ref 22. This shows that two d shells have an effect for calcium but very little for magnesium. For the more strongly bound hydroxyl ligand there is a 2 kcal/mol effect from doubling the polarization with Mg^{2+} and 8 kcal/mol with Ca^{2+}. Two d shells were therefore retained and used for both dications. It was found that these shells could be transferably contracted by an analogous optimization of the interaction with water. The exponents and contraction coefficients are reported in Table 2. The d component of atomic population for these dications is always small. We therefore do not expect to find comparable changes from f functions.

For the group IIB ions we use the large CEP basis sets reported in ref 21 which are dense with basis functions in the valence space. Here there is an occupied spd shell of electrons separating the metal valence shell from the effective potential regime which should guarantee that the results would be equivalent to a relativistic all-electron calculation. These basis sets have also been shown to accurately reproduce the all-electron energetics for distinct atomic states.[21]

The role of polarization functions was examined for group IIB. Additional more diffuse d shells had very small effects on the HF structures and interactions and small effects on the MP2 binding energies. The Zn 411 and Cd 311 contractions developed for the outer occupied d-shell energetics[21] thus appear to also suffice for representing the small valence d character and polarizations. An f-shell exponent was optimized to maximize the binding strength for each dication with a water ligand. The f-shell exponents listed in Table 2 are also approximately optimal for hydroxyl and ammonia ligands. The summary of HF properties and MP2 binding energies is given in Table 5.

For all ligands the added f shell has a modest effect at the HF level but the correlated binding becomes significantly stronger. A dominant dispersion-like interaction between the outer dication d shell and the ligand valence shell electrons appears to be responsible for this. The f shell is required to properly represent the group IIB d electron excitations. Additional f shells or higher angular momentum functions were not considered.

The treatment for zinc was compared with all-electron calculations using a triple-ζ basis set for all atoms provided in the Gamess[25] quantum chemistry package. Polarization shells given in Table 2, including the f shell for zinc, were retained. A water ligand optimized to a contact distance of 1.89 Å with binding energy of −89.3 kcal/mol after BSSE correction. A hydroxyl ligand contact distance was 1.74 Å with a binding energy of −412.4 kcal/mol. The CEP basis optimized distances are given in Table 6 and their corrected HF interactions are −88.7 and −414.9 kcal/mol, respectively. These results show the modest variations we expect from using the CEP approximation and more limited valence basis sets.

All of the geometry optimizations have been performed at the HF level with fixed ligand geometries previously used with the Sibfa molecular modeling method.[13] The f shells were not included at this stage because the Gaussian code used lacks gradient capability for f shells mixed with CEP's. The basis set selection described above was limited by the need to perform calculations on complete ligand shells for this work. Results from single-ligand complexes are also being used to update the Sibfa force field.[13] Comparisons with complete shells are required for this purpose as well because of the extensive many-body interactions in this force field.

Interactions computed with the current methods are probably within a few kilocalories per mole of HF-limit energetics and should be qualitatively correct for representing trends from the energy component analysis. However, the correlated methods probably can have double-digit errors in the worst case. The BSSE at the MP2 level as measured by the complete counterpoise correction is greater than 10 kcal/mol for a few of the calculations with the anionic ligands. The HF BSSE is always only a fraction as large and usually less than 2 kcal/mol.

Results

The HF-optimized cation–ligand distances are given in Table 6 for a selection of representative biological ligand models. The force constants for stretching the close contact are listed also. These were computed numerically from several small distance variations at the HF and MP2 levels and with BSSE correction. The stretching motion for the bidentate formate structures was applied along the C_{2V} axis. The numerical force constant determination also yielded estimates for the correlation effect on the contacts which was usually an increase in distance of only 0.01 or 0.02 Å. The BSSE corrections were always less than 0.01 Å and caused less than 2% changes in the force constants.

The force constants span a range of values, but it is not as wide as the range of binding energies reported in Table 7 because the force constants for neutrals and anions are overlapping. The large differences in the electrostatic interaction dominate in the binding energy differences with different net charges. However, the inverse first-power distance dependence of the charge interactions should produce increased negative curvature for anionic ligands. The other interaction terms with shorter range and potentially greater curvature are therefore operating with relatively larger effect on the force constant trends.

A specific trend in the force constant behavior shows up in comparing zinc with magnesium or cadmium with calcium. The force constants for the neutral ligands and formate are almost always slightly larger for a group IIB ion compared with the group IIA ion of roughly corresponding radius. The other anionic ligands generally have the opposite trend with some relatively large differences favoring stiffer contacts for magnesium and calcium. The concentration of negative charge at the ion contact is therefore important in the comparative behavior of the ions from different columns of the periodic table.

Work being carried out to parametrize Sibfa potential energy functions using RVS analysis terms has required a more extensive study of structural variations than reported here.[13] This may better indicate physical origins of these force constant trends. The differences may operate to produce minor thermodynamic zero-point corrections to the interactions given here, but the methods and goals of this work do not put us in a position to calculate these accurately or to relate to condensed phase trends. However, it is interesting to see that force constants can be as distinctive in this context as they commonly are for chemical bonds in organic molecules.

Ion Selectivity Trends and RVS Analysis. Before discussing the binding characteristics of specific ligands we will discuss general results from the RVS analysis. The energetics of binding for all single ligand structures considered in this work are given in Table 7. A simple observation is that the polarization plus charge transfer coming from the cations is a minor effect. The magnitude of this parallels the relative polarizability of the individual cation cores in the order Cd > Zn > Ca > Mg. The small magnitudes make these terms relatively unimportant in comparisons of selectivity factors.

The selectivity of various ligands for ions may be examined through plots such as Figure 1 showing the differences in the larger energy terms between zinc and magnesium. The total selectivity between the dications is the ΔBE calculated at the

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Table 6. Close Contact Distances from HF Optimization (R) and Corresponding Stretching Force Constants (FC in kcal/(mol Å^2)) after BSSE Correction

		OH_2	CH_3OH	H_2NCHO	NH_3	$NHMe_2$	imidazole	HCO_2^-	OH^-	CH_3O^-	CH_3SH	CH_3S^-
Zn	*R*	1.90	1.88	1.80	1.98	1.98	1.89	1.98	1.75	1.75	2.31	2.18
	FC_{HF}	343	381	501	307	304	422	363	668	639	218	294
	FC_{MP2}	318	351	459	268	253	365	334	585	524	176	244
Mg	*R*	1.92	1.90	1.80	2.07	2.04	1.95	1.94	1.69	1.69	2.42	2.24
	FC_{HF}	288	319	457	234	246	337	337	780	763	170	281
	FC_{MP2}	296	327	469	232	239	330	337	789	773	159	272
Ca	*R*	2.29	2.26	2.13	2.46	2.40	2.31	2.23	1.94	1.95	2.81	2.50
	FC_{HF}	162	182	273	136	151	199	279	572	550	108	247
	FC_{MP2}	162	181	270	134	144	192	268	563	541	102	232
Cd	*R*	2.15	2.13	2.05	2.22	2.21	2.11	2.19	1.97	1.97	2.53	2.39
	FC_{HF}	231	264	351	235	236	322	332	525	484	177	253
	FC_{MP2}	217	246	325	207	197	279	310	458	386	144	204

Table 7. Binding Energies, Correlation, and RVS Components for Dication–Ligand Complexes (in kcal/mol)

		OH_2	CH_3OH	H_2NCHO	NH_3	$NHMe_2$	imidazole	HCO_2^-	OH^-	CH_3O^-	CH_3SH	CH_3S^-
Zn	BE_{MP2}	–95.6	–109.6	–144.4	–131.5	–151.9	–169.3	–404.0	–433.9	–418.3	–137.5	–424.1
	CORR	–6.9	–9.2	–6.0	–14.5	–20.2	–15.4	–18.4	–19.0	–21.6	–17.7	–28.7
	C	–73.1	–76.3	–108.3	–97.3	–92.8	–116.1	–356.5	–424.7	–384.9	–59.3	–334.9
	EX	34.4	39.7	50.8	46.8	50.2	60.6	70.6	93.6	89.4	37.4	73.6
	POL_L	–36.3	–47.3	–63.0	–43.2	–60.6	–70.1	–70.0	–46.1	–60.9	–66.1	–76.7
	$CT_{L\rightarrow C}$	–9.5	–11.5	–11.2	–18.3	–23.0	–21.3	–22.3	–26.3	–28.7	–27.9	–50.5
	$POL_C + CT_{C\rightarrow L}$	–1.7	–1.8	–2.6	–1.7	–1.8	–2.6	–4.5	–5.9	–5.6	–0.8	–1.8
Mg	BE_{MP2}	–77.2	–87.0	–121.1	–94.7	–106.7	–127.5	–362.7	–381.6	–369.6	–90.0	–349.5
	CORR	1.9	1.5	6.7	0.3	–2.3	0.9	4.4	5.3	3.0	–0.5	–3.2
	C	–66.1	–68.6	–99.8	–82.3	–79.2	–101.1	–353.2	–402.6	–369.2	–48.3	–318.2
	EX	22.7	26.4	35.6	29.5	34.4	41.0	59.4	71.7	68.8	23.8	59.2
	POL_L	–33.3	–44.1	–59.7	–39.1	–56.6	–65.0	–67.0	–50.8	–64.4	–59.1	–72.8
	$CT_{L\rightarrow C}$	–2.1	–2.1	–3.3	–2.2	–2.3	–2.9	–5.5	–3.9	–6.0	–5.5	–13.9
	$POL_C + CT_{C\rightarrow L}$	–0.1	0	–0.1	–0.2	–0.1	–0.2	–0.3	–0.8	–0.7	–0.1	–0.4
Ca	BE_{MP2}	–52.7	–59.3	–88.8	–60.5	–68.7	–88.0	–305.7	–331.5	–319.7	–53.9	–280.6
	CORR	–0.1	–0.9	3.1	–1.0	–3.4	–1.6	1.6	0.9	–1.7	–1.3	–3.0
	C	–49.2	–50.9	–81.8	–57.6	–56.4	–77.8	–321.8	–368.0	–336.9	–36.1	–290.8
	EX	19.0	23.3	35.0	23.7	30.4	38.3	71.2	93.5	86.7	21.4	75.2
	POL_L	–18.7	–25.1	–36.3	–20.5	–32.2	–38.3	–41.3	–32.2	–42.1	–32.1	–43.1
	$CT_{L\rightarrow C}$	–3.6	–4.4	–7.2	–4.2	–5.9	–7.3	–13.1	–19.7	–19.9	–5.2	–16.1
	$POL_C + CT_{C\rightarrow L}$	–0.4	–0.6	–0.8	–0.6	–0.7	–0.9	–2.5	–4.6	–4.3	–0.2	–1.7
Cd	BE_{MP2}	–73.8	–84.8	–114.9	–105.1	–122.5	–138.0	–362.8	–392.8	–376.8	–110.5	–386.0
	CORR	–6.4	–8.9	–5.7	–14.2	–20.8	–16.0	–19.7	–21.4	–24.0	–17.7	–31.2
	C	–58.5	–60.7	–90.1	–77.8	–73.2	–95.6	–327.5	–378.5	–344.0	–49.6	–307.3
	EX	27.5	32.2	42.1	40.3	43.5	53.9	65.8	85.7	80.4	35.5	73.2
	POL_L	–23.8	–31.8	–47.7	–27.5	–40.0	–51.0	–47.9	–30.0	–40.7	–43.5	–49.4
	$CT_{L\rightarrow C}$	–8.4	–10.6	–6.5	–20.5	–25.8	–21.8	–24.2	–33.7	–34.2	–30.6	–61.9
	$POL_C + CT_{C\rightarrow L}$	–1.6	–1.9	–2.7	–2.1	–2.1	–3.0	–3.5	–7.9	–6.7	–1.1	–3.0

MP2 level. Water is seen to be the least discriminatory ligand by having the smallest magnitude of ΔBE favoring zinc. This result also holds for the other dication pairs examined in Figures 3 and 4. The different selectivities lead to large energies for exchange reactions such as

$$ZnOH_2^{2+} + MgSCH_3^{+} \rightarrow MgOH_2^{2+} + ZnSCH_3^{+} \quad (2)$$

which is estimated to have ΔE = –56 kcal/mol.

The trends in ΔBE might qualitatively predict ion selectivity changes as water ligands in solution are replaced by other species. The energy component selectivity contributions would indicate the approximate physical origin of the results. It is important to realize that these selectivity effects are also liable to be exaggerated because of the lack of a complete ligand shell. This makes the calculational problem easier but might tend to misleadingly indicate that differences of less than 5 kcal/mol are significant. In the solution environment such relatively small differences may be reduced to insignificance by the influence of the rest of the ligand shell. Therefore, only the numerically largest contributions to selectivity will be discussed here.

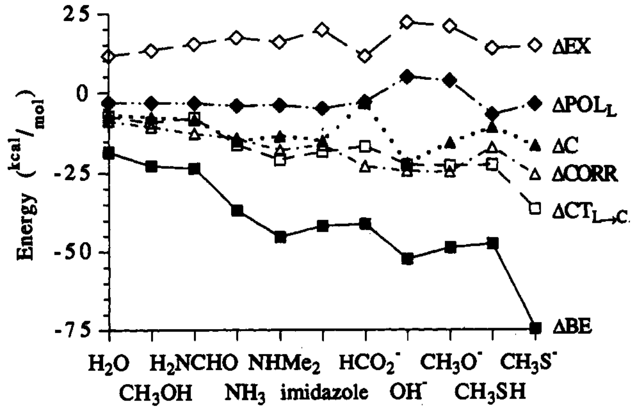

Figure 1. Selectivity from binding energy and components for Zn^{2+} over Mg^{2+}.

We first examine the Figure 1 comparison of Zn^{2+} and Mg^{2+}, two cations with similar size but with soft versus hard selectivity. The energy term with the closest correlation to the total selectivity for zinc over magnesium is the ligand-to-cation charge transfer, $CT_{L\rightarrow C}$. The selectivity contribution from the charge transfer also parallels the magnitude of the charge transfer contribution for each cation. Therefore, ligands which easily donate charge tend to be most selective between these dications. The polarization terms are larger but contribute generally smaller effects to the selectivity which do not parallel the total ΔBE.

The lack of a close relationship between the effects of charge transfer and polarization is an indication that these RVS definitions correspond to different physical effects. All of the electron density of the ligands is exposed to a strong field from

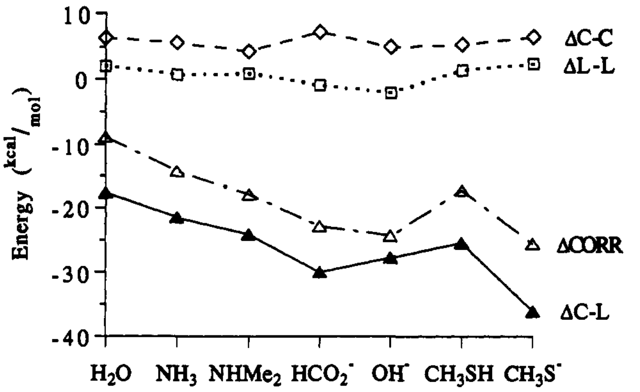

Figure 2. Selectivity for Zn^{2+} over Mg^{2+} from CORR and the component pair correlation contributions of cation–cation, ligand–ligand, and cation–ligand (dispersion-like) excitations.

either dication and contributes to polarization energy but little to the selectivity. The ligand polarizability is most closely related to the polarizable volume of electron density. The charge transfer term is probably attuned to the polarizability of the lone pairs close to the cation and to the ligand charge. The selectivity comes from the different cation virtual space characters accepting charge from various qualities of donors.

The charge transfer must also depend on the overlap of orbital spaces. The energetic effect should therefore be strongly dependent on the cation–ligand distances. This may partly lead to a lesser contribution for binding methanethiol compared to the thiolate, for example. The methanethiolate sulfur lone pairs also should be more diffuse and polarizable which aids charge transfer. Finally, there is the factor that the protonated ligand will have intrinsically greater attraction toward electrons which might be transferred to the cation. A more detailed discussion of the results of these effects is provided below with the discussion of the individual ligands and a complete shell of water molecules.

The correlation energy term also contributes positively to the total zinc–magnesium selectivity. This roughly mirrors the total correlation effect for each dication. A negative correlation contribution to binding is found primarily with zinc and is a larger effect generally for the ligands with more polarizable lone pairs, leading to the observed selectivity factor.

It was noted that negative values of CORR and the selectivity consequences were strongly enhanced by adding an f shell for zinc which suggests a dispersion effect. It was possible to directly confirm this by further decomposing CORR as described in the Methods section. We have reproduced the effects of the three terms of CORR on the selectivity for Zn^{2+} over Mg^{2+} in Figure 2. The ΔC–L component indicates the selectivity effect of dispersion-like correlation which roughly agrees with the selectivity changes in CORR for different ligands. The hard ligands have relatively nonpolarizable lone pairs and the group IIA ions have comparatively little core electron density to produce this interaction. Experience with weak nonbonded complexes[17] indicates that even the diffuse basis sets used in this work are likely to systematically underestimate the magnitude of the dispersion interaction, an approximately variational energy term, and probably also the selectivity changes indicated in Figure 2. This type of interaction has not previously been specifically noted to be associated with HSAB-type selectivity.

The ΔL–L component is of interest because it might in part represent differential effects from one-electron charge transfer as distinct from the purely dative transfer allowed in the Hartree–Fock ansatz. Modification of the CT to represent a preference for one-electron transfer should produce a strong pair correlation effect within the ligand bonding lone pair which has been partially transferred to the cation valence space at the HF level. However, both the ΔL–L and ΔC–C components produce small binding energy effects and only mild selectivity changes which do not correlate with the softness of the ligands.

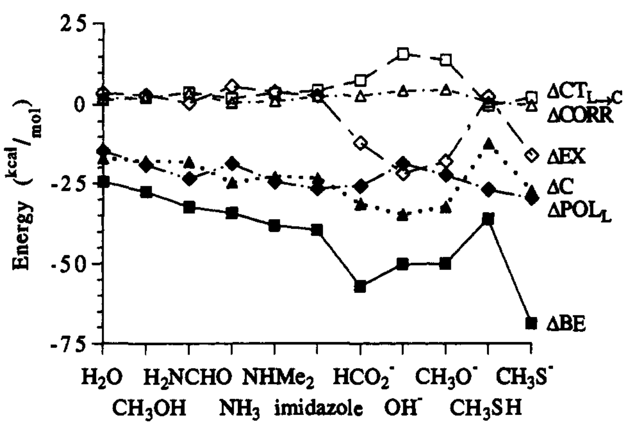

Figure 3. Selectivity from binding energy and components for Mg^{2+} over Ca^{2+}.

A dispersion interaction should also be strongly distance dependent. Together with the increased polarizability after deprotonation, this may help to explain such effects as the larger CORR magnitude for methanethiolate over the more weakly bound methanethiol.

It is also important to examine the effects of the other terms. The Coulombic interaction has a weak correlation with the selectivity when many of the possible pairs of ligands are considered. However, it does not markedly contribute to the selectivity over water for several of the most selective ligands. The selectivity from the exchange term is approximately a mirror image of the Coulombic selectivity. Therefore, the sum of these terms which do not principally involve electronic relaxation gives roughly zero selectivity.

It could be though that these behaviors are at least partly an indirect result of the other strongly selective and attractive relaxation terms. The effect of the charge transfer should be to shorten the contacts to zinc preferentially for the most selective ligands. Shorter contacts strengthen the attractive Coulomb interaction and the repulsive exchange interaction which might at least explain their mirror image character in Figure 1. However, the optimal distances from Table 6 do not have exactly a pattern where the most selective ligands for zinc also have the most shortened contacts compared with magnesium. The differences favor shorter zinc contacts except for the anionic ligands with oxygen donors and these are very selective for zinc. A similar trend is seen in comparing the contact distances for cadmium and calcium. Therefore, a scan of the components versus contact distance would seem to be required to firmly pin down these distance trends and their side effects on the final energy components.

Different factors operate to produce the differences for magnesium versus calcium represented in Figure 3. In this case the selectivity is more clearly a matter of ionicity for the ligands. The Coulomb interaction is naturally larger in magnitude with the smaller magnesium and so the selectivity for magnesium parallels the strength of the electrostatic interaction for each ligand.

A more surprising trend is that the exchange term also parallels the overall selectivity. The exchange interactions are in fact larger for calcium with the more strongly bound anionic ligands even though the effective ionic radius is still larger for calcium. This might indicate greater charge cloud overlap with calcium for these ligands in their final optimized positions. The anions have more diffuse charge clouds and do penetrate to a cation more closely because of typically stronger attractive energy terms.

EX is the sole repulsive term and its positive gradient with respect to distance must counterbalance the negative gradients of the other terms at the optimum. Comparing the optimal distances for the neutral and anionic ligands shows that the anions have roughly 0.25–0.29 Å smaller distances for magnesium over

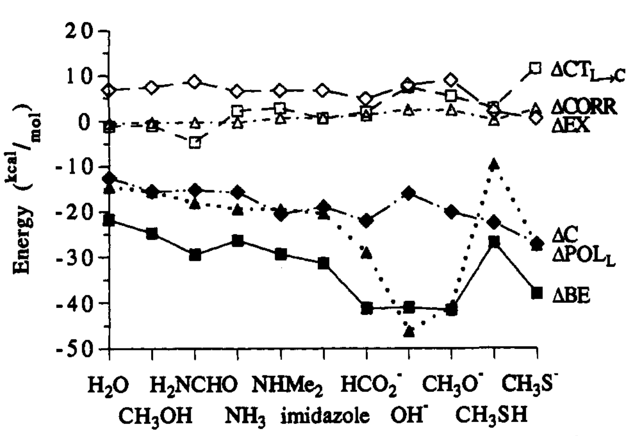

Figure 4. Selectivity from binding energy and components for Zn^{2+} over Cd^{2+}.

calcium while the neutrals have a range of 0.33–0.39 Å. The distance and selectivity trends thus indicate that the distance dependence of the EX term may be generally weaker for calcium, allowing the greater attraction of the anions to have more effect. The exchange energy therefore also attains larger values for calcium with anions before the EX gradient counterbalances the attractive terms, indirectly leading to the observed selectivity.

The other components do not correlate very closely with the overall selectivity. However, the polarization selectivity is at least understandable in terms of the smaller size and stronger electrostatic influence of magnesium. The more polarizable ligands are more sensitive to this difference and so the magnitude of POL_L correlates with this component of the magnesium–calcium selectivity of a ligand. For the polarization magnitudes there are the sequences imidazole > dimethylamine > ammonia and methanethiolate > methoxy > hydroxyl, for example, which agree with POL_L selectivity trends in Figure 3.

The ligand-to-cation charge transfer energy favors binding calcium which goes against the idea that charge transfer should be promoted by the stronger positive electrostatic potential of the smaller cation. The total relaxation energy, $POL_L + CT_{L\rightarrow C}$, however, always favors the smaller dication and is secondary to the effect of the first-order terms, *C* and EX. The selectivity plot also shows that the more negative $CT_{L\rightarrow C}$ energies for calcium do not generally promote an enhanced preference of calcium for the softer ligands.

The corresponding difference plot for zinc versus cadmium is given in Figure 4. Here, the electrostatic changes also appear to be dominant in the selectivity but the exchange term has a smaller role in comparison with the previous case. The EX term is always smaller for the larger dication in contrast to the more complicated behavior for magnesium–calcium. The anions have shorter contact distances by 0.21–0.22 Å for zinc over cadmium and the corresponding range for the neutrals is 0.22–0.25 Å.

The other energetics depicted in Figure 4 are qualitatively similar to those in Figure 3. The polarization and its selectivity contribution again often parallel expected ligand polarizability trends. The $CT_{L\rightarrow C}$ term again generally favors the larger cation. However, this trend is reversed for the relatively hard neutral oxygen donors tending to have the least charge transfer. This gives the other ligands a favorable component of selectivity for the larger cation which is absent for group IIA. The $CT_{L\rightarrow C}$ energy therefore promotes binding cadmium over zinc to the softer ligands while not having a similarly consistent effect in selecting between calcium and magnesium. The correlation energy has a similar though smaller effect of favoring binding of the softer ligands to cadmium over zinc and also has little effect in selecting between calcium and magnesium.

Continuing this line of investigating specific selectivities related to ion size and electronic structure would invite a comparison of cadmium and calcium. However, both factors will be operating in this case. The selectivity contributions from each term are therefore more complicated and harder to interpret. The total selectivity however qualitatively resembles the plot in Figure 1 for zinc–magnesium but with a larger range of ΔBE's.

Partial Charge Analysis of Charge Transfer. Seeing that charge transfer plays an important role in energetic selectivity factors spurred this comparison of the charge transfer effect as measured by intrinsic ion partial charges. The amounts of charge transfer given in Table 8 were determined as described in the Methods section. The results show that the relative propensities of ligands for transferring charge are similar regardless of the paired dication. The magnitudes approximately correlate with the $CT_{L\rightarrow C}$ energies given in Table 7. Water has the least propensity for charge transfer. The addition of aliphatic side chains or other increases in the polarizable volume of the ligand produce modestly increased charge transfer.

Hard versus soft cation behavior can be compared from Table 8 indicating that the soft cations accept moderately greater charge. Comparison with the $CT_{L\rightarrow C}$ energies from Table 7 shows that the ratio of the energetic contributions of the charge transfer is usually several times greater than the ratio of the electron density transfers. This points out a strong role for the virtual orbital energies of the accepting cation in determining whether the transfer that does occur is very energetically favorable. If ligand pairs such as methanethiolate and water are compared for any single cation the average ratio of energetic contributions is also larger than the ratio of electron density transfer. Therefore, the donating ligand occupied orbital energies also clearly determine the energetic results of the transfer.

We noted above that the larger cation has slightly larger $CT_{L\rightarrow C}$ energy magnitudes within a column for almost all of the ligands. Table 8 shows that increasing ion size produces a uniform decrease in the amount of electronic charge transfer. Both trends are generally largest for the ligands which donate the most charge. Since the apparently opposite results from the different measures occur both in comparing magnesium–calcium and zinc–cadmium, we are reluctant to attribute this to some uncertainty in the analysis. The charge transfer energetics could be assumed to become more favorable for smaller cations because their virtual orbital energies are lower. But such a simple relationship seemingly cannot explain the results of both measures of the physical charge transfer. A complete theory of charge transfer then must probably consider all of the interactions in the final relaxed system within the framework of molecular orbital or valence bond theory.

We next report structural details for individual ligands and analysis features within related ligand subsets and for alternative geometries.

Water. All of the dications optimize to positions along the C_{2v} axis. This ligand has the smallest magnitude for all of the important energy terms and the least selectivity for a particular dication. Most of the analysis features below are discussed with reference to the characteristics of a water ligand.

Methanol. Methanol represents the substrate cation binding mode in zinc alcohol dehydrogenase enzymes. The dications optimize to positions analogous to water, i.e. in the C_s plane and very close to the C–O–H angle bisector. The ligand polarization term has the largest change of any which corresponds with expectations from the substantial additional polarizable charge density in the methyl group. This increase occurs for all of the dications and therefore only makes a small contribution to the selectivity concerning ion size. The charge transfer energy magnitudes and charge donation are also increased by relatively small amounts compared with water.

This offers a clear view of the effect on gas-phase basicity usually called a charge induction from the methyl group. The decomposition indicates approximately a pure polarization effect

Table 8. Ligand-to-Cation Charge Transfer in Fractions of an Electron

	OH_2	CH_3OH	H_2NCHO	NH_3	$NHMe_2$	imidazole	HCO_2^-	OH^-	CH_3O^-	H_2S	CH_3S^-
Zn	0.28	0.36	0.37	0.40	0.53	0.50	0.60	0.54	0.57	0.62	0.96
Mg	0.22	0.27	0.29	0.28	0.38	0.38	0.46	0.39	0.42	0.46	0.72
Ca	0.17	0.21	0.24	0.21	0.31	0.31	0.40	0.37	0.38	0.29	0.51
Cd	0.24	0.30	0.32	0.36	0.49	0.44	0.54	0.52	0.57	0.53	0.87

internal to the ligand. The change in selectivity between group IIA and IIB is very minor compared with other ligands discussed below because of the negligible change in the properties of the oxygen lone pairs.

Formamide. This ligand represents a possible carbonyl binding mode for several families of peptide hydrolysis enzymes employing dication-binding active sites. The optimized positions of the dications are close to the carbonyl axis but rocked slightly away from the NH_2 group. The C–O–M angles are 151°, 169°, 171°, and 153° for M = Zn, Mg, Ca, and Cd, respectively. Stronger binding than water or methanol is due to increased electrostatic interaction strength and polarization response. The only major selectivity factor introduced compared with water is a preference for the smaller cations and their stronger electrostatic fields. The interaction distances are shortened and the force constants for stretching the metal contact are increased substantially compared to water or methanol.

We thought it worthwhile to see if the carbonyl moiety behaved as though cylindrically symmetric for variations in the cation position since the optimized positions are not too far from the carbonyl axis. The locations were varied to change the C–O–M angle within the formamide plane or to move the cation slightly out of the molecular plane. The force constants for these motions were numerically calculated by the lowest order finite difference rule. The force constants governing the C–O–M angles within the plane were in the range of 7.5×10^{-3} to 9×10^{-3} kcal/(mol deg^2) for all four dications. The Mg and Ca force constants for angular motion out of the plane were in the same range so that their interaction with the carbonyl is approximately axially symmetric. The Zn and Cd force constants had values of 4×10^{-3} to 4.5×10^{-3} kcal/(mol deg^2) so that motion out of the plane is notably easier. These dications may experience some attraction for the π system of the carbonyl bond and might also be more likely to have a secondary minimum structure, possibly binding to pyramidalized nitrogen.

Anionic amide nitrogen is though to be able to weakly bind zinc in place of the proton cis to the carbonyl in its inhibition of the enzyme carbonic anhydrase. The observed weakness of the contact might be due to the difficulty in removing an amide proton. The gas-phase structures without other ligands are predicted to be bidentate with both N and O contacts. The binding energies are −418.6, −373.7, −314.7, and −377.2 kcal/mol for Zn, Mg, Ca, and Cd, respectively, which can be compared with the neutral binding mode results given in Table 7.

This binding mode is predicted to be more favorable toward the group IIB cations than neutral formamide or water ligands. The zinc–magnesium selectivity is now similar to that of dimethylamine. An RVS decomposition was not carried out to examine this selectivity change, but the correlation energy effect is available and it was found to be a partial contributor to the increased selectivity for group IIB cations. The HF-level optimization gave a shorter contact of the nitrogen atom for the group IIB cations. The oxygen contact was the shorter one with group IIA cations. The nitrogen contact probably allows for greater charge transfer stabilization which is more important with group IIB. The nitrogen contact is therefore also the more critical one in condensed phase and the group might adopt a unidentate configuration analogous to what is often found for carboxyls in which the carbonyl oxygen instead has stabilizing H bond contacts. This formamide anion is also more selective toward smaller cations, but this trend can be ameliorated in condensed phase because of the greater ligand repulsion around smaller cations as discussed for hydroxyl below.

Carbonyl groups might also bind to dications as anionic or neutral gem diols. The cation selectivity effects should be similar to those for other oxygen-donor ligands discussed here. The anionic form would certainly be more attractive for smaller cations, but the gas-phase trends in this aspect again might not hold up well for a condensed phase.

Ammonia. All of the energy components are increased in magnitude relative to water in spite of the larger contact distances and smaller ligand dipole. This agrees with the view of ammonia as having more strongly directional and polarizable lone pair electrons.

The amine nitrogen is usually though of as binding preferentially to group IIB over group IIA. This must be viewed in terms of replacing a water ligand by an amine for either dication. The selectivity plot in Figure 1 shows that the $CT_{L\rightarrow C}$, Coulomb, and CORR energy terms are responsible for the increased preference for this replacement around zinc compared with magnesium. The weak preference for binding smaller ions compared with water illustrated by Figures 3 and 4 is primarily due to the stronger Coulomb interactions. The coordination of ammonia is usually found to be similar to that of water ligands, indicating that ligand steric interactions may be similar which is less true for most of the other ligands considered here. The different electrostatics may therefore account for the experimental observation of weak affinity of Mg^{2+} for amines while Ca^{2+} has practically none.[4]

Dimethylamine. The angles M–N–C and M–N–H are equal to within a few degrees for all of the dications. Stronger binding compared to ammonia is found and the largest contributor to this is the ligand polarization energy. This gives a modestly increased selectivity for the small dications compared with ammonia, but it is known that increased steric repulsion can reverse this affinity effect in aqueous solution. Other terms contributing to increased strength are $CT_{L\rightarrow C}$ and CORR. These changes act to slightly increase the selectivity for zinc and cadmium. The metal ion partial charges also indicate greater charge transfer. It is interesting to see that the much larger change in POL_L from ammonia in contrast has no effect at all on the Zn^{2+}–Mg^{2+} selectivity. These changes are qualitatively equivalent to those from water to methanol but larger.

Imidazole. Histidine imidazole is a common ligand in a large number of enzyme binding sites tending to discriminately bind softer dications than group IIA. The dications are located in the imidazole plane along the nitrogen lone pair axis. However, the M–N–C angle for the carbon linked to the N–H group is smaller than the other M–N–C angle by 3–12°. Imidazole binds more strongly than the aliphatic nitrogen donors due to stronger electrostatic and polarization interactions. This may be the cause of the contact distances being approximately 0.1 Å shorter. These changes also produce a somewhat greater selectivity toward the smaller cations.

The charge transfer is generally similar to what is determined for dimethylamine whether measured by the energy term or the ion partial charges. The overall selectivity between zinc and magnesium is also similar to the aliphatic ligand. Previous calculations of the π system populations in a metalloenzyme active site model with various dications had given a total of approximately 6 electrons.[26] This showed that the π system donates little electron

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(26) Garmer, D. R.; Krauss, M. *J. Am. Chem. Soc.* **1992**, *114*, 6487.

density to the dication which agrees with the current analysis showing that the imidazole charge transfer is similar to that of an sp^3 lone pair.

The force constants for angular motions of the cations were computed. The HF values for Zn, Mg, Ca, and Cd respectively are 3.2×10^{-2}, 2.2×10^{-2}, 1.4×10^{-2}, and 3.1×10^{-2} kcal/(mol deg^2) for in-plant motion and 0.8×10^{-2}, 0.7×10^{-2}, 0.5×10^{-2}, and 0.8×10^{-2} kcal/(mol deg^2) for perpendicular motion. The stiffness for in-plane motion may result from repulsion toward the adjacent C–H protons and some attraction of the dications for the electron-rich π system. The forces are somewhat stronger than those reported above for formamide having two formal lone pairs and a π system.

Formate. Carboxylate ligands are known to bind all of these dications in various biomolecules. Bidentate C_{2v} optimal structures are found from these single-ligand optimizations but unidentate contacts are very common in proteins with exterior hydrogen bonding to the outer oxygen. The negative charge produces extremely strong binding and selectivity for the smaller dications through the Coulomb interaction. In the solution environment the shorter contacts also produce stronger repulsion for other ligands which tends to ameliorate most or all of this selectivity.[4]

The other energy terms turn out to be comparable to those from imidazole, as is the zinc–magnesium selectivity indicated in Figure 1. The isolated functional group in a solution environment also has a greater affinity for group IIB dications, but the selectivity is less than that found for ammonia.[4] For this ligand the solution environment therefore reduces the softness compared with the neutral nitrogen ligands. Pearson has suggested that anionic ligands in general behave as harder ligands in solution than in gas phase.[2] However, hydroxyl anion does not appear to be less selective between groups IIB and IIA than ammonia in water[4] so the extent of this effect may very much depend on detailed structural considerations for ligands.

Compared with the other oxygen donor anions only the polarization energy may have a larger magnitude for formate. The CT$_{L\to C}$ interaction is generally weaker but the partial charges show a comparable or larger charge transfer than for hydroxyl or methoxy. This may be due to the greater delocalization of the formate charge transfer which must come equally from either oxygen. Charge transfer from one oxygen would lower the total energy by increasing its attraction to the dication but could conceivably act to weaken the contact of the other oxygen. This result agrees with the pattern shown below for charge transfer in a complete ligand shell, i.e. the amount of charge transfer is much larger than for a single ligand complex but its energy stabilization is relatively modest.

We have also examined a constrained unidentate structure for each dication in which an M–O–C angle was set to 120°. These structures produce shorter contacts [Zn, 1.78 Å (−0.20); Mg, 1.79 Å (−0.15); Ca, 2.06 Å (−0.17); Cd, 2.00 (−0.19)] and weaker binding [Zn, −377.7 kcal/mol (26.3); Mg, −334.6 kcal/mol (28.1); Ca, −285.1 kcal/mol (20.6); Cd, −340.2 kcal/mol (22.6)], where the changes from the bidentate optima are given in parentheses. The decrease of the close contact length gains back only several kilocalories per mole of the loss from moving an oxygen away from the dication. The energy loss does not markedly change the group IIA–IIB selectivity but unidentate configurations should be more favorable for the larger dications in solution if the repulsive effects of other ligands are not considered.

The metal ion partial charges for the unidentate structures show a loss of 0.10 electron of charge transfer for zinc and magnesium, 0.07 electron loss for cadmium, and 0.06 electron for calcium. However, the CT$_{L\to C}$ energies change by only about ±1 kcal/mol from the bidentate results for each dication which supports the view of the charge transfer interactions given above for the bidentate case. That is, the charge transfer through the contact is not a strong antibonding component for another close contact in a unidentate configuration. The exchange and correlation effects are also roughly invariant while the electrostatic and polarization terms strongly favor bidentate structures.

With minor modification, the results presented here for formate anion probably hold also for the various binding modes of phosphate groups. Therefore, explicit calculations have not been carried out for this functional group.

Hydroxyl. The M–O–H angles were optimized giving 118°, 180°, 180°, and 116° for M = Zn, Mg, Ca, and Cd, respectively. The group IIB ions strongly favor bent structure by 17 kcal/mol for zinc and 20 kcal/mol for cadmium. The group IIA ions favor linear structure by 2 kcal/mol for magnesium and 8 kcal/mol for calcium. As discussed above, the terms most consistently producing selectivity changes between the group IIA and group IIB ions are the charge transfer and correlation energies. Larger magnitudes of CT$_{L\to C}$ and CORR were also found to be the primary distinctive source for the smaller M–O–H angles for group IIB cations. For all of the ions, electrostatics strongly favors bent structures and the polarization weakly while the exchange repulsion is much stronger for the bent structures.

Hydroxyl has a significantly increased selectivity for zinc over magnesium in relation to the selectivity of water. This is due to increased differences in the Coulomb, CT$_{L\to C}$, and CORR energies. The influences of the rest of the first shell and bulk solution in water convert this gas-phase acidity difference of 34 kcal/mol into a solution free energy difference of 2.6 kcal/mol.[27] The larger 40 kcal/mol difference for cadmium over calcium is similarly reduced to 6.4 kcal/mol in water.

Selectivity is also more pronounced for the smaller cations than for water as can be seen in Figures 3 and 4. The magnesium–calcium gas-phase acidity difference of 26 kcal/mol is reduced to a solution difference of 1.6 kcal/mol. However, the zinc–cadmium gas-phase acidity difference of 19 kcal/mol is apparently reversed in water so that cadmium is more acidic by 2.2 kcal/mol. The effect of solution in relation to ion size is thus seen to be particularly hard to predict with simple model calculations that ignore the rest of the first shell, the bulk solution polarization, and the entropy variations.

Methoxy. Deprotonated alcohol is considered to be a transiently bound species in zinc alcohol dehydrogenases but this type of functional group is more commonly found with cations of +3 oxidation state. The M–O–C angles optimize in a pattern similar to hydroxyl anion [Zn, 131°; Mg, 180°; Ca, 180°; Cd, 129°], with the methyl protons in trans and gauche relationships to zinc and cadmium. The cation binding is weaker than for hydroxyl primarily because the electrostatic interactions are reduced. This is probably due to some of the negative charge being distributed into the methyl group in the isolated ligand where it interacts less favorably with a cation. This contrasts with the behavior of water and methanol where the added methyl group increases binding strength.

The polarization increases with the added methyl because of the extra polarizable density. There is a small uniform increase in the charge transfer magnitudes and decrease in the exchange interaction. Since all of these changes are roughly equivalent for all dications there is little change in the selectivity pattern from hydroxyl discussed above.

Methanethiol. The dications optimized to positions expected for a sulfur lone pair interaction with M–S–C–H(S) dihedral angles from 104° to 115°. The binding characteristics to Mg and Ca are similar to those of methanol except for weaker electrostatics which is compensated by stronger polarization interactions. These results would be expected in view of the longer contacts and more diffuse polarizable electron density of sulfur compared to oxygen. Zinc and cadmium contacts also gain

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[27] Burgess, J. *Ions in Solution: Basic Principles of Chemical Interactions*; Ellis Horwood Ltd.: London, 1988; p 64.

Table 9. Structural, Energetic, and Electronic Results for $M^{2+}(OH_2)_6$ Complexes[a]

	Zn	Mg	Ca	Cd
R_{M-O}, Å	2.14	2.10	2.44	2.36
BE_{MP2}, kcal/mol	−346.6	−325.0	−244.7	−290.7
CORR	−7.7	12.1	2.2	−13.0
C	−258.3	−253.1	−217.0	−232.5
EX	62.2	47.7	55.0	62.2
POL_L	−132.9	−134.3	−82.7	−97.0
$CT_{L\to C}$	−13.2	−5.1	−7.9	−13.1
$POL_C + CT_{C\to L}$	−1.7	−0.2	−0.2	−2.0
Waters' repulsion	7.3	7.8	5.5	5.8
CT, e	0.85	0.65	0.67	1.01

[a] The RVS analysis considered the water shell as one component.

significantly more energy lowering from charge transfer and correlation energies than for methanol. This makes for an increased selectivity of methanethiol for the group IIB cations over group IIA and probably also contributes to the shorter contacts for the group IIB cations.

The methanethiol optimal structures do not have the dications in a reflection plane as is necessary to calculate partial charges by the method described above. Hydrogen sulfide was used as a substitute to obtain this condition. We would expect the addition of a methyl group to increase the charge transfer slightly over these values given in Table 8. The results show that group IIA dications receive more electronic charge than from the methanol lone pairs but this is just not as energetically favorable as for the group IIB dications.

There is little evidence concerning methanethiol or protonated cysteine as a ligand. This was just used as a cheaper alternative to dimethyl sulfide which might represent the methionine residue electronic characteristics. Methionine is an uncommon residue type and is so far known only to bind copper ions in proteins. Cu^{2+} may be a better charge transfer acceptor than even the group IIB ions because it is considered softer in HSAB scales.[1] However, there is nothing obvious in the methanethiol electronic characteristics to produce poor binding of the group IIB ions compared with many of the other ligands. We suggest that a possible source of unfavorable energetics for methionine association with dications might be a steric conflict of the two bulky CH_nX groups clashing with other first-shell constituents.

Methanethiolate. Deprotonated cysteine residues are commonly used by enzymes to bind soft dications. Mercaptate groups such as in the inhibitor thiorphan are known to have similar binding properties. In the optimized models the ions all bind with sharp M–S–C angles [Zn, 104°; Mg, 107°; Ca, 119°; Cd, 105°], with the protons in trans and gauche positions relative to the cations. Similar angles are observed in crystal structures with mercaptate ligands. Methanethiolate has the strongest selectivity for the group IIB over the group IIA cations indicated by Figure 1. This selectivity is largely due to a strong charge transfer component and smaller increments from others. There is also a large electron density transfer as measured by the ionic partial charges. The magnitude of this effect is a principal difference between this ligand and the methoxy anion.

There is also a selectivity for smaller dications as with the other anions. Increased repulsion with other ligands might similarly eliminate much of this in an aqueous solution or protein as was noted above for hydroxyl. However, Zn^{2+} and Mg^{2+} ions are of similar size and results of the selectivity effects for such pairs should qualitatively hold in the solvated state.

Water Shell. Six water molecules were optimized in T_h symmetry to be compared with the results for one ligand. The optimized ion–water distances, total binding energies, and electronic charge transfer are listed in Table 9. The RVS components and correlation correction were computed by considering the entire ligand shell as one component. This means that the ligand occupied and virtual orbitals used as the initial guess in the RVS analysis were obtained in the optimized configuration of six waters. The initial water electron density is therefore mildly polarized away from the center of the cluster as a result of the repulsive water interactions. The computed Coulomb interaction with the dication is thus weakened and does not obey pair-additivity. An additional obvious effect from the slightly lengthened contacts compared with a single water should be a modest weakening of all of the interaction components. Since we are primarily concerned with selectivity effects in this work, these modifications should not be of critical importance.

Total ligand repulsion energies at the MP2 level are reported separately in Table 9 to show that with neutral ligands this is a minor factor in selectivity. The presence of anionic ligands would probably produce a much larger effect on the size selectivity from this source.

All of the RVS energy components are reduced in magnitude compared with ideal pair additivity which would magnify all of the terms by six times over results with one water. The primary energy components also have qualitative differences in this respect. The polarization energies of the ligand shells are 3.5 to 4.5 times the magnitudes found for the single water ligand. The corresponding ratios of the Coulomb energies are very similar. The factors affecting this reduction for the Coulombic interaction were noted above but the polarization interaction has the additional factor that the ligand charge densities become more repulsive toward their neighbors when polarized toward the dication.

The ratio of the $CT_{L\to C}$ energy in the complete shell to one water ligand is only 1.5 to 2.5. The charge transfer in terms of electron density has higher ratios of 3 to 4.2. This shows that the charge transfer from each water ligand is not so much inhibited by the other ligands but becomes much less of an energy-lowering force. Charge transfer from a lone pair orbital may improve the bonding character for the ligand–cation contact but gives an antibonding effect on the other ligands. With the polarization effect being not so localized in the region of the metal–ligand contact there is less of a repulsive interaction with other ligands and less energetic non-additivity.

The cation partial charges show that charge transfer from adding five ligands is approximately increased by four times for the larger cations and by three times for the smaller cations. The larger shell distances may lessen the effect of other ligands in reducing charge transfer although the associated energy terms do not show such a clear effect. The effective weakening in this aspect of ligand repulsion may be an important component in the finding of a lower pK_a for cadmium compared with the smaller zinc ion in aqueous solution.

The greater charge transfer from ligands to the group IIB cations should affect the energy increments for adding successive ligands. Here the addition of the first water ligand is favored for zinc over magnesium. However, once a shell of five water ligands is built up the zinc ion has lost significantly greater positive charge to weaken the interaction with the incoming sixth water. The results of Probst[28] in studying such incremental interactions show that the addition of the sixth water ligand has become more favorable around magnesium although the total cluster binding energy favors zinc as reported here. This type of cooperative CT influence may have complex effects on solution properties which cannot be explored easily with the expensive *ab initio* calculations used here. However, gas-phase incremental binding energies are becoming available[29] and these results show how the energetics could be interpreted in terms of the electronic structure.

The exchange energy is also strongly reduced from additive values in each complex. This term is expected to be strongly distance dependent which may account for this reduction. The modification of the initial guess orbitals in the complete shell may have a similar effect. The quantum mechanical definition

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(28) Probst, M. M. *J. Mol. Struct. (Theochem)* **1992**, *253*, 275.

(29) Blades, A. T.; Jayaweera, P.; Ikonomou, M. G.; Kebarle, P. *J. Chem. Phys.* **1990**, *92*, 5900.

of EX allows for explicit non-additivity, but we have not examined this effect because there is currently no physical model for rationalizing it.

Since the correlation energy was identified as an important factor in the selectivity of ligands for group IIA and group IIB cations, it is interesting to compare the behavior of the CORR and $CT_{L\rightarrow C}$ terms in going from one water ligand to a complete first shell. The cleanest comparison relevant to HSAB behavior is between zinc and magnesium. The results in Table 7 show selectivity contributions favoring zinc over magnesium with one water ligand of 7.4 kcal/mol from charge transfer and 8.8 kcal/mol from correlation. From Table 9 the complete shell gives respective contributions of 8.1 kcal/mol and 19.8 kcal/mol favoring zinc.

This is consistent with the idea of a greater dispersion interaction between group IIB ions and their ligands. Many-body dispersion effects are considered to be of relatively small magnitude because triple excitations are required for the lowest order effect. A cation–ligand dispersion interaction should therefore be weakened in the complete ligand shell primarily because of the slightly longer contact distances. The charge transfer is additionally minimized by a direct electronic repulsion of other ligands. Therefore, a dispersion-like interaction could possibly often be the more dominant factor in condensed phase selectivity trends between group IIA and group IIB ions.

Conclusions

The analysis reported here is most informative in what is revealed about the selectivity of ligands for a "hard" cation such as magnesium compared with a "soft" cation such as zinc which is of similar size (see Figure 1 and its analysis above). The experimental situation of greatest interest is the aqueous environment in which ligand substitutions for water molecules affect which ions are bound. The results presented here suggest that no substitution of the most common biological ligand types can result in a binding site which is more favorable for magnesium.

The charge transfer and correlation effects would consistently favor binding the group IIB cation to ligands other than water. The other terms generally produce negligible selectivity or canceling effects for dication pairs of similar size. All of the ligands examined here therefore behave as softer ligands than water and manifest this also in producing stronger energy-lowering charge transfer and correlation effects in interaction with any dication. Only the methanol and formamide results are even relatively close to water in apparent electronic "hardness".

Given that zinc and magnesium are of similar size, we would not expect the condensed phase environment to reverse these effects. The example of a complete ligand shell studied here retains the trends in the energy terms producing selectivity although the magnitude of the charge transfer is not an additive function of ligand additions or substitutions.

The diffuse, polarizable electron density for ligand lone pairs allowing for maximal charge transfer would also facilitate a dispersion interaction with the dication core electrons. A soft dication with low-energy vacant orbitals appears to require a high charge density in the outer core shells which would increase the dispersion effect. The lower energies of vacant orbitals allow for greater energy lowering from charge transfer. Therefore, large magnitudes for the CORR and $CT_{L\rightarrow C}$ terms are naturally found together for soft ligands and cations.

It would appear to be inconsistent that a dispersion-like interaction with the group IIB cations could be an effective interaction while the cation electron relaxation at the Hartree–Fock level is not very significant. The ionic core electrons are very strongly bound by a weakly shielded nuclear charge. Polarization at the Hartree–Fock level requires that this charge density distort so that some attractive interaction with the nucleus must be lost. The dispersion interaction however may not require a large bulk distortion of the ion shells to operate since only instantaneous electronic correlations are required. Greater external interactions might therefore be generated without sacrificing nuclear attraction energy as our results appear to indicate.

It is also true that the ligand valence electrons have a spatial overlap with the ion core from the close contact and the charge transfer. This must help to account for the numerical significance of these correlation effects. In this case, electronic correlation partly has the effect of producing a "Coulomb hole", a localized correlation effect in the wave function apparent at short interelectronic distances for overlapping electron pairs. This is only the strong-overlap limit of a dispersion interaction and long-ranged correlation still must contribute to the overall energetic effect.

The widely accepted view of the HSAB concept is that hard acids are attracted most strongly to hard bases and soft acids to soft bases. A theoretical statement on gas-phase HSAB behavior has been given by Parr and Pearson.[1] From density functional arguments they emphasize the energy-lowering charge transfer and accompanying covalent attraction which is maximized for soft–soft pairs. This is borne out by the present analysis but with the additional role for a dispersion-like correlation effect which may actually be the most dominant selective force in a condensed phase environment in which charge transfer is inhibited.

Parr and Pearson associated hard–hard interactions with ionic or electrostatic interaction strength. This direct interaction analysis shows that soft cations can have practically identical stabilization from this source. This would predict that a base which appears to be hard by binding hard dications should in fact have a comparable or slightly stronger affinity for soft dications of similar size. A relatively hard binding site is therefore only expected to have a lesser selectivity compared with a soft binding site because the energy lowering terms associated with this selectivity must have relatively small magnitudes.

The observation of strong hard–soft associations violating the primitive HSAB principle is an important factor which led Martin to question the usefulness of the concept in bioinorganic chemistry.[5] The general consideration that hard binding sites are simply less selective between hard and soft cations should be a more reliable starting point for considering electronic effects in binding. This hypothesis appears to be borne out for the aqueous state in a collection of log K_1 values for small ligands reported by Hancock and Marsicano.[4]

Soft cations are present in relatively lower concentrations in biological fluids. Chemical equilibrium would favor the observation of hard cations binding to relatively nonselective binding sites composed of hard ligands. Under these conditions it is understandable that the HSAB concept could be initially interpreted to favor the binding of hard cations to hard ligands. Extensive exceptions would then be found particularly in substitution experiments related to situations such as metal poisoning.[5] Binding of soft ions in flexible proteins which normally accommodate hard ions may also cause distortion of the binding site to bring in available soft ligand groups or induce new binding sites as is common with mercury ions. This again may allow for misleading conclusions concerning the selectivity of the natural binding site.

There is less to say about the comparison of the binding of hard and soft ligands to a particular cation in a condensed phase. There are no hard–soft ligand sequences which have predictably equivalent subsets of the interaction terms around which selectivity arguments could be built. We would also have to consider such differential effects as ligand crowding which has been invoked as an important component in empirical correlations of binding constants.[4]

However, the present analysis suggests that a binding site consisting of soft ligands but nevertheless observed binding a hard cation might have an exceptional affinity for a soft cation of similar size and charge because of the added stabilizing interaction components. Such a binding site must have strongly stabilizing electrostatics similar to what is found with hard-ligand binding sites. A high coordination number may aid in this but the softer ligands studied in this work are generally found to produce low coordination numbers in proteins. The examination of a complete shell discussed above also showed that the extent of charge transfer stabilization could be modified in potentially complex ways. The further development of molecular modeling approaches using force fields including the important electronic effects of ion binding[13] may offer the only reliable theoretical approach to differentiating such binding sites.

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