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Energetics of Reactions Involving Transition Metal Complexes: Calculation of Relative Electrode Potentials for Cobalt Complexes at Various Ionic Strengths Using Density Functional and Poisson−Boltzmann Methods

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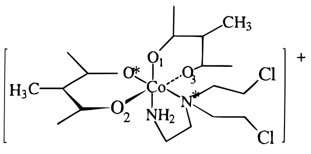
Abstract: A combination of nonlocal density functional calculations and the Poisson−Boltzmann method for the evaluation of free energies of hydration has been used to evaluate the electrode potential of $[Co(NH_3)_6]^{3+}$ and $[Co(en)_3]^{3+}$ (where en = $H_2NCH_2CH_2NH_2$) using $[Co(dien)_2]^{3+}$ as a reference (where dien = $H_2NCH_2CH_2NHCH_2CH_2NH_2$). For $[Co(en)_3]^{3+}$, the electrode potential has been calculated to within 61 mV of the experimental value. For $[Co(NH_3)_6]^{3+}$, the electrode potential is reproduced to within about 300 mV of experiment. The geometries of the complexes were optimized using the local spin density (LSD) method, with a LSD-optimized double-ζ plus polarization Gaussian basis set. Single-point nonlocal calculations were carried out at the optimized geometry using the Becke and Perdew combination of functionals for exchange and correlation to obtain both the energies and potential-derived charges. The potential-derived charges were used in the Poisson−Boltzmann calculations. The variation of the electrode potential of $[Co(en)_3]^{3+}$ with ionic strength is reproduced well. The suitability of the Poisson−Boltzmann method for treating hydration in these systems is critically assessed in light of the agreement between theory and experiment.

Introduction

The lead bioreductive hypoxia-selective anti-cancer agent[1] $[Co(Meacac)_2(dce)]^+$ provides not only an excellent example of the application of coordination chemistry to medicinal problems but also a challenging test system for theoretical calculations. Here, Meacac represents the 3-methylpentane-2,4-dionato anion and dce represents *N*,*N*-bis(2-chloroethyl)ethylenediamine.



Compound $[Co(Meacac)_2(dce)]^+$

In the Co(III) complex, the lone pair on the mustard nitrogen (N*) is tightly coordinated to the cobalt; hence, the complex is inert. However, because *high-spin* Co(II) complexes are more labile, the lone pair becomes available and the drug is therefore activated under reducing conditions, which are frequently found in solid tumors.[2,3] While this complex does show a marked hypoxic-oxic differential activity *in vitro*, *in vivo* it is far too toxic,[4] probably because of excessive lability.

Elsewhere we have shown, using density functional calculations, that the LUMO of the Co(III) complex is antibonding in the region between the cobalt and the mustard nitrogen;[5] the HOMO of the Co(II) complex is very similar. This not only explains the lability of the Co(II) complex, but also suggests a rational strategy for improving the properties of the lead compound: the synthesis of improved analogues of $[Co(Meacac)_2(dce)]^+$ should ideally be directed toward compounds which are predicted by calculations to have much more bonding character in the region between the cobalt and the mustard nitrogen so as to reduce the lability. It is also important that the electrode potential is not shifted significantly from the window for optimum activity which ideally lies between about −400 and −200 mV. Indeed, the electrode potential of the the lead compound $[Co(Meacac)2(dce)]^+$ does lie within this window. Consequently, the studies described here were initiated with a view to investigating the feasibility of calculating electrode potentials of cobalt complexes *ab initio*. Indeed, the prediction of electrode potentials *ab initio* for transition metal complexes is a major unsolved problem since the effect of ligand substitution is nowhere near as predictable as it is for organic compounds. Here we describe investigations employing nonlocal density functional calculations and the Poisson−Boltzmann method for the evaluation of free energies of hydration to calculate the electrode potential of $[Co(NH_3)_6]^{3+}$ and $[Co(en)_3]^{3+}$ using $[Co(dien)_2]^{3+}$ as a reference (en = $H_2NCH_2CH_2NH_2$; dien = $H_2NCH_2CH_2NHCH_2CH_2NH_2$).

Progress in the prediction of two-electron electrode potentials for quinones[6] came largely through the advent of free energy perturbation simulations, which enabled free energy differences to be predicted *in aqueous solution* to remarkable accuracy for favorable cases.[7] Some of these calculations employed molecular orbital methods, with electron correlation treated by second-

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order Møller−Plesset perturbation theory. However, the extension to one-electron electrode potentials ideally requires a more thorough treatment of electron correlation; this is not currently available from traditional molecular orbital methods within a method that scales well with molecular size. Second-order Møller−Plesset methods scale as the fifth power of the number of basis functions, but more reliable methods scale as the sixth or seventh power, and so such methods may never yield practical methods which are applicable to real problems in chemistry. The main advance in this area has been the advent of reliable nonlocal density functionals for the exchange and correlation energy. For example, nonlocal density functional methods have been used to predict both two-electron quinone electrode potentials[8] and one-electron nitroimidazole electrode potentials[9] to similar accuracy. Other recent applications of density functional methods[10] showing their successes are listed in ref 11. Moreover, the great advantage of density functional methods is that they are equally applicable to transition metal systems whereas traditional molecular orbital-based methods are usually difficult to apply because of the large numbers of low-lying states. Density functional methods essentially scale with the size of the problem in the same way as Hartree−Fock methods and so can be applied to realistic systems.

Methods

Density functional methods have been used to calculate $\Delta G°(g)$ for reaction 1 (entropy and zero-point effects have been ignored as they will be small for this reaction since there are no major geometry changes[6] and there is no difference in the degeneracy of the radicals). The electrode potential difference (eq 3) is obtained from $\Delta G°(aq)$ for reaction 2; $\Delta G°(aq)$ is obtained from $\Delta G°(g)$ (reaction 1) and the free energy of hydration of each complex in reaction 1. Here the labels a−d represent the complexes as listed in order in eqs 1 and 2.

$$[\mathrm{Co(en)_3}]^{3+}(\mathrm{g}) + [\mathrm{Co(dien)_2}]^{2+}(\mathrm{g}) \rightleftharpoons [\mathrm{Co(en)_3}]^{2+}(\mathrm{g}) + [\mathrm{Co(dien)_2}]^{3+}(\mathrm{g}) \tag{1}$$

$$[\mathrm{Co(en)_3}]^{3+}(\mathrm{aq}) + [\mathrm{Co(dien)_2}]^{2+}(\mathrm{aq}) \rightleftharpoons [\mathrm{Co(en)_3}]^{2+}(\mathrm{aq}) + [\mathrm{Co(dien)_2}]^{3+}(\mathrm{aq}) \tag{2}$$

$$\Delta E° = -(\Delta G°(\mathrm{g}) - \Delta G_{\mathrm{a}}(\mathrm{hyd}) - \Delta G_{\mathrm{b}}(\mathrm{hyd}) + \Delta G_{\mathrm{c}}(\mathrm{hyd}) + \Delta G_{\mathrm{d}}(\mathrm{hyd}))/F \tag{3}$$

The geometries were optimized within the local spin density (LSD) method, with the Vosko−Wilk−Nusair local functional used for correlation .[12] The calculations used a DZVP LSD-optimized double-ζ plus polarization Gaussian basis set to build the wave function, and an appropriate (A1) auxiliary basis set of Gaussians to represent the electron density.[13] The Co−N bond length is reproduced with a mean absolute error of only 0.013 and 0.015 Å for $[\mathrm{Co(en)_3}]^{3+}$ and $[(\mathrm{Co(dien)_2}]^{3+}$, respectively; overall the Co−N−C framework is reproduced with a root mean square error of 0.029 and 0.035 Å, respectively; thus, the LSD method reproduces the crystal geometries[14] very well.

Single-point nonlocal density functional calculations were performed at the optimized geometry using the Becke '88 functional for exchange[15] and the Perdew '86 functional for correlation[16] (denoted BP). The numerical integrations involved a fine grid with 2500 points per atom; the SCF convergence criterion for the total energy was 10^{-7}. For comparative purposes, the calculations were also performed using a medium grid of 1100 points per atom. The density functional calculations were performed using DGAUSS 3.0.[13,17]

In recent years, continuum methods have been used with much success in the calculation of free energies of hydration. The method of Cramer and Truhlar[18] has been particularly successful regarding electrode potential calculations,[8,9] but the Poisson−Boltzmann method[19−21] has also given encouraging results.[22] Here the latter has been used, since the former is applicable only to organic systems. Following normal practice,[21] the dielectric constant of the solute was set equal to 2.0 since all particles apart from the electrons were treated explicitly. However, values of the solute dielectric ranging from 1.0 to 4.0 were used to test the sensitivity of the calculations to this parameter. Three sets of atomic radii were also used: the OPLS radii,[23] the AMBER radii,[24] and the PARSE Poisson−Boltzmann optimized radii of Honig.[25] In all cases, the atomic radii were increased by 1.4 Å in line with common practice since this corresponds to the closest distance of approach of a water molecule. Unless otherwise stated, the free energies of hydration were determined using the OPLS radii since these were derived to reproduce solution properties. The atomic charges required were determined so as to reproduce the nonlocal density functional molecular electrostatic potential[26] around the LSD-optimized geometry.

The electrode potentials were measured experimentally at high ionic strength (and extrapolated to zero ionic strength); consequently, the free energies of hydration have been determined at a variety of ionic strengths, as permitted by the nonlinear Poisson−Boltzmann method implemented in the UHBD program.[27] In order to ensure that the results did not depend on the position of the solute within the grid, the results recorded in Table 1 were the mean of 10 random orientations of the molecule in a 75 × 75 × 75 grid which had a spacing of 0.4 Å. The potential at the boundary of the grid was set to the sum of the potentials of all of the atoms treated as independent Debye−Hückel spheres.

Results

The free energies of hydration at different ionic strengths are recorded in Table 1, with the corresponding electrode potentials given in Table 2; the variation of the electrode potential with ionic strength is displayed in Figure 1. The dependence of the free energy of hydration and the associated electrode potential with the solute dielectric constant is recorded in Tables 3 and 4, and the dependence of the free energy of hydration and the associated electrode potential with atomic radii is recorded in Tables 5 and 6.

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Table 1. Hydration Free Energies (kcal mol^{-1}) at Various Ionic Strengths, Calculated Using the Nonlinear Poisson−Boltzmann Method, As Incorporated into the UHBD Program Version 4.01[a]

	ionic strength (mM)				
compound	108.5	19	9.5	3.0	0.0
$[Co(dien)_2]^{3+}$	−376.63 ± 0.13	−375.60 ± 0.15	−375.38 ± 0.15	−375.13 ± 0.15	−374.79 ± 0.15
$[Co(dien)_2]^{2+}$	−165.36 ± 0.07	−164.93 ± 0.07	−164.84 ± 0.07	−164.73 ± 0.07	−164.58 ± 0.07
$[Co(en)_3]^{3+}$	−387.91 ± 0.10	−386.87 ± 0.11	−386.64 ± 0.11	−386.38 ± 0.11	−386.05 ± 0.11
$[Co(en)_3]^{2+}$	−170.07 ± 0.01	−169.63 ± 0.01	−169.53 ± 0.01	−169.42 ± 0.01	−169.27 ± 0.04

[a] The calculations employed a local dielectric constant of 2.0, the OPLS radii for the solute atoms, and a probe radius of 1.4 Å. As in the other tables, the free energy of hydration is the average of 10 independent orientations of the molecule within the grid, and the error reported is the standard deviation; the true error will include other contributions.

Table 2. Calculated Electrode Potentials, *E* (mV), at Different Ionic Strengths, Using $[Co(dien)_2]^{3+}$/$[Co(dien)_2]^{2+}$ at Zero Ionic Strength as a Reference[a]

		ionic strength (mM)									
		108.5		19.0		9.5		3.0		0.0	
compd	method	*E*	err	*E*	err	*E*	err	*E*	err	*E*	err
$[Co(en)_3]^{3+}$	exptl	−210		−195		−189		−186		−180	
$[Co(en)_3]^{3+}$	NLSD	−287	(−77)	−261	(−66)	−256	(−67)	−249	(−63)	−241	(−61)
	LSD	−340	(−130)	−314	(−119)	−309	(−120)	−302	(−116)	−294	(−114)
$[Co(dien)_2]^{3+}$	NLSD	−279		−253		−247		−241			

[a] The error bars in the calculated electrode potential (derived from the standard deviation in the free energies of hydration (see Table 1)) are generally about 23 mV. The true errors are much larger as can be seen from the error, err = *E*(calcd) − *E*(exptl), which is given in parentheses.

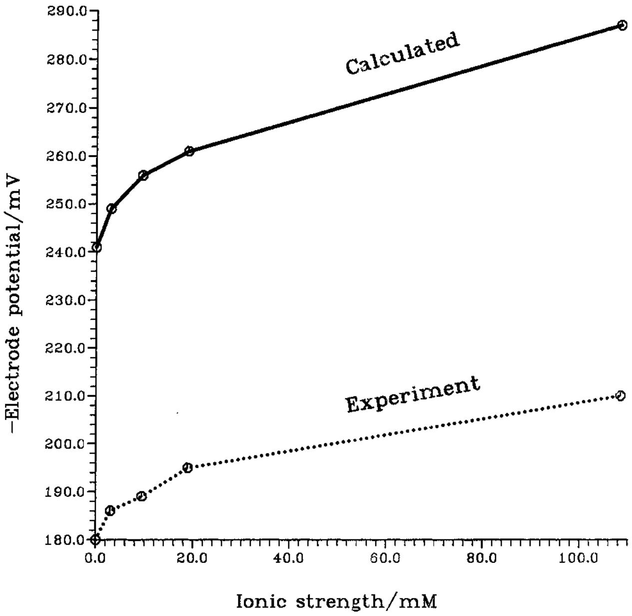

Figure 1. Variation of experimental and calculated electrode potential with ionic strength.

Table 3. Variation in the Hydration Free Energy (kcal) with Local Dielectric Constant[a]

	local dielectric constant		
compd	1.0	2.0	4.0
$[Co(dien)_2]^{3+}$	−374.33 ± 0.31	−374.79 ± 0.15	−372.44 ± 0.08
$[Co(dien)_2]^{2+}$	−164.46 ± 0.09	−164.58 ± 0.07	−163.42 ± 0.05
$[Co(en)_3]^{3+}$	−385.35 ± 0.28	−386.05 ± 0.11	−383.70 ± 0.05
$[Co(en)_3]^{2+}$	−169.09 ± 0.05	−169.27 ± 0.04	−168.09 ± 0.03
$[Co(NH_3)_6]^{3+}$	−431.61 ± 0.24	−434.88 ± 0.14	−435.37 ± 0.09
$[Co(NH_3)_6]^{2+}$	−185.99 ± 0.19	−187.11 ± 0.10	−187.19 ± 0.05

[a] The calculations employed the OPLS radii.

Discussion

As shown in Table 2, using $[Co(dien)_2]^{3+}$ as a reference compound, the electrode potential of $[Co(en)_3]^{3+}$ is predicted to be −241 mV using the nonlocal BP method with a DZVP basis set, in combination with the free energy of hydration determined using the Poisson−Boltzmann method. This value was obtained using a dielectric constant of 2.0 and the OPLS atomic radii. The accuracy of this calculation is hard to assess as the experimental standard electrode potentials for $[Co(en)_3]^{3+}$ range[28] from −180 to −255 mV, with the most recent value[29] of −180 mV probably being the most reliable. The calculated result is therefore within 61 mV of the experimental result. However, a number of observations are worthy of note. Firstly, the LSD results for $[Co(en)_3]^{3+}$ are also good. Secondly, the most reliable value for $[Co(en)_3]^{3+}$, the NLSD value, falls well within the range of experimental values and gives a probable error of 61 mV, assuming that the standard electrode potential of $[Co(en)_3]^{3+}$ is −180 mV.[29] Thirdly, errors due to the numerical integration of the functionals are unlikely to be significant: the electrode potential evaluated using the medium grid results is −277 mV. This is within 97 mV of the experimental value and within 36 mV of the fine grid result. Earlier calculations on quinones would support this view.[8]

It is clearly important to include the effects of hydration in these calculations since spreading the charge more on oxidation (as in $[Co(dien)_2]^{3+}$) results in an increase in the *ab initio* energy which opposes the change in the free energy of hydration. Indeed, the relationship between the *ab initio* energy change and the hydration free energy change is linear, as shown in Figure 2. Such relationships may be general since they have also been observed in the nitroimidazole/nitroimidazole radical anion system.[9] Moreover, while Table 4 confirms the need to include the hydration component since it is actually larger than the density functional component, the existence of such linear relationships suggests that the free energy of hydration component may be estimated from the *ab initio* component. (The relationship shown in Figure 2 also gives additional justification for evaluating the electrode potential using eq 3 which involves taking differences between large numbers.) Thus, although both $[Co(en)_3]^{3+}$ and $[Co(dien)_2]^{3+}$ have similar electrode potentials, the calculations are not trivial.

While there is debate as to the most appropriate dielectric constant to use for the solute,[21] for $[Co(en)_3]^{3+}$] the electrode potential results (Table 4) are not very dependent on this choice;

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Table 4. Electrode Potential, *E* (mV), Calculated Using Different Values of the Solute Local Dielectric Constant and the $[Co(III)(dien)_2]^{3+}$/$[Co(II)(dien)_2]^{2+}$ Couple as a Reference[a]

		dielectric constant						
		1		2		4		exptl
compd	method	*E*	err	*E*	err	*E*	err	*E*
$[Co(en)_3]^{3+}$	LSD + PB	−286	(−106)	−294	(−114)	−295	(−115)	−180
	NLSD + PB	−234	(−54)	−241	(−61)	−242	(−62)	
$[Co(NH_3)_6]^{3+}$	LSD + PB	−386	(−444)	−464	(−522)	−534	(−592)	58
	NLSD + PB	−210	(−268)	−289	(−347)	−358	(−416)	
$[Co(en)_3]^{3+}$	PB	−277		−285		−286		
$[Co(NH_3)_6]^{3+}$	PB	−1550		−1629		−1698		
$[Co(en)_3]^{3+}$	NLSD	277						
$[Co(NH_3)_6]^{3+}$	NLSD	1573						

[a] The error, err, given by *E*(calcd) − *E*(exptl), is given in parentheses. The table also shows the hydration contribution, denoted PB, calculated using the OPLS radii, and the nonlocal gas phase density functional contribution, denoted NLSD.

Table 5. Hydration Free Energies (kcal mol^{-1}) Calculated Using Different Radius Sets (Refs 23−25)[a]

compd	OPLS radii	AMBER radii	PARSE radii
$[Co(dien)_2]^{3+}$	−374.79 ± 0.15	−389.05 ± 0.22	−394.10 ± 0.10
$[Co(dien)_2]^{2+}$	−164.58 ± 0.07	−171.56 ± 0.08	−174.03 ± 0.05
$[Co(en)_3]^{3+}$	−386.05 ± 0.11	−401.90 ± 0.13	−407.50 ± 0.12
$[Co(en)_3]^{2+}$	−169.27 ± 0.04	−177.02 ± 0.10	−179.75 ± 0.07
$[Co(NH_3)_6]^{3+}$	−434.88 ± 0.14	−454.99 ± 0.19	−463.90 ± 0.14
$[Co(NH_3)_6]^{2+}$	−187.11 ± 0.10	−197.98 ± 0.20	−202.18 ± 0.31

[a] The calculations employed a local dielectric constant of 2.0 for the solute and a probe radius of 1.4 Å and were performed at ionic strength 0.0.

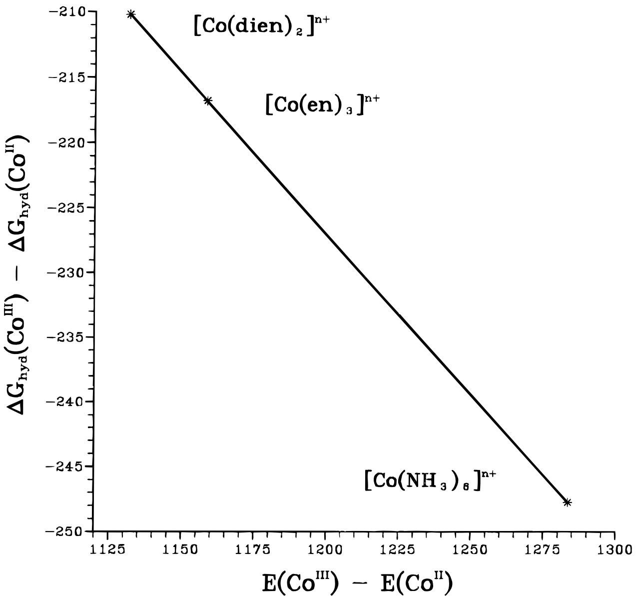

Figure 2. Inverse relationship between the electron affinity, $E(Co^{III}) - E(Co^{II})$, calculated using the BP/DZVP method, and the difference in the free energy of hydration between the two cations, calculated using the Poisson−Boltzmann method.

neither are they dependent upon the choice of atomic radii for the solute atoms (Table 6). This is despite the observation that free energies of hydration computed using the related self-consistent reaction field method are very dependent upon the cavity radius. Indeed, the individual hydration free energies computed here also depend on the radii, but the differences between the three sets of hydration free energies remain constant. Finally, the Poisson−Boltzmann calculations predict the variation of the electrode potential of $[Co(en)_3]^{3+}$ with ionic strength remarkably well (Table 2). The value at $I = 0.109$ M is predicted to be 46 mV lower than the value at $I = 0$, compared to the experimental difference[29] of 30 mV; these results are shown in Figure 1.

The results in Table 4 show that the electrode potential for $[Co(NH_3)_6]^{3+}$ is not predicted so well. The NLSD calculations with a solute dielectric constant of 2.0 give a calculated electrode potential of −289 mV compared to an experimental value of +58 mV—an error of 347 mV. There are various possible reasons for such a large error. One possible explanation is that the Poisson−Boltzmann method is not sufficiently reliable because it does not take into account the molecular nature of the solvent. Another explanation is that $[Co(dien)_2]^{3+}$ and $[Co(NH_3)_6]^{3+}$ are actually quite different and that, in order to predict the electrode potential of $[Co(NH_3)_6]^{3+}$, a more similar reference compound is required. The discussion in the next section would support this, as would analysis of the individual density functional and hydration contributions to the electrode potential since these are both over 1500 mV. An alternative explanation may be that the Poisson−Boltzmann method only accounts for the polarizability of the solute in an average way through the solute dielectric constant and that here this approximation is inadequate because the polarizabilities are quite different. Interestingly, the variation in the electrode potential with dielectric constant is significant for $[Co(NH_3)_6]^{3+}$ but not for $[Co(en)_3]^{3+}$. (The variation in the change of hydration free energy on reduction with dielectric constant is significant for $[Co(NH_3)_6]^{3+}$ but not for $[Co(en)_3]^{3+}$.) Since $[Co(NH_3)_6]^{3+}$ is small and highly charged, it will certainly not be as polarizable as $[Co(en)_3]^{3+}$, and so a smaller dielectric constant may be appropriate. Using a dielectric constant of 2.0 for $[Co(dien)_2]^{3+}$ and 1.0 for $[Co(NH_3)_6]^{3+}$ reduces the error for $[Co(NH_3)_6]^{3+}$ to 254 mV. This is a significant improvement and suggests areas where the Poisson−Boltzmann method may be improved.

Assessment of Errors. It is only recently that the Poisson−Boltzmann method has been shown to give a quantitative treatment of hydration. This was shown most effectively by Jean-Charles *et al.* who examined the electrostatic contribution to the free energy of hydration for a number of molecules and singly charged ions.[22] The most significant contribution toward this has probably been the advent of finite-difference methods which have permitted the use of molecular-shaped cavities. While Poisson−Boltzmann methods have been successfully applied to highly charged enzyme systems,[30] it is not clear to what extent they are genuinely applicable to triply charged ions. In an investigation of the Born equation, which is a special case of the Poisson−Boltzmann equation, Rashin[32] effectively showed that the free energies of hydration of singly, doubly, and triply charged cations were reproduced with a mean error of 2.2%, 2.4%, and 2.3%, respectively; it could be argued that such errors are largely due to dielectric saturation.[31] By comparing the magnitudes of these free energies,[32] it is clear that the cobalt

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Table 6. Calculated Electrode Potentials, *E* (mV), Using the OPLS, AMBER and PARSE Radii Sets and the $[Co(dien)_2]^{3+}$/$[Co(dien)_2]^{2+}$ Couple as a Reference[a]

		OPLS		AMBER		PARSE		
compd	method	*E*	err	*E*	err	*E*	err	exptl
$[Co(dien)_2]^{3+}$	LSD	−294	(−114)	−330	(−150)	−342	(−162)	−180
	NLSD	−241	(−61)	−277	(−97)	−289	(−109)	
$[Co(NH_3)_6]^{3+}$	LDS	−464	(−522)	−549	(−607)	−642	(−700)	58
	NLSD	−289	(−347)	−374	(−432)	−466	(−524)	

[a] The errors, err, given by *E*(calcd) − *E*(exptl), are given in parentheses.

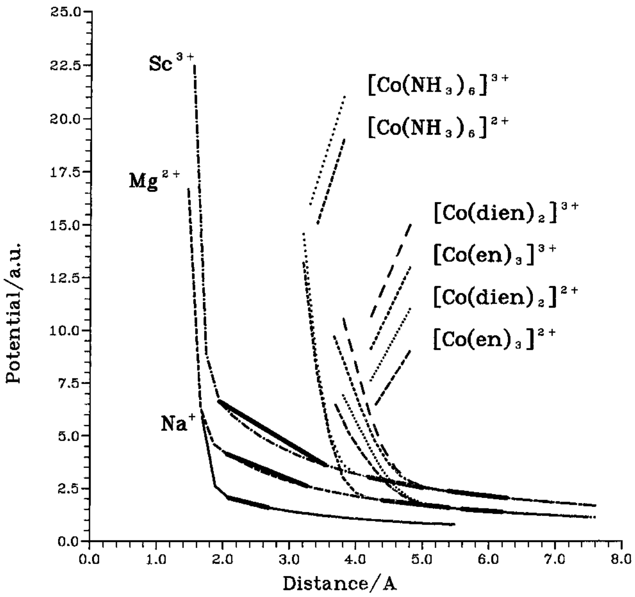

Figure 3. Mean electrostatic potential (in atomic units) in a spherical shell of thickness 0.1 Å as a function of distance around various cations. The region where the maximum and minimum potential differs by 10% or 0.05 au is marked by a bold line. For the dien and en complexes, this region overlaps considerably. For the NH_3 complexes, the region lies midway between that for the simple ions and the dien reference.

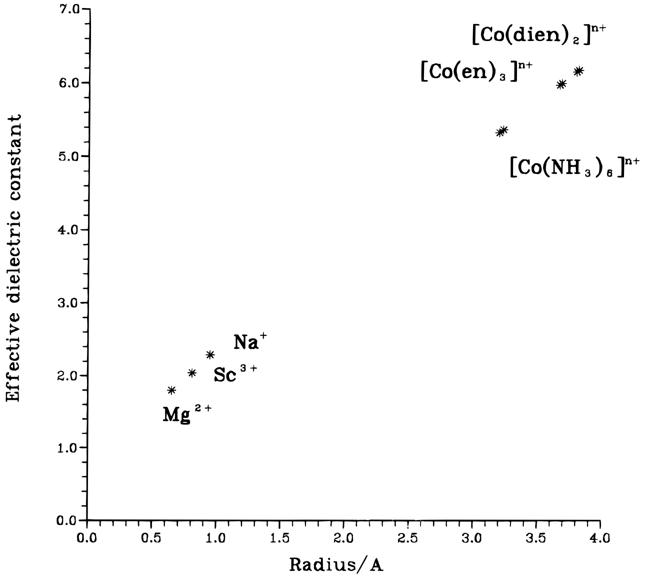

Figure 4. Variation of the effective dielectric constant with cation radius. The radii for the cobalt complexes were computed from the volume by assuming that the complex was spherical. The effective dielectric constant was determined using the relationship given by Noyes.[33]

complexes in this study are behaving more like singly and doubly charged species rather than doubly and triply charged ions. The main reason for this is that the first hydration shell, where dielectric saturation effects may be significant, has been effectively replaced by the dien and en ligands. This can be seen graphically in Figure 3 which shows a plot of the mean potential within a spherical shell of thickness 0.1 Å against distance. Because of the nonspherical nature of the complexes, and the use of a grid, this mean potential may include contributions from both sides of the interface between solute and solvent. This intermediate region has been identified by thick black lines which join the region where the maximum and minimum potentials differ by 10% (left) or 0.05 au (right). From the magnitude of the potential in this region and just beyond, it is clear that the triply charged cobalt complexes correspond to simple ions with a charge of two or less and the doubly charged complexes correspond to simple ions with a charge of one or less. It also appears that triply charged ions lie on the same line; likewise, doubly charged ions lie on the same line. However, for the dien− and en−cobalt complexes, the interface between solute and solvent lies about 3.5 Å further out, at much lower values of potential than for the simple ions. Clearly, this distance corresponds to at least one shell of water. Noyes[33] has suggested for ions, regardless of the charge, that the effective dielectric constant is linearly related to the radius; his equation would result in an effective dielectric constant of about 6 (Figure 4) which is clearly much closer to the bulk value than is the case for simple ions. The implications of this are that dielectric saturation is likely to be much less of a source of error for the cobalt complexes than it is for simple ions, thus justifying the use of the Poisson−Boltzmann method in this context. In both Figures 3 and 4, the ammonia complexes lie between the simple ions and the dien and en complexes, adding weight to the idea that dien is probably not the ideal reference compound for calculations on $[Co(NH_3)_6]^{3+}$ since dielectric saturation and electrostriction effects[31] will clearly be different.

Thus, a comparison with the studies of Rashin suggests that the free energies of hydration are likely to be in error by 2%; this corresponds to an error in the calculated electrode potentials of 300 mV. Although surface area and cavity terms have been neglected, the resultant errors will be pretty small since the calculation involves differences for similar compounds. Indeed, the necessity of taking differences for similar compounds means that many errors will cancel, and so the error in the calculated free energies of hydration is likely to be considerably below the value of 300 mV. This analysis suggests that the error obtained here for $[Co(en)3]^{3+}$, 61 mV, is very much on the low side of what can be expected. However, even with large errors which are comparable to this value of 300 mV, as for $[Co(NH_3)_6]^{3+}$, this approach is likely to be useful in the rational modification of cobalt complexes with particular redox properties.

There is no reason why this approach cannot be applied to transition metal systems other than cobalt provided that the

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(31) Jayaram, B.; Fine, R.; Sharp, K.; Honig, B. *J. Phys. Chem.* **1989**, *93*, 4320−4327.

(32) Rashin, A. A.; Honig, B. *J. Phys. Chem.* **1985**, *89*, 5588−5593.

(33) Noyes, R. M. *J. Am. Chem. Soc.* **1962**, *84*, 513−522.

compound and reference have the same charge and electronic configuration. Indeed, since high-spin cobalt(II) complexes have a d^7 electronic configuration with three unpaired electrons, this is probably one of the more difficult transition metal systems to treat quantum mechanically. It may be more difficult to obtain a good wave function for high-spin d^4, d^5, and d^6 octahedral complexes with four or five unpaired electrons, resulting in less accurate quantum mechanical energies and free energies of hydration. Generally, however, applications to other systems would appear to be feasible provided that the following caveats are observed. Firstly, the polarizability of the compound and the reference should be as similar as possible. Secondly, for small, or more highly charged, complexes, the errors will be larger because the magnitude of the free energies will be higher and dielectric saturation may be more significant. Finally, it is also possible that complexes with more polar ligands will not be described quite so well.

Elsewhere we have shown for quinones that where reduction results in a *change* in the number of internal hydrogen bonds, continuum models do not perform as well as explicit water models.[6] Further investigation will be required to assess more precisely the bounds of applicability of the methods used here, but the initial results are very encouraging.

Reversibility of the Reduction. In many instances it would be more useful to predict whether a redox reaction was irreversible or not than to predict its electrode potential (which is only meaningful for a reversible reaction). Elsewhere[5] we have suggested that for the cobalt bioreductive agents such as $[Co(Meacac)_2(dce)]^+$, the lack of reversibility in the reduction may be associated with antibonding character in the Co−N region of the LUMO. (It must be stressed that antibonding character in a bond does not necessarily imply that dissociation will occur on reduction, but because cobalt(II) is high spin there is an increased chance of dissociation because two new orbitals are occupied, each with antibonding character.) In contrast to earlier work,[5] the cobalt(II) complexes studied here were stable to geometry optimization. However, it is interesting to note that experimentally the reduction of $[Co(en)_3]^{3+}$ is only approximately reversible[28] and indeed $[Co(en)_3]^{3+}$ does show antibonding character in the Co−N region of the LUMO and LUMO + 1. This is mirrored very closely by the antibonding character in the two corresponding occupied orbitals in $[Co(en)_3]^{2+}$, as shown in Figure 5. On reduction to high-spin cobalt complexes, both the LUMO and LUMO + 1 will be occupied. It is possible that here too the lack of reversibility on reduction is associated with excessive antibonding character in the CO−N region of the orbitals.

Conclusions

The electrode potentials of $[Co(en)_3]^{3+}$ and $[Co(NH_6)_6]^{3+}$ relative to $[Co(dien)_2]^{3+}$ have been calculated using a combination of nonlocal density functional calculations and the Poisson−Boltzmann method for determining the free energy of hydration. The electrode potential results for $[Co(en)_3]^{3+}$ are extremely good and suggest that these methods have much potential in molecular design applied to transition metal complexes. The electrode potential is predicted to be −241 mV which falls well within the range of the experimental values and is within 61 mV of the best experimental result. The variation in the electrode potential with ionic strength is also reproduced well (Table 2). $[Co(NH_3)_6]^{3+}$ provides a much harder test of the methodology because its electron affinity is much greater than that of the reference compound and the corresponding free energy of hydration difference is also much larger. Nevertheless, the results are within the range which could be expected from such methods. Moreover, these calculations suggest that the results for $[Co(NH_3)_6]^{3+}$ could be improved by methods which explicitly include polarization of the solute.

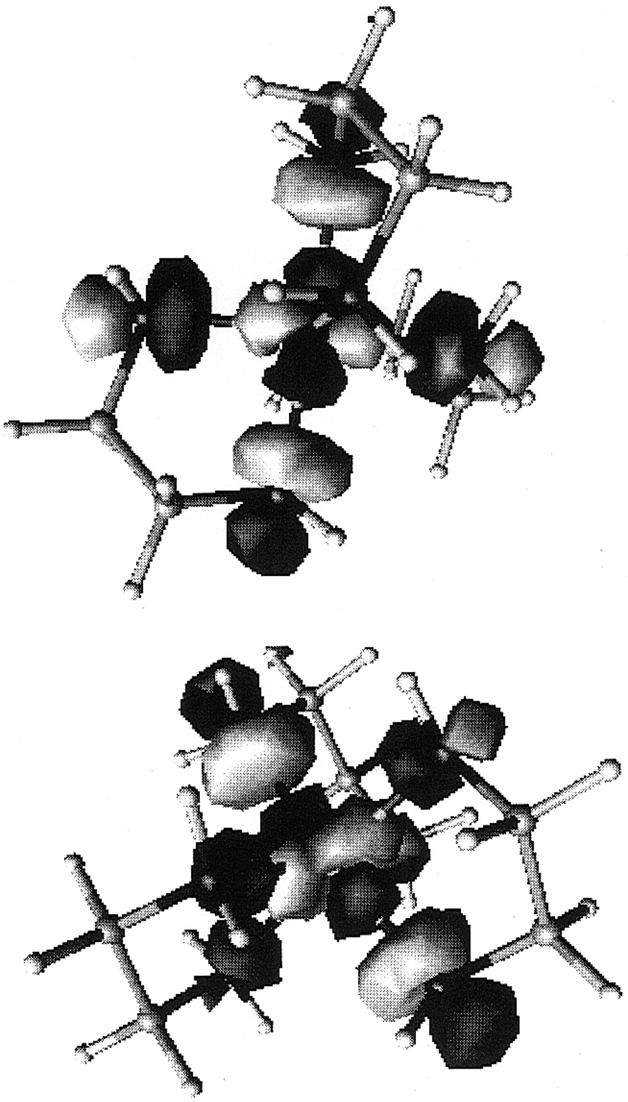

Figure 5. HOMO (top) and HOMO − 1 (bottom) of $[Co(en)_3]^{2+}$. These orbitals involve the cobalt $d_{x^2-y^2}$ and d_{z^2}-like orbitals, respectively.

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Supporting Information Available: Local and nonlocal density functional energies and coordinates and atomic charges at the LSD-optimized geometry (4 pages). See any current masthead page for ordering and internet access instructions.

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