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Second-Sphere Coordination of Transition-Metal Ammine Complexes by Lasalocid A, a Natural Ionophore

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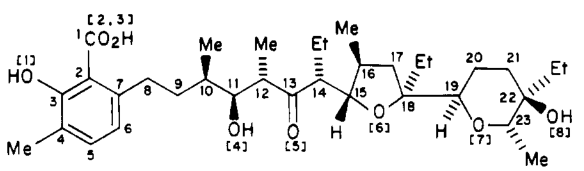
Complexes having the stoichiometry [cation^{n+}][lasalocid A$^-$]$_n$ have been prepared and characterized for the inorganic cations [Co(NH$_3$)$_6$]$^{3+}$, [Cr(NH$_3$)$_6$]$^{3+}$, [Pt(NH$_3$)$_6$]$^{4+}$, [Co(NH$_3$)$_5$Cl]$^{2+}$, and Δ- and Λ-[Co(en)$_3$]$^{3+}$. The crystalline complexes dissolve readily in solvents of low polarity such as chloroform and are characterized in this solvent by molecular weight data and by UV–visible, CD, and ^{13}C NMR spectroscopy. Complexation with lasalocid A anions does not cause rearrangement or rupture of the metal–N bonds in the first coordination sphere of the cations. Molecular weight data show that these complexes are not appreciably dissociated in chloroform solution. The ammine cations are believed to interact with lasalocid A anions through M–N–H···O hydrogen bonds.

Introduction

Lasalocid A (I)[1] is a microbially produced, carboxylic ionophore capable of transporting mono-, di-, and trivalent metal cations across natural and artificial membranes.[2-4] Over the past 15 years various researchers have explored the ligating properties of this extremely flexible molecule in the solid state and in solution. Crystallographic studies[5-9] of the Na$^+$, Ag$^+$, and Ba^{2+} complexes of the lasalocid A anion, hereafter abbreviated LAS, reveal that in all but one case the cations are sandwiched by two LAS ligands, each of which has a cyclic conformation stabilized by intramolecular hydrogen bonds. Most of the oxygens lie on the inside of the complex, leaving a hydrophobic outer surface. The five oxygens O$_4$, O$_5$, O$_6$, O$_7$, and O$_8$ bind the cation in all six of the published structures. A carboxylate oxygen is bound to the cation in only two structures, and in no case is O$_1$ involved in cation binding.



I

Lasalocid A complexes in the solution phase have been examined by a variety of experimental techniques, and there are a number of instances where the solution-phase pattern of ligation clearly differs from that found in the solid state. These are summarized in a recent paper[10] from this laboratory in which we further demonstrate that the specific LAS oxygens used for cation binding are determined by both the solvent polarity and the cation charge. Another recent study[11] involving the Ca^{2+} and La^{3+} complexes of LAS indicates that in chloroform solution a dynamic, intramolecular ligand donor exchange occurs in which at least two ligands "take turns" binding via O$_4$, O$_6$, and O$_7$ while remaining attached to the cation at O$_3$ and O$_8$. In both studies, crystalline complexes having the general stoichiometry M^{n+}(LAS)$_n$·xCHCl$_3$ were prepared and characterized for M = Ca^{2+}, Mn^{2+}, Gd^{3+}, and La^{3+}. Here, x is an integer or half-integer.

Lasalocid A is also known for its ability to bind and transport amine cations. Most of the previous work in this area has involved biogenic amines, and the existence of 1:1 complexes in various solvents and their role in membrane transport is well established.[2-4,12-14] In 1977, Westley et al.[15] first reported the isolation and characterization of *crystalline* 1:1 LAS amine complexes. An X-ray crystallographic study of the LAS complex of (R)-(+)-1-amino-1-(4-bromophenyl)ethane showed that the amine cation binds LAS via hydrogen bonds from –NH$_3^+$ to O$_3$, O$_6$, and O$_8$. The overall conformation of the LAS backbone was found to be the same as that in crystal structures of LAS complexes of metal cations. However, unlike the dimeric Na$^+$ and Ag$^+$ complexes, the amine complex is monomeric.

Transition-metal ammine complexes are known to form adducts with crown ether ionophores such as 18-crown-6 and dibenzo-18-crown-6.[16-19] X-ray crystal structures of several of these adducts reveal the presence of M–N–H···O hydrogen bonds similar to those found for the LAS amine complex described above. However, we are unaware of any previous reports of transition-metal ammine adducts of natural ionophores.

As part of our continuing interest in the ligating properties of lasalocid A, we have prepared and characterized several stoichiometric adducts of LAS with kinetically inert, Werner-type ammine complexes.

Experimental Section

Materials. NaLAS was purchased from Aldrich Chemical Co. and used without further purification, since ^{13}C NMR chemical shifts were in good agreement with reported values[7,20] and no signals attributable to impurities could be detected. The hydrochloride salt of (R)-(+)-α-methylbenzylamide (Aldrich Chemical Co.) was prepared by passing

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Table I. Characterization of [cation^{n+}](LAS)$_n$ Adducts

complex	mp, °C	% C calcd	% C found	% H calcd	% H found	% N calcd	% N found
$[Co(NH_3)_5Cl](LAS)_2$[a] (**1**)	154	57.99	57.56	8.63	8.60	4.94	4.57
$[Co(NH_3)_6](LAS)_3$ (**2**)	168–170	63.46	63.80	9.24	9.51	4.35	4.28
$[Cr(NH_3)_6](LAS)_3$[a] (**3**)	150–153	62.08	62.14	9.02	9.00	4.24	3.83
Δ-$[Co(en)_3](LAS)_3$ (**4**)	149–150	64.58	64.22	9.18	9.00	4.18	4.19
Λ-$[Co(en)_3](LAS)_3$ (**5**)	149	64.58	64.10	9.18	9.18	4.18	4.22
$[Pt(NH_3)_6](LAS)_4$ (**6**)	141–142	61.49	61.20	8.73	8.67	3.16	2.97

[a] Contains $^1/_2$ $CHCl_3$.

HCl through a solution of the amine in ethyl ether. The resulting precipitate was washed several times with ethyl ether and then dried in vacuo.

The following inorganic ammine complexes were prepared according to published methods: $[Co(NH_3)_6]Cl_3$,[21] $[Co(NH_3)_5Cl]Cl_2$,[22] $[Co(en)_3]I_3$,[23] $[Cr(NH_3)_6]Cl_3$,[24] $[Pt(NH_3)_6]Cl_4$.[25] Δ and Λ enantiomers of $[Co(en)_3]^{3+}$ were separated by fractional crystallization of their D-tartrate salts and then converted to iodide salts by using the procedure of Broomhead et al.[23] Specific rotations found for Δ and Λ iodide salts at 589 nm are −74° and +91°, respectively. (Corresponding literature values[23] are −90° and +89°.)

Preparation of LAS Complexes. The procedure used to prepare LAS adducts of inorganic ammine complexes is a slight modification of that reported previously for preparation of LAS complexes of metal cations.[10,11] In a typical preparation, a 30-mL aqueous solution containing 10 mmol of the transition-metal ammine complex is divided into three 10-mL portions. Each portion, in turn, is stirred vigorously for 2–3 h with 25 mL of a chloroform or methylene chloride solution containing 1 mmol of NaLAS. Subsequent filtration of the nonaqueous layer followed by removal of the solvent in vacuo affords a crystalline product that is further dried in vacuo at 60 °C for 24 h. The LAS adduct of the cation of (*R*)-(+)-α-methylbenzylamine was prepared by the same procedure, except that the nonaqueous layer was washed several times with water and then dried over molecular sieves prior to filtration and evaporation of solvent.

Instrumentation. Proton and carbon-13 NMR spectra were obtained on a Bruker WP-80 FT spectrometer operating at 80 MHz (^1H) or 20 MHz (^{13}C). Carbon-13 spectra were run at the ambient probe temperature of 37 °C with 8 K data points. Proton spectra were recorded over the temperature range −60 to +50 °C with 4 K data points. Elemental analyses were carried out on a Hewlett-Packard Model 185B C, H, and N analyzer located in the Department of Medicinal Chemistry. Repeated analyses of the *same sample* on this instrument spanned a range of 0.5% for C and 0.4% for H and N. Nitrogen analyses were usually low. Molecular weight determinations were made in chloroform solution at 37 °C on a Hewlett-Packard Model 302 vapor pressure osmometer. The osmometer was calibrated with recrystallized benzil, and solutions were in the concentration range of 1–10 mM. Utraviolet and visible absorption spectra were recorded on a Perkin-Elmer Model 555 spectrophotometer. Optical rotations at 589 nm were measured with a Sargent manual polarimeter, and CD spectra were obtained on a Cary Model 60 spectropolarimeter with a Model 6001 CD accessory. All melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Results and Discussion

Ammine complexes of Co(III), Cr(III), and Pt(IV) were chosen because of their kinetic inertness and their range of overall charge, 2+, 3+, and 4+. It was of interest to determine whether these large, nearly spherical coordination compounds would form stoichiometric "adducts" with LAS and whether the adducts would be ionic or molecular. The adducts are readily obtained in crystalline form by the procedure described in the Experimental Section. They are insoluble in water, moderately soluble in methanol, acetone, benzene, and diethyl ether, and very soluble in chloroform and methylene chloride. The adducts have the same colors as the ammine complexes used to prepare them.

Table II. Effective Molecular Weights of Lasalocid A Adducts in Chloroform Solution[a]

complex	mol wt calcd	mol wt found	complex	mol wt calcd	mol wt found
1	1419	1222	**4**	2009	2250
2	1930	1878	**5**	2009	2199
3	1983	1821	**6**	2656	2435

[a] Determined by vapor pressure osmometry at 37 °C.

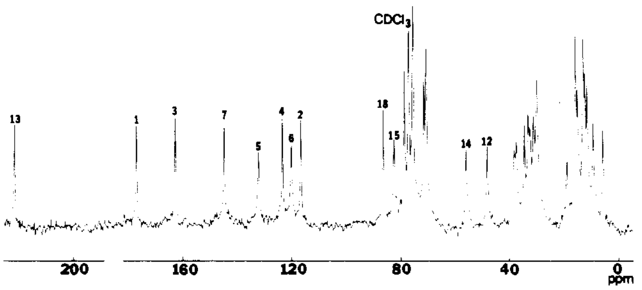

Figure 1. 20-MHz carbon-13 NMR spectrum of $[Co(NH_3)_6](LAS)_3$ in chloroform-*d* solution.

Results [illegible] elemental analyses are presented in Table I. In all cases, th[illegible] nalyses are consistent with the simple stoichiometry [cation[illegible] S]$_n$. In two cases a stoichiometric amount of solvent is assoc[illegible] vith the complex as is the case also for LAS complexes [illegible] le metal cations.[10,11] Effective molecular weights in chlor[illegible] ıre shown in Table II, and ^{13}C NMR chemical shifts are list[illegible] Table III. The ^{13}C NMR spectrum of [Co(NH$_3$)$_6$[illegible])$_3$, which is representative of the series, is shown in Figure [illegible] The spectrum is very similar to that of NaLAS.[10] The presence of $^1/_2$ $CHCl_3$ in adduct **1** was verified by ^1H NMR in acetone-d_6 solution.

Several attempts to prepare LAS adducts of *monovalent* ammine complex cations were made. Results of elemental analyses indicated incomplete adduct formation in these cases, even though large excesses of cation were used in efforts to force the equilibrium.

Absorption spectra in the ligand field region were recorded for the Co(III) and Cr(III) ammine complexes before and after reaction with LAS. In the LAS adducts, the high-energy, ligand field band is obscured by an intense absorption from LAS in each case. (This is a $\pi \rightarrow \pi^*$ transition with λ_{max} around 310 nm and ϵ_M of 5000.[26]) However, the low-energy, ligand field band ($^1A_{1g} \rightarrow {}^1T_{1g}$ for Co(III) and $^4A_{2g} \rightarrow {}^4T_{2g}$ for Cr(III) in O_h symmetry) remains largely unchanged upon adduct formation, indicating that the primary coordination sphere of the transition-metal ion remains intact. Wavelength maxima (λ_{max}, nm) and molar extinction coefficients (ε) found for the low-energy band of the ammine complexes (as chloride salts in water) and their LAS adducts (in $CHCl_3$) are compared: $[Co(NH_3)_6]^{3+}$, 474 (54); $[Co(NH_3)_6](LAS)_3$, 472 (65); $[Co(NH_3)_5Cl]^{2+}$, 530 (52); $[Co(NH_3)_5Cl](LAS)_2$, 522 (60); Δ-$[Co(en)_3]^{3+}$, 460 (96); Δ-$[Co(en)_3](LAS)_3$, 460 (102); Λ-$[Co(en)_3]^{3+}$, 460 (100); Λ-$[Co(en)_3](LAS)_3$, 460 (94); $[Cr(NH_3)_6]^{3+}$, 462 (37); $[Cr(NH_3)_6](LAS)_3$, 460 (48).

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Table III. Carbon-13 NMR Chemical Shifts for Lasalocid A Adducts[a,b]

				adduct no.				
carbon	HLAS	NaLAS	MBA-LAS	**1**	**2**	**4**[c]	**5**[d]	**6**
C_1	173.4	176.5	175.9	176.3	176.0	176.1	176.2	176.5
C_2	111.3	118.1	116.0	116.3	116.4	116.4	117.2	115.4
C_3	161.8	160.8	162.3	161.8	162.0	161.0	161.0	161.3
C_4	124.4	123.0	123.6	123.4	123.0	122.9	123.3	123.1
C_5	135.2	131.3	132.2	131.8	131.8	131.8	132.1	132.1
C_6	121.5	119.9	120.1	120.1	119.9	119.8	120.1	120.1
C_7	144.3	143.3	144.6	143.8	144.2	143.5	143.5	143.7
C_{11}	72.7	70.4	70.6	71.2	70.9	71.5	71.9	71.6
C_{12}	49.0	48.6	49.3	48.7	48.6	48.0	48.6	48.8
C_{13}	214.6	218.5	218.4	220.0	220.0	217.2	217.4	218.7
C_{14}	55.3	55.6	56.5	56.1	56.3	55.7	56.0	55.7
C_{15}	84.1	82.7	83.1	82.8	82.6	83.0	83.5	83.8
C_{18}	86.4	87.2	87.7	87.0	86.6	85.9	86.0	86.3
C_{19}	70.9	68.3	70.3	70.4	70.9	71.5	71.9	71.6
C_{22}	73.2	71.0	71.1	71.7	71.7	71.5	72.5	72.5

[a] In ppm from Me_4Si; data obtained in chloroform-*d* solution. [b] Data for complex **3** are not shown because of its paramagnetism. [c] Signal from en carbons at 45.3 ppm. [d] Signal from en carbons at 45.6 ppm.

Similarly, circular dichroism spectra of Δ- and Λ-$[Co(en)_3]I_3$ (in water) and the corresponding LAS adducts of these cations (in chloroform) were recorded. Δε values at the 490-nm maximum for the $^1A_1 \rightarrow {}^1E$ band for the iodide salts and LAS adducts are as follows: Δ-$[Co(en)_3]^{3+}$, −1.34; Δ-$[Co(en)_3](LAS)_3$, −1.46; Λ-$[Co(en)_3]^{3+}$, +1.57; Λ-$[Co(en)_3](LAS)_3$, +1.41. These results also demonstrate that adduct formation with LAS does not lead to rupture or rearrangement of the metal–nitrogen bonds.

Effective molecular weights of the adducts, determined in chloroform solution by vapor pressure osmometry, are within 2–14% of the calculated values. Complete dissociation of one or more LAS ligands from an adduct would have the effect of lowering the observed molecular weight to half or less of the calculated value. Observed molecular weights are slightly less than the calculated values for four of the six adducts, but they are higher for **4** and **5** by 12% and 9%, respectively. If the observed deviations for **4** and **5** are assumed to be indicative of the experimental error, then the lower molecular weights observed for **1**–**3** and **6** are probably not significant. Assuming the deviations are real, the upper limit to dissociation is 16%, using data for **1**. Thus, these adducts undergo little, if any, dissociation in chloroform solution. The LAS anions appear to be firmly bound to the cation in each case either via hydrogen bonds or by forming tight ion pairs.

Crystallography has shown that the cation of (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane binds LAS via hydrogen bonds to O_3, O_6, and O_8.[15] Other amine or ammine cations may also bind LAS in this manner in the solid state, but not necessarily in solution (see Introduction). In an attempt to establish the nature of the interaction between the ammine complexes and LAS in the solution phase, proton and carbon-13 NMR spectra of the adducts in chloroform solution were examined. The proton NMR spectra proved to be insufficiently resolved for this purpose, since most LAS proton resonances occur under broad envelopes between 0.5 and 4.5 ppm. Chemical shifts of well-resolved ^{13}C signals having firm assignments[7,20,27,28] are given in Table III. Chemical shifts for HLAS (lasalocid acid), NaLAS, and the LAS adduct of the (*R*)-(+)-α-methylbenzylammonium cation (abbreviated MBA-LAS) are also given for comparison. MBA-LAS was examined because of its close relationship to the adduct of the (*R*)-(+)-1-amino-1-(4-bromophenyl)ethane cation.

It is readily apparent from Table III that spectra of the ammine adducts are more closely related to those of NaLAS and MBA-LAS than to that of HLAS. The largest differences between the chemical shifts for NaLAS and those of the ammine adducts occur for C_2, C_{13}, and C_{19}, indicating possible *differences* between Na^+ and ammine cation binding interactions at the carboxyl group (O_2 or O_3), O_5, and O_7. Unfortunately, the binding sites used by Na^+ in solution are not known.

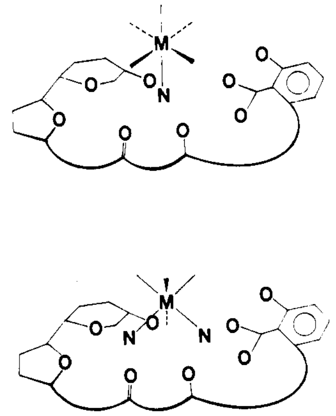

Figure 2. Schematic illustration of the interaction of one or two coordinated ammine ligands with the lasalocid A anion.

Smaller chemical shift differences between the adducts and MBA-LAS are found. This is particularly true for adducts **1** and **2**, where the differences are 0.8 ppm or less for all carbons except C_{13} (1.6 ppm) and C_{18} (1.1 ppm). Furthermore, for **1** and **2**, the direction of shifts (upfield or downfield) relative to those of MBA-LAS is the same for every carbon. The close similarity of chemical shifts for **1** and **2** implies that their ammine-LAS interactions are the same. If it is assumed that the MBA cation binds LAS in solution in the same manner as its brominated analogue in the crystalline phase, the observed similarities in chemical shifts between MBA-LAS and adducts **1** and **2** indicate that $[Co(NH_3)_5Cl]^{5+}$ and $[Co(NH_3)_6]^{3+}$ form hydrogen bonds to LAS at O_3, O_6, and O_8. $[Cr(NH_3)_6]^{3+}$ very likely binds LAS in the same manner; however, because of its paramagnetism, NMR spectra of adduct **3** are not available for comparison. Molecular models demonstrate that the very flexible LAS anion can interact with a single $M-NH_3$ group or it is capable of spanning two adjacent $M-NH_3$ groups, as illustrated schematically in Figure 2.

For adducts **4**–**6**, chemical shifts generally deviate more from those of MBA-LAS, possibly indicating a different pattern of hydrogen bonding. For **4** and **5**, this could result from the fact that only two protons on each nitrogen of the en ligands are available for hydrogen bonding. In the case of adduct **6**, a different hydrogen-bonding pattern may occur because the tetravalent cation must accommodate four bulky LAS ligands. Clearly, an unambiguous picture of the ammine-LAS interactions cannot be derived from these spectra.

A previous paper from this laboratory demonstrated that the LAS ligand is extremely flexible, and its complexes of simple metal cations such as Ca^{2+} and La^{3+} in chloroform solution undergo an intramolecular donor exchange that is intermediate or fast on the

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NMR time scale.[11] Thus, it is possible that the ammine adducts described here are also involved in exchange processes and that the observed NMR spectra represent time averages of spectra of several instantaneous structures. In an attempt to "freeze out" exchange processes, proton NMR spectra of **1** and **2** in chloroform-*d* solution were recorded at a series of temperatures from +50 to −60 °C. These present no definitive evidence for the occurrence of exchange but do not rule out the possibility that exchange is fast on the NMR time scale, even at −60 °C. Notable changes are observed only for two signals as the temperature is lowered. A broad signal at ~15 ppm, assigned[28] to 3-OH, sharpens for both **1** and **2**. Another signal at 6.4 ppm for **1** and 6.1 ppm for **2**, tentatively assigned to 22-OH by comparison with the spectrum of NaLAS,[11] shifts downfield by 0.3 ppm for **1** and decreases in intensity for **2** as the temperature is lowered. These changes are reversible for both adducts. If the assignment for 22-OH is correct, the changes observed are consistent with an ammine-LAS interaction at O_8, but further interpretation of the data would be unduly speculative.

In summary, LAS adducts of several Werner-type complexes are shown to have the stoichiometry $[\text{cation}^{n+}](\text{LAS})_n$. The LAS anions are second-sphere ligands that are believed to interact with the cations via hydrogen bonds with ammine protons. The LAS anions remain bound to the cations in chloroform solution. The close similarity of carbon-13 NMR spectra of adducts **1** and **2** to that of the (*R*)-(+)-α-methylbenzylammonium cation indicates that O_3, O_6, and O_8 of LAS may be involved in hydrogen bonding. Carbon-13 spectra of the other adducts are sufficiently different from those of **1** and **2** to suggest a different pattern of hydrogen bonding. Low-temperature proton NMR experiments did not clearly reveal the occurrence of exchange processes involving the second-sphere ligands. It is possible that exchange among several instantaneous structures is fast on the NMR time scale. Instantaneous structures in which a given LAS anion is involved in hydrogen bonding to one or two transition-metal-coordinated ammine ligands seem plausible. These are illustrated schematically in Figure 2.

Registry No. **1**, 96243-09-3; **2**, 96243-10-6; **3**, 96243-11-7; **4**, 96243-12-8; **5**, 96243-13-9; **6**, 96243-14-0.

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A Force Field for Molecular Mechanics Modeling of Cobalt(II) Amine Complexes and a New Model of Electron Transfer for Cobalt(III)–Cobalt(II) Redox Couples

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A molecular mechanics force field for the description of cobalt(II)–hexaamine complexes is developed by modeling the cage complex $[\text{Co}^{\text{II}}(\text{sepulchrate})]^{2+}$ and is applied to all isomers and conformers of the $[\text{Co(dien)}_2]^{3+/2+}$ system. The results for $[\text{Co(dien)}_2]^{3+/2+}$ correlate well with the observed reduction potentials of the different isomers. Relative energies of conformers are found to be quite different in the cobalt(III) and cobalt(II) states, and in some cases the global energy minima correspond to different conformational arrangements, which has implications for the electrochemical reduction of the cobalt(III) species. Conventionally, electrode processes involving reduction of cobalt(III) to cobalt(II) are treated as single step processes

$$\text{Co(III)} + e^- \xrightleftharpoons{E^\circ,\ k_s,\ \alpha} \text{Co(II)}$$

(E° = standard redox potential, k_s = heterogeneous rate constant for electron transfer, α = charge-transfer coefficient). However, when different conformational geometries are accessible and, especially, when the minima in free energy are associated with different conformers, the redox data cannot be treated via the use of the above equation. Rather a reaction of the kind (simplified)

$$\begin{tikzcd}
A_1 + e^- \arrow[r, shift left, "{E^0_1, (k_s)_1}"] \arrow[d, shift left] & A'_1 \arrow[l, shift left] \arrow[d, shift left] \\
A_2 + e^- \arrow[u, shift left, "K_1"'] \arrow[r, shift left, "{E^0_2, (k_s)_2}"] \arrow[d, dotted, "K_j"] & A'_2 \arrow[u, shift left, "K'_1"'] \arrow[l, shift left] \arrow[d, dotted, "K'_j"] \\
A_j + e^- \arrow[r, shift left, "{E^0_j, (k_s)_j}"] & A'_j \arrow[l, shift left]
\end{tikzcd}$$

must be used, where A_j and A'_j represent conformers in different oxidation states and K_j and K'_j are equilibrium constants. It is concluded that many heterogeneous and homogeneous redox reactions will need to be reexamined to take account of conformational energy differences.

Introduction

Molecular mechanics modeling of metal complexes was first reported more than 15 years ago, and the majority of studies performed since then have concerned cobalt(III)–hexaamine complexes. We recently developed a revised force field, which has proved significantly more successful than previous models and facilitates extension of the method to metals other than cobalt(III).[3] A force field for cobalt(II) species is of particular interest; these complexes are generally kinetically labile and hence less accessible, yet their stabilities are important for understanding the Co(III)/Co(II) redox couples which have been the subject of extensive investigation.[4]

In almost all electrochemical investigations of cobalt(III)/cobalt(II) redox couples a simple model of electron transfer has been proposed (eq 1), in which the standard redox potential, E°, a

$$[\text{Co(amine)}]_x^{3+} + e^- \xrightleftharpoons{E^\circ,\ k_s,\ \alpha} [\text{Co(amine)}]_x^{2+} \qquad (1)$$

heterogeneous charge transfer rate constant, k_s, and a charge-

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