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[2]-Cryptates: Stability and Selectivity of Alkali and Alkaline-Earth Macrobicyclic Complexes

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Abstract: The stability constants of the [2]-cryptate inclusion complexes formed by the macrobicyclic ligands **1–6** with alkali and alkaline-earth cations have been measured. The origin of the stability sequences is discussed in terms of ligand structural features (topology, binding sites). The optimal alkali cryptates display much higher *stability* than any previously known complex. This high stability may be ascribed to the macrobicyclic topology of the ligands; this *cryptate effect* is several orders of magnitude larger than the macrocyclic effect with respect to an open chain chelating ligand. The selectivity of the complexes is also remarkable. Optimal fit of the cation into the intramolecular cavity agrees with the selectivity of ligands [2.1.1], [2.2.1], and [2.2.2] for Li^+, Na^+, and K^+, respectively. The smaller ligands display *peak* selectivity whereas the larger ones display *plateau* selectivity, with only small differences in stability for K^+, Rb^+, and Cs^+. Unusual selectivities are observed for the alkaline-earth cryptates, e.g., the high Ca^{2+}/Mg^{2+} and Sr^{2+}, Ba^{2+}/Ca^{2+} ratios of ligands [2.2.1] and [2.2.2], respectively. Furthermore, M^{2+}/M^+ selectivities are also of interest, especially the unique $Li^+ > Mg^{2+}$, Ca^{2+} selectivity of ligand [2.1.1]. Changing from water to methanol solution generally leads to a marked increase in cryptate stability and selectivity. The results described provide strategies for the rational design of other specific ligands for metal cations.

The preferred complexation of a substrate S by a ligand L implies a *recognition* of S by L and its *selection* among the collection of possible substrates. Selectivity may be controlled by monitoring ligand structure, each specific feature representing an *information* bit. Information may be stored in: (1) the *topology* of the ligand, (2) its *binding* sites, (3) its *layer* properties. Medium and counterion are also expected to affect the stability and possibly the selectivity of the complex. A more detailed treatment of these general considerations is given in ref 2. The simplest substrate is a *spherical ion*, which, in addition to its simple shape, may also interact much more strongly with the ligand than a neutral species. The spherical *alkali* and *alkaline-earth metal cations* form complexes with various macrocyclic ligands of natural[3] or synthetic[4,5] origin.

Macrobicyclic ligands give 1/1 inclusion complexes with these cations, [2]-*cryptates*, in which the cation is contained inside the molecular cavity. We have recently described the formation and the structure of such cryptates[6] of the diazapolyoxamacrobicyclic ligands (*"cryptands"*) **1–6**.[7] We analyze here our results about the *stability* and *selectivity* of these complexes in terms of the ligand parameters mentioned above and discussed in more detail in previous reports.[2,6,7]

Since the cryptates are inclusion complexes, we shall formulate them by using the mathematical symbol of inclusion $\subset$, for instance $[K^+ \subset 2.2.2]$, (K^+ included in ligand [2.2.2]) in order to distinguish them from addition complexes [L,S] (see ref 2, footnote 2). We also make use of the previously defined ligand nomenclature, [2.1.1], [2.2.1] etc., where the figures represent the number of oxygen atoms contained in each bridge of the bicyclic molecule.[2,6-8] All complexes of ligands **1–6** are macrobicyclic complexes, i.e., [2]-cryptates.[2]

Results

Determination of the Stability Constants. The complexation of a metal cation M^{n+} by a ligand L in a solvent S is represented by eq 1.

$$(L)_{solv} + (M^{n+}, mS) \underset{k_d}{\overset{k_f}{\rightleftharpoons}} [L,M^{n+}]_{solv} + mS \qquad (1)$$

where k_f and k_d are respectively the rates of formation and

Table I. Stability Constants (log K_S) of Alkaline and Alkaline-Earth Metal Cation Cryptates (K_S in l. mol^{-1} at 25°C)[a]

Ligand	Solvent	pK_1 ±0.05	pK_2 ±0.05	Log K_S with cation: Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
[2.1.1]	W	7.85	10.64	5.5	3.2	<2.0	<2.0	<2.0	2.5 ± 0.3	2.50	<2.0	<2.0
	M/W	6.56	11.00	7.58	6.08	2.26	<2.0	<2.0	4.0 ± 0.8	4.34	2.90	<2.0
	M	–	–	>6.0	6.1	2.3	1.9	<2.0	–	–	–	–
[2.2.1][b]	W	7.50	10.53	2.50	5.40	3.95	2.55	<2.0	<2.0	6.95	7.35	6.30
	M/W	6.60	10.42	4.18	8.84	7.45	5.80	(3.90)[f]	<2.0	9.61	10.65	9.70
	M	–	–	(>5.0)	>8.0	>7.0	>6.0	(~5.0)[f]	–	–	–	–
[2.2.2][c]	W	7.28	9.60	<2.0	3.9	5.4	4.35	<2.0	<2.0	4.4	8.0	9.5
	M/W	6.64	9.85	1.8	7.21	9.75	8.40	3.54	<2.0	7.60	11.5	(12)[g]
	M	–	–	2.6	>8.0	>7.0	>6.0	4.4	–	–	–	–
[3.2.2]	W	7.33	8.50	<2.0	1.65	2.2	2.05	2.0	<2.0	~2.0	3.4	6.0
	M/W	6.55	9.14	<2.0	4.57	7.0	7.30	7.0	<2.0	4.74	7.06	10.40
	M	–	–	2.3	4.8	>7.0	>6.0	>6.0	–	–	–	–
[3.3.2]	W	7.31	8.16	<2.0	<2.0	<2.0	<0.7	<2.0	<2.0	~2.0	~2.0	3.65
	M	–	–	–	3.2	6.0	6.15	>6.0	–	–	–	–
[3.3.3]	W	6.96	7.70	<2.0	<2.0	<2.0	<0.5	<2.0	<2.0	<2.0	<2.0	
	M	–	–	–	2.7	5.4	5.7	5.9	–	–	–	
[2.2.c_8][13]	M/W	6.60	9.92	–	3.00	4.35	–	–	–	–	–	<2.0
	M	–	–	≤2.0	3.5	5.2	3.4	2.7	–	–	–	–
8[13]	M/W	6.70	9.28	–	3.26	4.38	–	–	–	4.4	6.1	6.7
	M	–	–	–	3.7	5.3	4.3	–	–	–	–	–
9[14]	M/W			–	3.35	4.80	–	–	–	–	–	–
10[4,d]	W	–	–	0.6	1.7	2.2	1.5	1.2	–	0.4[5]	3.24	3.6
	M	–	–	–	4.1	6.0	–	4.6	–	–	–	–
12 EDTA[12,e]	W	–	–	2.85	1.79	0.96	0.59	0.15	9.12	11.0	8.80	7.78
14[12,e]	W	–	–	5.61	3.33	1.94	–	–	8.19	8.31	6.93	6.13
Enniatin B[40,41]	M	–	–	1.28	2.38	2.92	2.74	2.34	1.20	2.95	2.65	2.93
Valinomycin[41]	M	–	–	<0.7	0.67	4.90	5.26	4.41	<0.7	2.70	2.23	3.34

[a] Key: W, water; M/W, methanol/water 95/5; M, methanol. The precision of the measurements is discussed in the experimental section. Total ionic strength: 0.05 in W; 0.01 in M/W; 0.01 in M (see experimental section). pK_1 and pK_2, ±0.05. [b] With Ag^+ log K_S = 10.6 (W). [c] With Ag^+ log K_S = 9.6; Tl^+, 6.3; Pb^{2+}, 12.0; Cd^{2+}, 6.8;[45,46] Hg^{2+}, 18.2[45] (W). [d] With Ag^+ log K_S = 2.35; Tl^+, 2.45; NH^{4+}, 1.35; Hg_2^{2+}, 1.6; Hg^{2+}, 2.75; Pb^{2+}, 4.9[5] (W). [e] K_1 values. [f] External complexes of ligand/cation 2/1 stoichiometry may be present. [g] Because of slow deprotonation kinetics at low pH, this value is very inaccurate (probably ±0.7).

of dissociation of the complex. Since the ligands **1–6** are diamines the following acid-base equilibria take place:

$$(LH_2^{2+})_{solv} \rightleftharpoons (LH^+)_{solv} + H^+ \quad (2)$$

$$(LH^+)_{solv} \rightleftharpoons (L)_{solv} + H^+ \quad (3)$$

$$[L,M^{n+},2H^+]_{solv} \rightleftharpoons [L,M^{n+},H^+]_{solv} + H^+ \quad (4)$$

$$[L,M^{n+},H^+]_{solv} \rightleftharpoons [L,M^{n+}]_{solv} + H^+ \quad (5)$$

Equations 2 and 3 define the pK_1 and pK_2 of the ligands and eq 4 and 5 represent the protonation pK_1 and pK_2 of the complexes. Addition of a metal cation M^{n+} will thus affect the basicity of a solution of the free ligand. The role of these equilibria will be considered in detail in the experimental section.

The thermodynamic stability constant K_{th} is given by

$$K_{th} = \frac{f_C|[L,M^{n+}]|}{f_L|L|f_M|M^{n+}|} \quad (6)$$

where f_C, f_L, and f_M are the activity coefficients of the three species. Since these coefficients are generally unknown, the quantities reported in this paper are the concentration stability constants K_S.

$$K_S = K_{th}\frac{f_L f_M}{f_C} = \frac{|[L,M^{n+}]|}{|L|\,|M^{n+}|} \quad (7)$$

The present ligands may exist in three different forms both in the free and in the complexed state.[6,7] K_S is thus in principle an average stability constant for the system at thermodynamic equilibrium with respect to conformation as well as to complexation (see also below). Two methods have been used for determining the K_S values. (i) Complexation greatly affects the basicity of the solutions of ligands **1–6** (eq 1–5), and the analysis of pH-metric titration curves[9] in the absence and in the presence of a cation allows K_S to be calculated. This method is best used for the higher stability constants (log $K_S \geq 2$). (ii) Direct measurement of uncomplexed cation concentration at equilibrium may be achieved using cation selective electrodes.[10] This method is best suited in the range $1 < \log K_S < 5$ (in water; 6 in methanol).

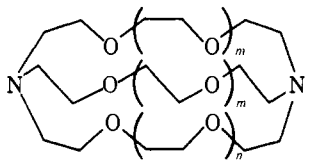
The experimental procedures and their reliability are considered in detail in the experimental section of this report. Measurements were performed in three solvents: water, methanol:water 95:5, and pure methanol. The interest of the mixed solvent is that it allows both high and low K_S values to be determined for almost all ligand-cation pairs using the pH-metric titration method. Some complexes are too unstable in aqueous solution for pH-metric measurements; others are too stable in pure methanol where cation selective electrodes have to be used. The mixed solvent cuts across these two classes.

Results. Table I contains the K_S values measured for the complexes of ligands **1–6** as well as the pK_1 and pK_2 values of the ligands. Additional data for complexes of ligands **7–14** are included for comparison purposes. Figures 1 and 2 provide a graphic representation of these results.

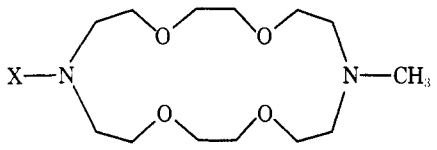
The present results should be considered as more accurate when they differ from previous reports.[2,8] For instance a more accurate determination of the pK's of the strongly basic ligand [2.1.1] leads to higher stability constants for its complexes. The data agree with a 1/1 cation/ligand stoichiometry except for complexes of Cs^+ with the smaller ligands **1** and **2**, where 2/1 compounds may be present. This point has not yet been studied in detail.

Discussion

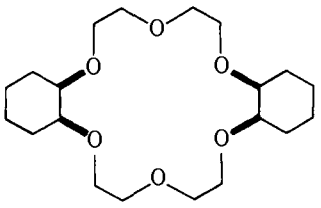
The *stability* of a cation complex results from the balance between free energies of solvation and of complexa-



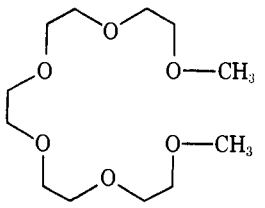
1, $m = 0$; $n = 1$ [2.1.1]
2, $m = 1$; $n = 0$ [2.2.1]
3, $m = n = 1$ [2.2.2]
4, $m = 1$; $n = 2$ [3.2.2]
5, $m = 2$; $n = 1$ [3.3.2]
6, $m = n = 2$ [3.3.3]
7, $m = 1$, (third bridge = $-(CH_2)_8-$ [2.2.C_8]



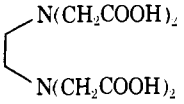
8, X = CH_3
9, X = $CH_2CH_2OCH_2CH_2OCH_3$



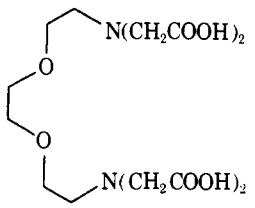
10, (isomer A)



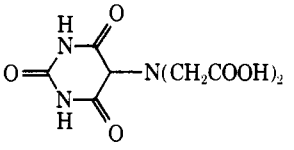
11



12 EDTA



13 EGTA



14

tion. The *selectivity* of a ligand for a given cation within a series depends on how the free energy of the complex changes with respect to the free energy of the solvated cation. The free energy of solvation increases continuously as the size of the cation decreases (Table II). The same would hold for the free energy of complexation by a polydentate ligand if it were able to adjust to all cation sizes. However, if this ligand contains a cavity of fixed size, the free energy of complexation will increase as the size of the cation decreases until it reaches the size of the cavity. For smaller cations it levels off; indeed no further increase in interaction energy is expected since the cavity cannot contract further so as to maintain contact between the cation and the binding sites. Thus, cation and cavity radii may be used as criteria for discussing complexation features. Enthalpy and entropy changes on complexation will be discussed in a later report.

Both the free macrobicyclic ligands and their complexes may exist in three forms, endo-endo (or in-in), endo-exo (or in-out), and exo-exo (or out-out), differing by the orientation of the nitrogen bridgeheads toward the inside or the outside of the intramolecular cavity.[6,7,11] K_s is thus in principle an average stability constant for the six species at thermodynamic equilibrium with respect to conformation as well as to complexation. In the cryptates, interaction of the nitrogen sites with the cation strongly favors the form having both sites turned inside. Which form of the free ligands is most abundant is not known at present and may change with the nature of the ligand and of the medium. Each species may also give a monoprotonated and diprotonated derivative. Protonated forms of the complexes are unimportant in the general cases since protonation destroys the complex (see also experimental section). Six protonated forms of the free ligands may, however, exist. Nothing is known about their relative energies but inside protonated forms are probably more stable than outside protonated ones by analogy with the macrobicyclic diamines of Simmons and Park.[11] The pK_1 and pK_2 values determined here apply to the rapidly interconverting equilibrium mixture of the three diamines and of the six mono- and diprotonated derivatives. A more detailed study of the mechanism and kinetics of complexation and of protonation will be given in a future report.

Table II. Ionic Radii, Hydration Numbers, and Free Energies of Hydration, $\Delta G°$, of Metal Cations. Approximate Cavity Radius and Number of Binding Sites of Ligands

Cation	Ionic radius r_i (Å)[42]	Hydration no.[3]	$-\Delta G°$ (kcal/mol) (25°C)[44]	Ligand	Cavity radius[2,8] (Å)[a]	No. of binding sites
Li^+	0.78	6	122	[2.1.1]	0.8	6
Na^+	0.98	6	98.5	[2.2.1]	1.1	7
K^+	1.33	6	80.5	[2.2.2]	1.4	8
Rb^+	1.49	6	75.5	[3.2.2]	1.8	9
Cs^+	1.65	6	68.0	[3.3.2]	2.1	10
Mg^{2+}	0.78	6	454	[3.3.3]	2.4	11
Ca^{2+}	1.06	8	379	10[4]	1.3–1.6	6
Sr^{2+}	1.27	8	340			
Ba^{2+}	1.43	8	314			

[a] Measured on Corey-Pauling-Koltun molecular models.

Stability of the Alkali Cation Cryptates. From the stability constants listed in Table I it is immediately apparent that the electrically neutral macrobicyclic ligands **1–6** give by far the strongest alkali cation complexes known to date. Highest stabilities are found for [$Li^+ \subset$ 2.1.1], [$Na^+ \subset$ 2.2.1], [$K^+ \subset$ 2.2.2], [$Rb^+ \subset$ 2.2.2], and [$Cs^+ \subset$ 3.2.2]. These optimum K_s values are several powers of ten higher than those of other types of organic ligands including natural ligands; for instance, [$K^+ \subset$ 2.2.2] is about 10^4 times more stable than [$K^+ \subset$ valinomycin]. This also holds for complexes with charged ligands, among which only a few Li^+ complexes of ligands bearing several anionic groups show marked stabilities. Among the ligands listed in a very extensive recent compilation,[12] compound **14** and to a lesser extent some diphosphonic acids and EDTA **12** form the most stable alkali cation complexes (see Table I). Only the [**14**, Li^+] complex reaches the stability of the optimum Li^+ cryptate, [$Li^+ \subset$ 2.1.1].

Topology Effects. One of the main ideas,[2,6,7] which initiated our work on the cryptates, was the expectation that the *topology* of a macrobicyclic ligand, which contains an almost spherical intramolecular cavity, should be particularly well adapted to the formation of stable and selective complexes with spherical cations. That such a *macrobicyclic cryptate effect* exists is seen from the data in Table I. Indeed the incorporation of the bicyclic topology in the [$K^+ \subset$ 2.2.2] cryptate leads to a 10^5 increase in complex stability (in methanol–water) with respect to the macrocyclic K^+

complexes of **8**,[13] or better of **9**[14] which exactly results from the opening of one bridge of the [2.2.2] ligand. Since a *macrocyclic effect* of about 10^4 is found between the K^+ complexes of the open chain ligand **11** and of its macrocyclic analog **10**,[4,15] the macrobicyclic effect amounts to about 10^9 with respect to **11**. The chelate effect in the complexes of **11** itself is difficult to estimate, since the stability constant for K^+ or Na^+ complexation for instance by tetrahydrofuran in methanol is unknown. Approximate stability constants for the stepwise complexation of Na^+ in pure THF have been determined.[16] The free energy changes corresponding to these ring order dependent, generalized chelate effects amount to as much as about 5 and 12 kcal/mol for the macrocyclic and macrobicyclic effects with respect to an open chain ligand. Enthalpic and entropic contributions will be analyzed in a later report.

Cavity size and shape also plays an important role. Along the series of ligands **1–6** the change in lengths of the bridges of the macrobicyclic system brings about a stepwise variation in size of the approximately spherical intramolecular cavity present in the in-in form of a macrobicyclic ligand. From the data in Tables I and II it is seen that the high stabilities of the [$Li^+ \subset$ 2.1.1], [$Na^+ \subset$ 2.2.1], and [$K^+ \subset$ 2.2.2] cryptates correspond to preferred complexation of those cations whose size most closely fits the intramolecular cavity. This is easily illustrated using space filling molecular models (see photographs of Figure 9 in ref 17). In the ligands **4–6** the cavity becomes too large (except for [$Cs^+ \subset$ 3.2.2]) so that contact between cation and binding sites introduces deformations and increased intraligand repulsions which destabilize the complex. Such deformations as well as any other *conformational changes* which may occur on complexation are unfavorable with respect to stability since they bring the ligand out of its own equilibrium conformation; they may also lead to higher exchange rates.

Effects of Binding Sites. The *number* of binding sites changes in the series of ligands **1–6.** This certainly affects the stability constants of the complexes, in addition to the cavity size. In all cases, the number of binding sites equals or exceeds the hydration number of the cations (Table II). Comparison of the data for [2.2.2] and [2.2.C_8], which have similar cavity size, shows that the stability of the Na^+ and K^+ cryptates decreases by a factor of about 10^4–10^5 (in methanol-water) on replacement of two oxygen binding sites by two CH_2 groups, i.e., a factor of ca. 10^2 per site. Molecular models show that in most complexes the maximum number of binding sites is not reached. For a minimum cavity radius of 1.40 Å, the radius ratio effect leads to a maximum coordination number of 12 oxygens in a cubooctahedral arrangement.[2,18,19]

The nature of the sites determines the nature of the cation–ligand interactions. Ligands **1–6** bear *electrically neutral binding sites* so that the cation-site interactions are of the charge-dipole and charge-induced dipole type. Oxygen sites have higher polarity but lower polarizability than nitrogen sites. Alkali cations are more strongly solvated by O than by N sites[2] except for Be^{2+} and perhaps Li^+. The cations Tl^+ and especially Ag^+ interact strongly with the nitrogen sites, as shown by shortened N···M^+ distances,[6,20,22] and form very stable cryptates (Table I, footnotes). Sites with larger dipole moments, like amides or sulfoxides, lining the interior of the cavity of a macrobiocyclic ligand could give even more stable complexes.

The *arrangement* of the binding sites has been studied by X-ray crystallography. The six oxygens and two nitrogens in the complexes of [2.2.2] form a bicapped trigonal antiprism.[20–22] All oxygen sites are turned inside in the cryptate whereas this is not so in the free ligand. Each pair of binding sites (X, Y) and the intervening $-CH_2-CH_2-$ fragment form a five-membered ring with the cryptated metal cation, which is thus part of several such rings when the whole ligand is considered. It is well known that five-membered ring chelates are more stable than six-membered and four-membered ones. Thus $X-CH_2-CH_2-Y$ arrangements are preferable to the homologous $X-(CH_2)_3-Y$ and $X-CH_2-Y$ ones.

Binding sites *reactivity* is of particular importance in the present complexes. Indeed, protonation of the bridgehead nitrogen sites destroys them, so that the stability constants decrease at low pH. Conversely, this factor allows linkage of proton levels and free cation levels, a phenomenon of interest in membrane transport studies.[2,23]

Stability of the Alkaline-Earth Cation Cryptates. Alkaline-earth cations are known to form very stable complexes with many acyclic polyanionic chelating ligands, like EDTA **12** (see Table I), EGTA **13** etc.[12] Despite the fact that ligands **1–6** are neutral, they do form some very stable alkaline-earth cryptates, and [$Ba^{2+} \subset$ 2.2.2] is more stable than the Ba^{2+} chelates of EDTA and EGTA (log K_s = 8.8).[12]

Comparison of the stability constants of the Ba^{2+} complexes of [2.2.2] and **8** leads to a *macrobicyclic cryptate effect* of about 10^5 (in M/W), similar to the effect found for K^+. Again the bicyclic topology is of prime importance in strongly raising the K_s values.

Cavity size affects the stability constants, as in the case of the alkali cations (see Tables I and II and Figure 2). However, the selectivity peaks are much less sharp than for the alkali cryptates.

The number of *binding sites* in the ligands would in most cases be sufficient to replace the hydration shell; however, it seems that the divalent cryptates generally complete their coordination shell with an anion and/or with water molecules; coordination numbers of 10 and 11 are observed in the crystal structures of $\{[Ba^{2+} \subset 2.2.2](SCN)^-(H_2O)\}^+$ and $\{[Ba^{2+} \subset 3.2.2](H_2O)_2\}^{2+}$ complex cations.[21] The higher stability of [$Pb^{2+} \subset$ 2.2.2] compared to the Ba^{2+} complex is analogous to the $Tl^+ > K^+$ stabilities mentioned above.

Complexation Selectivity. Alkali Cryptates. We have just seen that many complexes listed in Table I are very stable. However, high stability does not imply high selectivity; some ligands may form weaker complexes than others, but nevertheless be much more selective. The balances between Na^+, K^+, Mg^{2+}, and Ca^{2+} play a fundamental role in biology and highly selective processes participate to their regulation.[24–27] The ionic radii of the cations (Table II) indeed suggest that the Na^+/K^+ and Mg^{2+}/Ca^{2+} pairs would be particularly well adapted for selective complexation and regulation, since the change in radii is largest for these two neighboring cations in the series of alkali and alkaline-earth cations, respectively (not taking Be^{2+} into account). Table I shows that very pronounced cation selectivities are found among the alkali cation cryptates. Indeed for any pair of cations there is a ligand among **1–6** which has appreciably higher selectivity than those previously known, including the natural macrocyclic ligands,[3] except in the K^+/Na^+ case where valinomycin stands out by a factor of about 30 over [3.3.2] and [3.3.3], and the macrocyclic polyether dibenzo-[30]-crown-10[4] reaches into the selectivity range of the ligands **3–6.** No ligand shows marked preference for either Rb^+ or Cs^+.

Dimensionality, connectivity and overall cavity shape remain constant along the series of ligands **1–6.** The macrobicyclic ligands operate a three-dimensional discrimination (spherical cavity) against cations as compared to the two-dimensional discrimination generally performed by macrocyclic ligands ("circular" cavity).

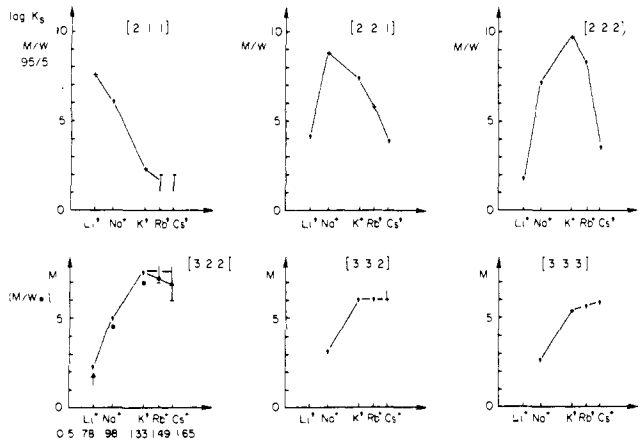


Figure 1. Stability constants of the alkali cryptates formed by ligands **1–6** (in methanol/water (M/W) 95/5 or pure methanol (M) at 25°C) as a function of ionic radius (in Å; Table II).

Cavity size strongly affects K_s as already noted, the preferred cation being that which best fits into the cavity. This *cavity selectivity*, which incorporates several types of primary effects (electrostatic and van der Waals attraction and repulsions, nature and number of binding sites, ligand conformational changes, enthalpy/entropy contributions), may be used as an operational criterion for predicting selectivity of complexation.

Ligand dynamics, i.e., rigidity, flexibility, conformational changes, act on cation selectivities often together with cavity size. Indeed, ligands with small cavities are generally quite rigid, almost by necessity, since a small cavity is delineated by short, relatively nonflexible chains. On the other hand larger ligands with cavities above a certain size are generally more flexible and may undergo more pronounced conformational changes. The following conclusions may then be drawn from the data in Table I or available in the literature (references in ref 2–5).

1. Rigid ligands display *peak selectivity*. They are able to discriminate against cations which are either smaller or larger than their cavity, since distortion of a rigid ligand either by contraction or by expansion of its cavity leads to pronounced destabilization. This is pictured in Figure 1. The ligands of the "rigid" type, [2.1.1], [2.2.1], and [2.2.2], present a stability peak for the optimal cation. That these macrobicyclic ligands present better *overall* selectivity than other types of ligands may be related to their bicyclic topology. Indeed they have higher connectivity (thus, higher rigidity) and higher dimensionality[2] (three-dimensional discrimination) than macrocyclic ligands. The case of [2.2.2] is particularly noteworthy, since, in an aqueous solution containing all alkali cations, it would complex Na^+, K^+, and Rb^+ and completely cut out Li^+ *and* Cs^+.

2. *Plateau selectivity* is observed for flexible ligands which contain large, adjustable cavities. In the series **1–6**, the "flexible" type begins with [3.2.2] whose maximum cavity size corresponds approximately to Cs^+. This general behavior is illustrated in Figure 1 where it is seen that in all three cases one reaches a stability plateau for K^+, Rb^+, and Cs^+, whereas K^+/Na^+ selectivity is large. The macrocyclic antibiotics also show a similar behavior (see enniatin B and valinomycin in Table I). It is especially striking that valinomycin, which shows such a high K^+/Na^+ selectivity, does not distinguish well between K^+, Rb^+, and Cs^+. Enniatin B has in fact low overall selectivity. This type of behavior (high K^+/Na^+ selectivity; weak K^+/Rb^+, Cs^+ selectivity) may be explained as follows: the complexation of small cations (e.g., Li^+, Na^+) requires a marked decrease in cavity size thus introducing destabilizing steric and binding site repulsions; larger cations (e.g., K^+, Rb^+, Cs^+) modify the cavity size by slight contraction or by expansion at comparatively little expense of energy. That the stability plateau generally starts at K^+ is not too surprising since the largest relative change in cation radius occurs between Na^+ and K^+: $[r_i(K^+) - r_i(Na^+)]/r_i(Na^+) = 0.36$; $[r_i(Rb^+) - r_i(K^+)]/r_i(K^+) = 0.12$.

In addition to these ligand features, an important contribution to this peak-plateau behavior also results from the fact that the coordination properties (see the free energies of hydration in Table II) change much less for K^+, Rb^+, and Cs^+ than for Li^+, Na^+, and K^+.

It is worth noting that two kinds of behavior may be distinguished for the permeability of cell membranes to alkali cations: permeability to Na^+ and Li^+ but not to K^+, Rb^+, and Cs^+; permeability to K^+, Rb^+, and sometimes Cs^+ but not to Li^+ and Na^+.[27] Also in the presence of valinomycin, mitochondria rapidly take up K^+, Rb^+, and Cs^+ but not Na^+ or Li^+.[28]

The absence of negative binding sites plays an important role in displacing selectivity orders in favor of cations of larger size or of lower charge (see below)[2] as compared to the complexone type ligand **12–14.**

Complexation Selectivity. Alkaline-Earth Cryptates. The complexation properties of the polyanionic acyclic ligands (see **13–15**) toward alkaline-earth cations generally display the selectivity sequence: $Ca^{2+} > Mg^{2+} > Sr^{2+} > Ba^{2+}$. The selectivities of the *electrically neutral* macrobicyclic ligands are quite different (Table I).

(1) High selectivities may be found among the bivalent cryptates for the different pairs of alkaline-earth cations. Except for [2.1.1], the sequence is of the type Mg^{2+}, $Ca^{2+} < Sr^{2+}$, Ba^{2+}, i.e., opposite to the usual sequence of anionic ligands. The same sequence is found for the natural or synthetic macrocycles but with much weaker selectivities.

(2) Ligand [2.2.1] displays very high Ca^{2+}/Mg^{2+} selectivity compared to other known ligands, probably even higher than for EGTA **13** (log K_s = 5.2 (Mg^{2+}), 11.0 (Ca^{2+}) in water).[12]

(3) [2.2.2] is at present the ligand which shows the highest selectivity for Sr^{2+} (factor 4000) and Ba^{2+} (factor 10^5) with respect to Ca^{2+}, while retaining high stability. This property has been used in experiments of radioactive strontium decorporation.[29] [2.2.2] contains a cavity suitable for Sr^{2+} and Ba^{2+} complexation but too large for Ca^{2+}.

(4) [3.2.2] presents a high Ba^{2+}/Sr^{2+} selectivity.

(5) No dichotomic peak/plateau behavior is observed as in the case of alkali cations (Figure 2). The largest bivalent cation Ba^{2+} has a radius between K^+ and Rb^+. The plateau behavior would probably only be visible from Ba^{2+} to larger cations (Ra^{2+}?). Thus, once the cavity is large enough Ba^{2+} always forms the most stable complex.

Complexation Selectivity. Bivalent Versus Monovalent Cryptates. The influence of ligand structure on the complexation selectivity of alkaline-earth vs. alkali cations M^{2+}/M^+ has been analyzed recently[3] and control over this selectivity in cryptates has been reported.[13] The anionic chelating agents favor M^{2+} very strongly. Neutral ligands are expected to decrease the M^{2+}/M^+ selectivity ratio which may even become much smaller than unity in several natural antibiotics (e.g., valinomycin, Table I) and in the cryptates of **7**, [2.2.C_8].[13] With ligands **1–6** the most stable complex encountered is always formed by a bivalent cation (Sr^{2+} or Ba^{2+}) except in the case of [2.1.1].

Since Mg^{2+} and Li^+, Ca^{2+}, and Na^+ have similar ionic radii the sequences $Mg^{2+} < Li^+$, $Ca^{2+} < Na^+$ displayed by [2.1.1] are not due to cavity size. The small number of neutral binding sites, the presence of nitrogen sites, and the organic skin which diminishes the interactions of the buried

cation with the polar medium (see below), all disfavor M^{2+} with respect to M^+.

Competition between bivalent and monovalent cations among the set Na^+, K^+, Mg^{2+}, Ca^{2+} plays a major role in biological processes.[24-27,30] It has been pointed out that it may be difficult to devise a ligand which favors Na^+ over Ca^{2+}.[24] [2.1.1] is such a ligand; its Mg^{2+}, $Ca^{2+} < Na^+$ selectivity, though weak in water, increases in less polar medium. Its very large Mg^{2+}, $Ca^{2+} < Li^+$ selectivity is unique and may be ascribed to a large part to the absence of negatively charged binding sites. Indeed, **14** complexes Li^+ as well as [2.1.1] but is poisoned by Mg^{2+} and Ca^{2+} ($Li^+ < Mg^{2+}$, Ca^{2+}, Table I). With [2.1.1] preference goes to Ca^{2+} whereas [2.2.2] and probably also all larger ligands favor K^+ over Ca^{2+}. According to previous results[13] on the $Ba^{2+} < K^+$ selectivity of ligand [2.2.C_8], a ligand displaying a high Na^+/Ca^{2+} ratio could be [2.2.C_5], where the $-(CH_2)_5-$ bridge reduces the cavity size with respect to [2.2.C_8].

Medium Effects on Cryptate Stability and Selectivity. Medium effects play a fundamental role on both stabilities and selectivities of complexation. They arise from changes in the balance (a) between solvation energy and ligand coordination energy and (b) between interaction with the dielectric medium outside the first solvation shell and the ligand shell. The first effect is expected to increase strongly the stability of the complexes and to affect selectivities, probably favoring small and/or more highly charged cations as the solvating power of the solvent decreases with respect to that of the ligand.

The second factor is represented by the Born equation[2,3]

$$\Delta G_B = -\frac{Z^2e^2}{2a}\left[1-\frac{1}{\epsilon}\right] = -163.8\frac{Z^2}{a\times 10^8}\ \text{kcal/mol} \quad (8)$$

ΔG_B is the electrostatic part of the free energy change due to the transfer of a cation of charge Z from vacuum into a medium of dielectric constant ϵ. a is the radius of the solvated or complexed cation (ionic radius + thickness of the first solvation shell or of the ligand).

The *stability* of all cryptates increases markedly from water to methanol, i.e., as the dielectric constant of the medium decreases. In most cases this increase is grossly proportional to the stability of the complex considered. In addition for complexes of comparable stabilities, those with small cations often show smaller increases.

The *selectivity* increases from water to methanol (or M/W 95/5, see Table I) favoring (i) the most stable complexes and (ii) larger cations over smaller ones. These two factors may operate in the same or opposite sense for a given M_i^+/M_j^+ selectivity, depending on the relative size of the cations and on the relative stability of their cryptates with a given ligand. As a consequence, the largest gains in selectivity occur in favor of the most stable cryptates formed with largest cation. Considering for instance the Na^+/Li^+, K^+/Na^+, and K^+/Rb^+ pairs (Table I) it is seen that the solvent change W → M/W favors Na^+ with respect to Li^+, and K^+ with respect to Na^+. K^+ is favored over Rb^+ as long as the Rb^+ cryptate is appreciably less stable (factor i dominant; cryptates of [2.2.1] and of [2.2.2]), whereas Rb^+ benefits slightly from the change in solvent once K^+ and Rb^+ cryptates have similar stabilities (factor ii dominant; cryptates of [3.2.2], probably also those of [3.3.2] and of [3.3.3]). The same general trends are found for the alkaline-earth cations. Both the Sr^{2+}/Ca^{2+} and Ba^{2+}/Sr^{2+} selectivities increase from water to methanol. Solvents of low dielectric constant favor monovalent cryptates over bivalent ones, in line with the change in the Born term ΔG_B (eq 8), according to which a decrease in ϵ is felt four times more strongly for the bivalent cations[2,3] (cases Ca^{2+}/Na^+ and Ba^{2+}/K^+).

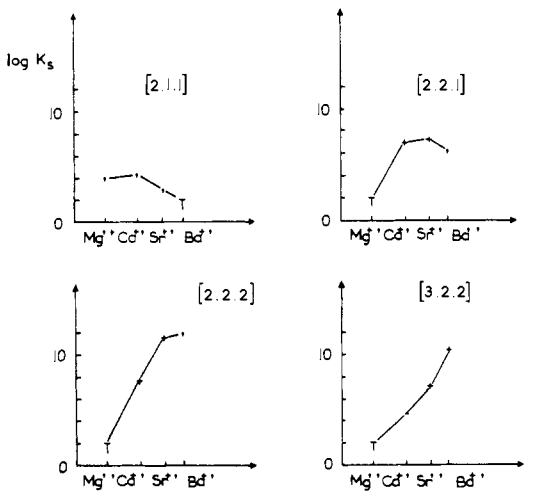


Figure 2. Stability constants of the alkaline-earth cryptates formed by ligands **1–4** (in water at 25°C) as a function of ionic radius (in Å; Table II).

Solvents of lower dielectric constant and solvating power than methanol should lead to even more stable complexes. Complexation selectivities may be markedly affected by diminishing the solvating power of the solvent.[3] Anion effects are negligible in the polar solvents used here. They may play a role in media of low solvating power.[2,3]

Finally, some remarks may be made with respect to the biological role of the cations Na^+, K^+, Mg^{2+}, and Ca^{2+}.[24-27] Na^+ and Ca^{2+} predominate in extracellular fluids whereas K^+ and Mg^{2+} are accumulated inside cells. These cation distributions are related to cell activity and may also have evolutionary significance.[24,25] Cells are separated from the environment by membranes, i.e., regions of low dielectric constant. Crossing of such a region via carriers or pores should be easier for K^+ than for Na^+, thus favoring accumulation of the less abundant cation K^+ already by a simple electrostatic effect. In the Mg^{2+}/Ca^{2+} case, it is again the less abundant Mg^{2+} which is accumulated although uptake through a medium of low ϵ by a neutral carrier should favor Ca^{2+}. In this case anionic binding sites may play an important role in the preference for Mg^{2+} accumulation.

Conclusion

[2]-Cryptates formed by the macrobicyclic ligands **1–6** with alkaline and alkaline-earth metal cations display a varied set of properties. High stabilities and selectivities are observed. Variations in these features are brought about by changing the cavity size, the number of oxygen binding sites, and the nature of the medium. One may expect that further control over complexation stability and selectivity may be achieved by changes in topological properties, in the nature of the binding sites, and in the organic layer properties of the ligand, the goal being the ability to design a selective ligand for a given cation.[2] Incorporation of trace metals, decorporation of harmful cations, and, in general, control of the cation levels in organisms are just one area of possible applications.

A deeper understanding of the thermodynamics of these complexation features requires the dissection of the free energies of complexation into enthalpies and entropies of complexation. An analysis of such data will be given in a future publication.

Experimental Section

Materials. The ligands **1–6** and their complexes have been described in earlier publications.[6,7] The inorganic salts were all reagent grade alkali and alkaline-earth chlorides. The solvents were deionized water containing less than 10^{-5} M metal cations and anhydrous methanol. The methanol/water 95/5 solvent was prepared by taking 50 ml of water and completing with methanol to a total of 1000 ml.

pH-Metric Method. (a) Principle. This method rests on the titration of diamines **1–6** by acid in the absence and in the presence of metal salts. The resulting titration curves are affected by the formation of the complexes, and analysis of the curves yields the stability constants. The stability constants of many complexes between metal cations and basic ligands have been determined by pH metric titration and the protonation and complexation equilibria involved have been analyzed in detail.[9,31,33]

The formation of the cryptates represents a simple special case of the general problem since the ligand/cation stoichiometry is 1/1. The corresponding protonation and complexation equilibria are represented in eq 1–5. The protonation equilibria of the complexes **4** and **5** may be neglected except in the case of the largest ligand **6** [3.3.3]. This is justified: (a) a posteriori by the fact that the stability constants obtained by taking only **1–3** into account are valid over the whole titration curve; (b) by the nonobservation of protonated complexes when acid is added to a very stable complex, like [$Ba^{2+} \subset$ 2.2.2]; only unshifted NMR signals of the complex and signals of the protonated ligand are observed in such a case.

After determination of the acidity constants K_1 and K_2 of the diprotonated LH_2^{2+} and monoprotonated LH^+ ligand, the stability constant K_s of a complex may be calculated from the titration curve in the presence of the corresponding inorganic chloride.

In aqueous solution all activity coefficients are assumed to be equal to 1. In methanol–water solution the problem becomes more complex. Many pH measurements have been performed in slightly aqueous organic solvents especially in dioxane–water.[35,36] The activity coefficients are very sensitive to the amount of water and are in general far from 1 for low water content. The activity coefficient of H^+ in methanol containing 2.7% water is $f_{H^+} = 21$.[37] In our solvent system methanol/water 95/5 $f_{H^+} = 16$. Indeed, the pH of 95/5 solutions containing H^+ concentrations of 10^{-4}, 10^{-3}, and 10^{-2} is respectively 2.80, 1.80, and 0.80. Thus:

$$-\mathrm{pH} = 1.20 + \log|\mathrm{H}^+| \tag{9}$$

$$\log f_{H^+}|\mathrm{H}^+| = 1.20 + \log|\mathrm{H}^+| \tag{10}$$

Using this activity coefficient, the concentrations $|H^+|$ are obtained from measured pH values.

The K_s values obtained from the titration curves in methanol/water 95/5 are in line with the results in pure methanol obtained from experiments with cation selective electrodes (see below). K_1 is determined at low pH ($4.5 < \mathrm{pH} < 7.5$) so that $|OH^-|$ may be neglected. K_2 is determined at pH >8.5 from several points on the titration curve by the following procedure: since $|OH^-|$ cannot be neglected the product $K_W = |H^+|\,|OH^-|$ has to be obtained. K_2 is calculated from the titration curve with an arbitrary K_W value which is then adjusted progressively and K_2 is recalculated each time, until experimental and theoretical curves coincide.

(b) Apparatus and Procedures. Measurements have been performed using a pH-meter Corning pH-12 (accuracy ±0.002 pH) coupled to a galvanometric recorder Graphispot-Secam. The electrodes used were: (i) a glass electrode Corning No. 476024 triple purpose with internal reference Ag|AgCl; (ii) a Philips calomel reference electrode in which the initial ionic bridge (KCl M/10) was replaced by a CsCl M/10 solution, this bridge cannot be used in the case of stable Cs^+ complexes; (iii) a Corning 476002 calomel reference electrode containing a saturated KCl solution fitted with an ionic bridge of $N(CH_3)_4Br$(M/100) in water or in methanol/water 95/5.

All measurements were performed in a glass cell maintained at 25.0 ± 0.1°C. In the case of very stable Na^+ complexes, the measurements were performed in a small polyethylene cell placed inside the glass cell.

The ionic strength was 0.047–0.063 for aqueous solutions and 0.01 for the methanol–water solutions, $N(CH_3)_4Br$ being the supporting electrolyte. The ligand and salt solutions were 0.05 M in the first case and 0.01 M in the second case.

Special Case of Very Stable Complexes. Titration by the Cation. The very stable cryptates dissociate very slowly so that on addition of acid the new protonation and complexation equilibria are only slowly established. For such cases the monoprotonated ligand LH^+ is first prepared and the solution is titrated with a solution of the salt. K_s may be obtained from the titration curve in the same way as for acid titration. This method has been employed for [2.2.1] + $SrCl_2$, $BaCl_2$; [2.2.2] + $SrCl_2$, $BaCl_2$. Cases have been found where even the deprotonation kinetics are slow.[38]

(c) Reliability, Errors. Only values of $\log K_s > 2$ are considered to be accurate and reliable with the present method. The errors resulting from the experimental scatter of $\log K_s$ values are about: $2 < \log K_s < 3$, $\Delta(\log K_s) \sim \pm 0.4$; $3 < \log K_s < 9$–10, $\Delta(\log K_s) \sim \pm 0.15$; $10 < \log K_s$, $\Delta(\log K_s) \sim \pm 0.5$ or more (specially in the case of slowly dissociating complexes; see above). These errors apply both to measurements in water and methanol–water solutions. Measurements performed on the same system at different ionic strengths from 0.005 to 0.3 gave less than 0.3 change in $\log K_s$.

Method Using Cation Selective Electrodes. (a) Principle. Cation selective glass electrodes allow direct potentiometric measurement of metal cation concentrations.[10] Cation selective liquid membrane electrodes are also available but could not be used in the present work since they appear not to differentiate between free cations and cationic complex formed. The emf of the electrodes is proportional to free cation activities. In practice the electrode is calibrated using solutions of known concentrations. The electrode potential is then

$$E = E_0 + k \log|\mathrm{M}^+| \tag{11}$$

The coefficient k lies between 0.045 and 0.065 and changes with cation concentration. It must be determined by means of appropriate calibration solutions in the effective concentration region of free cation in a solution containing salt, ligand, and complex at equilibrium. Knowing k, $|M^+|$ is obtained and the stability constant may be calculated.

The sensitivity of the electrodes may be acceptable over the following ranges: (i) in water, Li^+, Rb^+, Cs^+ ($10 < K_s < 10^4$), Na^+, K^+ ($10 < K_s < 10^{5.5}$); (ii) in methanol, Li^+ ($10 < K_s < 10^5$), Rb^+, Cs^+ ($10 < K_s < 10^6$), Na^+, K^+ ($10 < K_s < 10^7$–10^8).

(b) Apparatus. The electrode potentials were measured with a Corning pH-12 meter used as millivoltmeter (accuracy ±0.1 mV) and connected to a recorder (see above). The reference electrodes were the same as for the pH measurements. The Corning 476002 calomel reference electrode with saturated KCl bridge was separated from the solution to be measured by a second bridge containing 0.01 M $N(CH_3)_4Br$ in methanol. The cation selective electrodes were: (i) a Philips G15 Na electrode for measuring Na^+ and Ag^+ activities; (ii) a Philips G15 K or a Corning No. 476220 monovalent cation electrode for determination of the other alkali cations.

The anhydrous metal salts (LiI, NaCl, KCl, RbCl, CsCl, $TlNO_3$, $AgNO_3$) are dissolved in dry methanol (<0.05% water); successive dilutions of the standard 0.01 M solutions afforded the calibration solutions at concentrations 10^{-3}, 10^{-4}, and 10^{-5} M. The measurements were performed on solutions containing 0.1 mM ligand in 5 ml of 0.01 M salt in water or methanol (0.05 mM salt).

(c) Reliability, Errors. All K_s values in pure methanol and some values in water reported in Table I have been determined using cation electrodes. From the experimental scatter between K_s values the following error limits are obtained: $\Delta(\log K_s) < \pm 0.2$ in the optimal domain of measurement: $1 < \log K_s < 5$. $\Delta(\log K_s)$ becomes larger the more $\log K_s$ is outside the optimal domain (up to ±0.5 for $\log K_s \sim 7$). Accuracy rests on the emf change between salt solutions with and without ligand present. In all cases this change was at least 10 mV; reproductibility was within ±2mV.[47]

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Kinetics and Thermodynamics of Oxygen and Carbon Monoxide Binding to Simple Ferrous Porphyrins at Low Temperatures

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Abstract: The results of detailed kinetic and thermodynamic studies of oxygen and carbon monoxide binding to simple ferrous porphyrins are reported. In methylene chloride at −79° $Fe(TPP)(base)_2$ (where base = pyridine, piperidine, and 1-methylimidazole and TPP = *meso*-tetraphenylporphyrin) reacts with oxygen and carbon monoxide in a manner consistent with the dissociative process outlined in the following mechanism: $Fe(TPP)(base)_2 \rightleftharpoons Fe(TPP)(base) + base$; $Fe(TPP)(base) + O_2 \rightleftharpoons Fe(TPP)(base)(O_2)$; $Fe(TPP)(base) + CO \rightleftharpoons Fe(TPP)(base)(CO)$. Quantitative comparisons of O_2 and CO binding to the ferrous complexes, including the influence of the various axial bases, are discussed. Comparisons between these simple systems and natural oxygen carriers suggest that these systems may serve as satisactory models for the more complicated heme proteins. In part, the results show that if "distal" imidazole could bind to heme in the oxygen carrying proteins, it would seriously hamper the proteins' ability to function as an effective oxygen carrier.

The reactions of monomeric heme proteins (myoglobin and the isolated α- and β-chains of hemoglobin) with oxygen and carbon monoxide have been extensively studied.[1] In contrast, the reactions of simple ferrous porphyrins with carbon monoxide have received little attention,[2,3] and their reactions with oxygen have, until recently,[4] not been investigated due to irreversible oxidation of the iron center. However, such studies should be useful in elucidating the role of the protein in the reactions of hemoglobin and myoglobin with various ligands. They may even aid the understanding of structural variations which produce abnormal oxygen affinities[5] in heme proteins.

Following our recent communication on the reversible reaction of ferrous tetraphenylporphyrins with oxygen at low temperatures,[6] we have examined the detailed kinetics and equilibria of the reaction of these same ferrous porphyrins with oxygen[7] and carbon monoxide as a function of various axial bases. This study has been performed in methylene chloride at −79°. Care must be taken in comparing our kinetic parameters with those determined for the heme proteins because of the difference in temperature, and the nature of the solvent medium. However, the latter factor could be fairly similar in the two systems. Myoglobin is folded such that the heme is in a hydrophobic pocket, despite the