Applications of NMR Spectral Techniques for the Study of Macrocycle Host-Organic Guest Interactions. A Short Review

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Contents

I. Introduction.

Molecular recognition occurs in many chemical interactions including those involving enzymes, antibodies, antigens and stereoselective catalysts. The investigation of molecular recognition by synthetic receptors of inorganic and organic compounds was enhanced in 1967 with Pedersen's landmark publication of the macrocyclic crown ethers [1]. Since then, the syntheses of a multitude of macrocyclic ligands and their use for the recognition of other species have become important fields of research [2-6].

Understanding molecular recognition requires that the interactions involved be quantitated. Structural information of host-guest complexes must be available. These data provide the information needed to evaluate host-guest recognition and to predict the ligands which should be synthesized for a desired recognition.

Many qualitative and quantitative methods to study host-guest interactions have been used, including nmr spectroscopy [7,8], titration calorimetry [9,11], potentiometry [12], uv/vis spectroscopy [13], polarography [14], solvent extraction [15], liquid membrane transport [16], and chromatographic separation [17]. Nmr methods are advantageous in that experiments can be carried out with very small samples and useful structural information can often be obtained. Therefore, nmr spectral methods have been extensively used in molecular recognition studies.

This review describes various nmr methods which have been used to study the interactions of macrocyclic ligands with neutral, cationic and anionic organic compounds as well as a compilation of recognition data obtained using these methods. Those host-guest recognition results obtained by extraction experiments [18-21] are not included in this review because nmr spectral integration was used only to determine the amount of guest extracted.

II. NMR Spectral Methods.

A. Determination of Thermodynamic Parameters.

1. Determination of Equilibrium Constants (K) by a Direct Titration Method.

Nmr spectral methods have been used for the determination of equilibrium constants (K) for the interaction of a large number of crown ethers with metal cations [22-28]. For the interaction of macrocyclic compounds with organic species, ^{1}H nmr and ^{13}C nmr spectral titration techniques are available for the determination of K values. Since only small chemical shift changes in the ^{13}C nmr signals of ligand or guest are observed on forming a complex, the ^{13}C nmr titration technique is less accurate [28]. ^{13}C nmr titration techniques are useful only for certain complexation reactions [29], therefore, there are few reports for the determination of K values using this method [30]. In contrast, chemical shifts of protons are sensitive to complexation reactions. Therefore, the ^{1}H nmr titration technique is important for determination of K values for interactions of macrocyclic compounds with organic molecules. Nmr titration techniques using ^{19}F and ^{31}P nmr spectra are often possible for the determination of K values if those heteroatoms are present in the host or guest compounds [31].

The ^{1}H nmr spectral experiments involve titration of a guest (host) solution into a host (guest) solution until there is no significant change in the chemical shift value in successive nmr spectra. Individual concentrations of the host and guest can be obtained by spectral integrations [8] or according to the volume change if standard solutions of both host and guest are used [32]. Usually, eight to twelve successive spectra are required for an accurate determination of a K value. In the successive spectra, one population-average signal can be observed. This signal is the weighted average of the chemical shifts for the free and complexed macrocycles under conditions of fast exchange on the nmr time scale. If a 1:1 complex is formed, we have the following equation:

$$\delta_{obsd} = X_f\delta_f + (1\text{-}X_f)\delta_c \qquad (1)$$

where δ_{obsd} = observed average chemical shift of a specified signal, δ_f = chemical shift of the same signal for the free macrocycle, δ_c = chemical shift of the same signal for the complex, and X_f = the mole fraction of free macrocycle. By using a non-linear least-squares treatment, the best fit of the experimental data can be obtained through minimization of the function:

$$U = \Sigma\,[\delta_{obsd,i} - X_{f,i}\delta_f - (1\text{-}X_{f,i})\delta_c]^2 \qquad (2)$$

Since X_f is a function of K, U is a function of K also. The K value that results in a minimum U value is taken as the correct value. The calculation procedure can be done using an appropriate computer program [8].

The change in the chemical shift is a function of the host/guest mole ratio. In one case, an increase in the host/guest mole ratio gradually moves the chemical shift upfield or downfield and the change in chemical shift does not reach a limiting value even at very high mole ratios. This is indicative of the formation of a weak complex with a low K value. Values of K cannot be determined accurately if log K is less than ~1.5. In a second case, the chemical shift varies linearly with the mole ratio until a mole ratio of 1:1 is reached. A further increase in the mole ratio does not change the chemical shift. This is indicative of a stable 1:1 complex with a high log K value (greater than ~5.0). In this case, K values cannot be determined accurately. A third case has the chemical shift separated into signals for the free and the complexed macrocycle. The existence of two peaks shows that there is a slow exchange on the nmr time scale. In this case, the above mathmatical treatment is no longer applicable for the calculation of K values.

2. Determination of Equilibrium Constants (K) by a Competitive Complexation Method.

The direct ^{1}H nmr titration method described above can give accurate log K values if those values fall in a range of about 2-5. However, when log K values are greater than 5, the plot of chemical shift *vs.* host/guest mole ratio is a very steep curve. In this case, the direct titration method becomes unreliable. On the other hand, if very weak complexes are formed, the change in the chemical shift of a specified signal from free to complexed form is too small to be accurate for an equilibrium constant calculation. To solve these problems, competitive complexation experiments have been used by Reinhoudt and coworkers [7,33]. There are two kinds of competitive reactions. Two hosts compete for complexation with one guest or two guests compete for complexation with one host.

In a competitive experiment of two hosts for one guest, the total concentration of the two hosts is kept greater than the guest concentration in order to make the free guest concentration negligible. Consequently, the observed chemical shift of a specified signal of the guest is the weighted average value of the guest in both complexes under conditions of fast exchange. In equations (3)

$$\delta_{obsd} = X_A\delta_A + (1\text{-}X_A)\delta_B \qquad (3)$$

$$X_A = (\delta_{obsd} - \delta_B)/(\delta_A - \delta_B) \qquad (4)$$

and (4), δ_{obsd} = the observed chemical shift of a specified guest signal, δ_A = chemical shift of the same guest signal when complexed with host A, δ_B = chemical shift of the same guest signal when complexed with host B, X_A = [A-Guest complex]/[Guest]. From the observed chemical shift, it is possible to calculate the concentrations of complexes of the guest with A and with B. With these concentrations, free macrocycle concentrations and the relative K values as defined in equation (5) can be obtained. From the relative equilibrium constant and the one known equilibrium constant, the other equilibrium constant can be calculated. In equation (5).

$$K_{rel} = K_A/K_B = [AG][B]/[A][BG] \quad (5)$$

K_{rel} = the relative equilibrium constant, K_A = the equilibrium constant of the complex of host A with the guest, K_B = the equilibrium constant of the complex of host B with the guest, AG = the complex of host A and the guest, BG = the complex of host B and the guest.

For the competitive experiment of two guests for one host, a similar treatment is applicable.

3. Determination of Enthalpy (ΔH) and Entropy (ΔS) Changes [3,21].

In order to determine complexation enthalpy and entropy changes, equilibrium constants must be measured as a function of temperature. Enthalpy and entropy changes can be calculated according to equation (6) in the

$$2.303\ RT \log K = \Delta H - T\Delta S \quad (6)$$

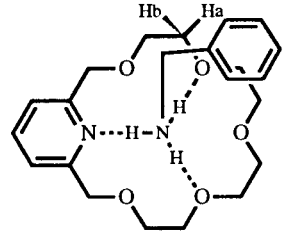
usual manner from the slope and the intercept of a plot of $\log K$ *vs.* T^{-1}.

The reliability of this method for the determination of ΔH and ΔS values has been evaluated by a comparison with the calorimetric titration method [8]. The results indicate that ΔH and ΔS values obtained by the ^1H nmr titration method have large standard deviations making interprelations based on them of questionable values. These large deviations probably result from the following reasons. First, each $\log K$ value obtained by the ^1H nmr titration method has a large standard deviation and the ΔH and ΔS values obtained from the $\log K$ - T^{-1} plot have even larger standard deviations. Second, the number of $\log K$ - T^{-1} data pairs is limited by the low temperature range of the solvent used. Low boiling solvents will allow only a low number of data pairs. Third, there is an assumption that ΔH values are independent of temperature in the temperature range covered. This assumption is not always valid.

B. Determination of Kinetic Parameters.

Kinetic measurements associated with host-guest interactions are important for an understanding of the origin of molecular recognition. An nmr spectral method has been used to determine kinetic parameters for the interaction of macrocyclic compounds with alkali metal cations by an nmr linear-shape technique [34-39]. For interactions of macrocyclic compounds with organic species, a variable temperature ^1H nmr procedure has been developed and used for the determination of rate constants and free energies of activation for the dissociation of host-guest complexes. Detailed discussions of the applications of this method for the determination of rate constants and free energies of activation have been given by Reinhoudt and de Jong [40] and Baxter and Bradshaw [41]. A more rigorous theoretical treatment can be found elsewhere [42].

The method utilizes the nonequivalence of hydrogen atoms in the complex. The magnetic equivalence of the two protons of a given methylene group of a macrocyclic ligand is destroyed upon complexing with an organic guest. This is caused by a loss of the plane of symmetry which bisects the host molecule. The proton which is on the same side of the macrocycle as the organic guest experiences a magnetic environment which is different from that experienced by the proton on the other side. This magnetic nonequivalence is shown for the protons labeled H_a and H_b in the following figure [41].



At room temperature, the association and dissociation of most host-guest complexes are so fast on the nmr time scale that only an average of the chemical shift of H_a and H_b is observed. However, by cooling the nmr probe, the complex with a relatively high dissociation activation energy can be "frozen out" and the exchange rate becomes slow on the nmr time scale. At this point H_a and H_b are observed as separate signals in the ^1H nmr spectrum. If the nmr probe is then gradually warmed, a coalescence temperature, T_c, is observed where the separate signals for H_a and H_b merge into a single signal. At this point, the dissociation and association of complexes become fast on the nmr time scale.

The rate of the dissociation process, which is thought to be the rate-determining step in most of the studies reported, can then be related to the difference of the chemical shift between the fully resolved signals for H_a and H_b. This relationship is given by equation (7), where k_c is the

$$k_c = \pi\Delta\upsilon/2^{1/2} \quad (7)$$

rate of the exchange process at the coalescence temperature and the $\Delta\upsilon$ is the chemical shift (Hz) separation between the resolved signals. The free energy of activation can then be calculated from the rate constant (k_c), the molar gas constant (R), the coalescence temperature (T_c), Plank's constant (h), and the Boltzmann constant (K). This relationship is given by equation (8).

$$\Delta G_c^{\ddagger} = -RT_c \ln k_c h/KT_c \quad (8)$$

The $\Delta G_c^{\ddagger}$ values obtained by this method have no firm relationship to thermodynamic quantities like ΔG or log

K [43], although two studies found a linear relationship between $\Delta G_c^{\ddagger}$ and ΔG values [40,44]. The values of $\Delta G_c^{\ddagger}$ are most useful for preliminary surveys of molecular recognition by these host-guest systems.

C: Complex Conformation Analysis Determined by ^{13}C NMR Relaxation Time Changes.

The ^{13}C nmr spin-lattice relaxation time (T1) measurements have provided much useful conformation information for the complexes of crown ethers [45-53], lariat ethers [54] and cryptands [55-59] with metal cations. T1 values are affected by immediate and remote molecular structural features, as well as by consideration of rapid ($>10^8$-10^{10} sec^{-1}) dynamic processes occurring in the specific system. In particular, T1 studies can yield useful information about rapid molecular motions on a time scale that is far shorter than is available with conventional nmr techniques [60]. The process of spin-lattice relaxation is an energy exchange between nuclear spins and the lattice resulting in the establishment of equilibrium between populations in the nuclear spin energy levels. There exist five types of the energy exchange (spin-lattice relaxation) mechanisms [61]: dipole-dipole interaction, spin-rotation, scalar interaction, chemical anisotropy and quadrupole interaction.

Generally, the T1 value for any given liquid molecule reflects molecular mobility (tumbling) and specific internal motions determined by the internal degree of freedom of the molecule [62,63]. A comparison of T1 values for the same carbon atom in each complex can give information about the relative stabilities of the complexes and an intramolecular T1 comparison can lead to estimates of the relative mobility of the different parts of the macrocyclic ring framework in solution. Compounds with large molecular weights tumble more slowly than smaller molecules and thus exhibit shorter relaxation times than the smaller systems. Formation of a complex results in an increase in molecular weight, therefore, the complex should tumble more slowly than its components in the free state resulting in a decrease in T1 values. It is possible to compare T1 values for specific sites within a molecule to understand changes to internal mobility that occur selectively at particular locations, thus giving information about molecular binding in the complex [51].

Experimentally, spin-lattice relaxation times (T1) for all carbons can be determined simultaneously by an inversion recovery technique. Recovery delays usually are set greater than five times the longest T1 value. In order to avoid the effect of paramagnetic impurity, all glassware should be washed carefully. The pulse width should be calibrated. Calculation of T1 values can be made by a direct least-square fitting to a multiparameter exponential equation which is available in modern nmr spectrometer computer programs.

D: Complex Conformation Analysis Determined by Two Dimensional (2D) NMR Techniques.

A correlation of the degree of molecular recognition with structural features of the host-guest complex is essential in understanding the origin of molecular recognition. Since molecular recognition involves a complicated steric fit between host and guest molecules, an understanding of molecular recognition requires a knowledge of the conformation of the complex. Obviously, X-ray and neutron diffraction crystallography can furnish this information in the crystalline state. However, crystal structures do not necessarily represent those in solution as proved by experimental results [64]. The development of modern nmr spectroscopic techniques makes possible the observation of important conformation features of complexes in solution by using the appropriate nmr experiments. For example, the change in degree and direction of specified chemical shifts in the host or guest molecule can sometimes reflect complex stability and conformation changes. 2D NOESY or ROESY spectra provide information about the spatial distance between two atoms in a molecule or complex as long as the motion of the molecule is not too fast for observation and the distance between the two atoms is shorter than 5 Å [65]. The structural information obtained from nmr spectroscopy, although not complete and not in fine detail in terms of atomic coordinates, has proved to be very helpful in understanding molecular interactions in solution [52,64,66,67]. For example, π-π interactions play an important role in chiral recognition in the associative interaction of chiral pyridino-18-crown-6 ligands with the enantiomers of chiral organic ammonium salts. The presence or absence of a π-π interaction and its effect on chiral recognition has been proved by chemical shift changes in the host and guest signals and by the NOESY spectra [52,66]. Relatively large chemical shift changes for proton signals in some positions may indicate that those positions are close in space to aromatic groups. Positive and negative chemical shift changes result from shielding and deshielding effects of aromatic rings depending on the relationship to the face or edge of the ring. In many cases, the presence of off-diagonal signals in the aromatic region of the NOESY spectrum can provide conclusive evidence for the presence of π-π interactions.

III. Applications.

Macrocyclic compounds can form complexes with inorganic cations, organic cations and organic neutral molecules. Complete thermodynamic and kinetic data for the interaction of macrocycles with inorganic and organic cations and neutral organic molecules have been collected [2-4]. The present review covers nmr methods and their applications to interactions of macrocyclic compounds

with organic guests. Therefore, only the thermodynamic and kinetic data determined by nmr spectral methods for the interaction of some macrocyclic hosts with organic guests are covered in this review. Tables I-IV list thermodynamic and kinetic values for the interaction of host-guest species determined by nmr spectral techniques.

A. Thermodynamic Values for the Interaction of Crown Ethers with Organic Guests.

Thermodynamic values for the interaction of simple crown ethers **1-42** (Chart I) with organic guests determined by nmr methods are listed in Table I. Takayama and coworkers [68] have examined the interactions of 18-crown-6 (**1**) with several sulfonamides and related aromatic amines in chloroform. The log *K* values obtained by the nmr titration method are comparable with those determined by a uv method. It was suggested that binding was caused by inclusion of the primary amine group on the 4-position of the aromatic sulfonamides into the cavity of the 18-crown-6 ligand.

de Boer, Reinhoudt and coworkers have studied the interactions of macrocyclic polyethers **1-34** with acetonitrile, malononitrile and nitromethane neutral molecules and with organic ammonium salts in organic solvents by

Chart I

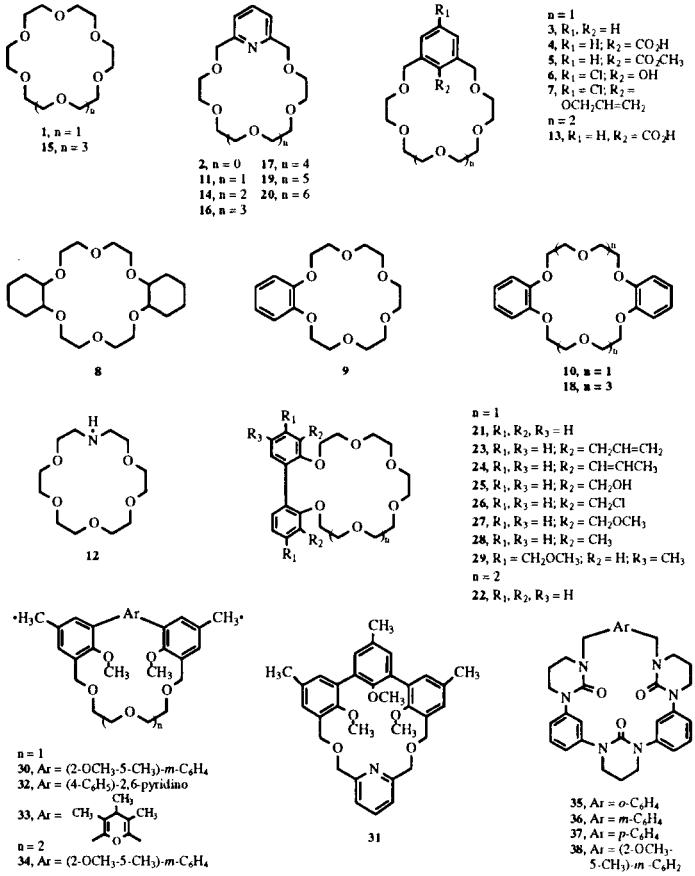
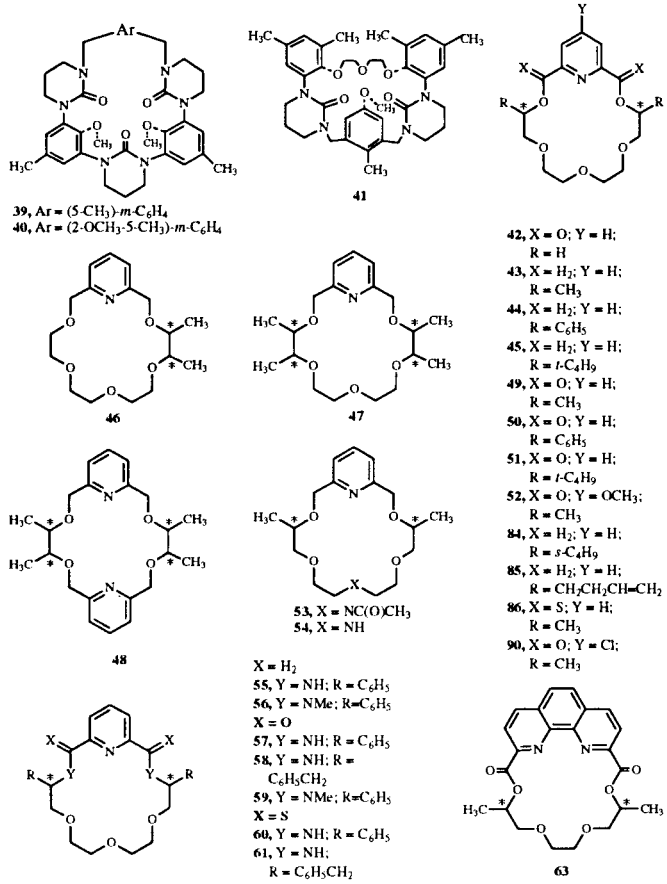


Chart I (cont.)



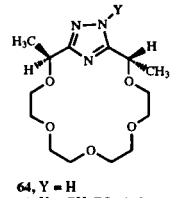
nmr spectral methods [7,50,69-71,75,76]. The results showed that complex stabilities depend on solvent, ring size, the nature of the host and the presence or absence of intraannular substituents. Nmr techniques provided data that help to explain the conformation changes in some of the complexation reactions. For example, ^{13}C nmr relaxation time (T1) studies of free and complexed hemispherands **30-34** clearly showed that mobilities of the ^{13}C nuclei hardly decreased upon complexation, indicating that those host molecules are preorganized [50].

Cram and Anthonsen have used nmr spectral methods to investigate the interactions of hemispherands **35-41** with *t*-butylammonium picrate [77]. The log *K* values vary by two powers of ten.

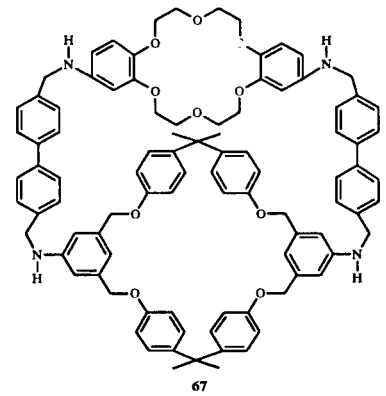
B. Thermodynamic Values for the Interaction of Chiral Crown Ethers with Organic Guests.

Enantiomeric recognition, as a special case of molecular recognition, involves discrimination between enantiomers of a guest by a chiral receptor or a chiral matrix. The successful design, synthesis and use of molecules capable of enantiomeric recognition of other species is of great interest to workers studying asymmetric separations,

Chart I (cont.)



64, Y = H
65, Y = CH_2CO_2cholesteryl
66, Y = $C_{12}H_{25}$



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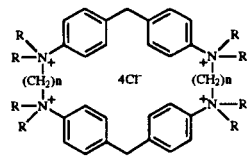
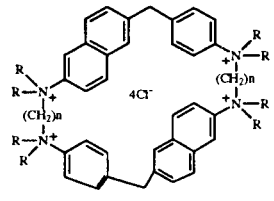
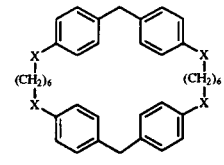


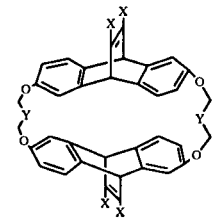
68, n = 4; R = H
69, n = 4; R = CH_3
70, n = 6; R = CH_3
71, n = 8; R = CH_3



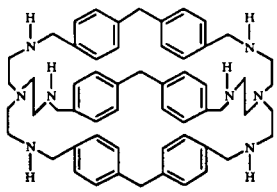
72, n = 4; R = H
73, n = 4; R = CH_3
74, n = 5; R = CH_3
75, n = 6; R = CH_3



76, X = N-S(O_2)
77, X = N-CO(O_2C)(SO_3^-)



78, X = CO_2CH_3; Y = p-C_6H_4
79, X = $CO_2^-Cs^+$; Y = p-C_6H_4
80, X = $CO_2^-Cs^+$; Y=1,4-cyclohexane



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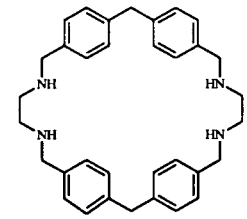

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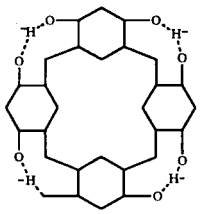

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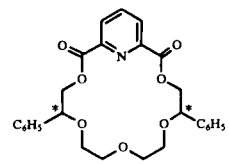

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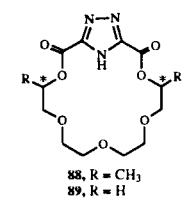
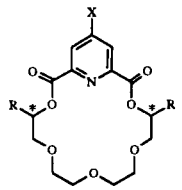
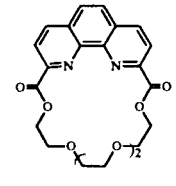


88, R = CH_3
89, R = H



91, X = $OCH_2C_6H_5$; R = H
92, X = $OCH_2C_6H_5$; R = CH_3
93, X = OH; R = H
94, X = OH; R = CH_3
95, X = OH; R = C_6H_5



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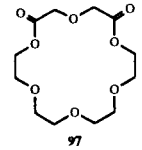

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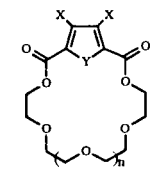
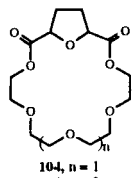
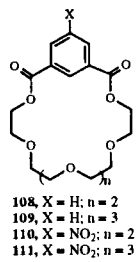


Y = O
98, X = H; n = 1
99, X = H; n = 2
100, X = H; n = 3
101, X = OCH_3; n = 1
102, X = OCH_3; n = 2
103, X = OCH_3; n = 3
Y = S
107, X = H; n = 3

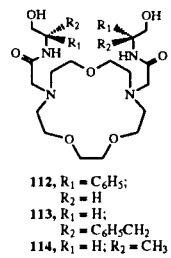
Chart I (cont.)



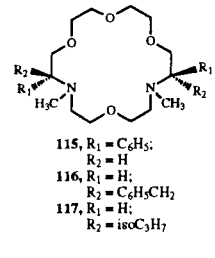
104, n = 1
105, n = 2
106, n = 3



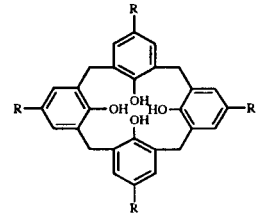
108, X = H; n = 2
109, X = H; n = 3
110, X = NO_2; n = 2
111, X = NO_2; n = 3



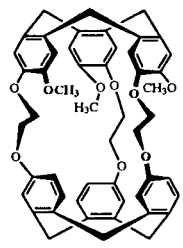
112, R_1 = C_6H_5; R_2 = H
113, R_1 = H; R_2 = $C_6H_5CH_2$
114, R_1 = H; R_2 = CH_3



115, R_1 = C_6H_5; R_2 = H
116, R_1 = H; R_2 = $C_6H_5CH_2$
117, R_1 = H; R_2 = $isoC_3H_7$



118, R = H
119, R = t-C_4H_9
120, R = $CH_2CH{=}CH_2$



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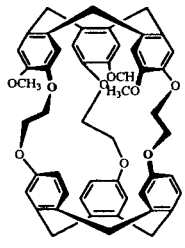

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enzyme functions, synthetic enzyme design, and other areas involving chiral recognition [43]. Enantiomeric recognition of chiral organic guests by chiral macrocyclic host ligands is an area of enantiomeric recognition that has been extensively studied since Cram first reported chiral macrocyclic ligands in 1973 [104]. Because most chiral macrocyclic ligands are expensive and their syntheses often require many steps, it is difficult to have large amounts of chiral macrocyclic ligands for recognition studies. Therefore, nmr spectral methods, which require small amounts of the chiral host, have been extensively used in studies of chiral recognition. The thermodynamic data for the interactions of chiral crown ethers **43-66** (Chart I) with various chiral ammonium salts (Chart II) are listed in Table II.

Bradshaw, Izatt and coworkers have systematically studied chiral recognition by 18-crown-6 type chiral ligands **43-63**, containing different subcyclic units and substituents on the macro ring, of chiral organic primary ammonium salts by determination of log K values [8,32,43,66,78-80]. The results showed that, in most cases, the $(R,R)[(S,S)]$ ligand formed a more stable complex with the $(S)[(R)]$ guest. Information on the conformations of some of the complexes were obtained by ^{1}H nmr NOESY spectra, relaxation time (T1) measurements and chemical shift changes [52,64,66,105]. In the complexation of chiral crown ligand (S,S)-**43** with the enantiomers of chiral α-(1-naphthyl)ethylammonium perchlorate ($NapEt^+$), the chemical shift changes of the aromatic protons in both host and guest molecules upon complexation and the strong off-diagonal signals in the 7.2-8.2 ppm range in the 2D NOESY ^{1}H nmr spectra confirm the presence of a π-π interaction as indicated by molecular

Table I

Log *K*, Δ*H*, Δ*S* Values for Organic Guest-Crown Ether Host Interactions.

ligand [a]	guest [b]	log *K* [c]	Δ*H* kJ/mol	Δ*S* J/K.mol	T °C	solvent [d]	ref
1	sulfamethoxypyridazine	0.50			24.5	C	68
	sulfaphenazole	0.74			24.5	C	68
	sulfadimethoxine	0.87			24.5	C	68
	sulfamethomidine	0.82			24.5	C	68
	sulfamethoxazole	0.89			24.5	C	68
	sulfisoxazole-N^1-acetyl	0.80			24.5	C	68
	p-chloroaniline	-0.33			24.5	C	68
	p-aminobenzoic acid	0.33			24.5	C	68
	p-nitroaniline	0.86			24.5	C	68
	acetonitrile	-0.10			9	B	69
	acetonitrile (2)	0.23			9	B	69
	acetonitrile	-0.22			17	B	69
	acetonitrile (2)	-0.05			17	B	69
	acetonitrile	-0.32			27	B	69
	acetonitrile	-0.44			36	B	69
	acetonitirle		-25.1	-92.1	9-36	B	69
	acetonitrile	0.32			25	T	74
	malononitrile	2.83			9	B	69
	malononitrile (2)	1.15			9	B	69
	malononitrile	2.59			17	B	69
	malononitrile (2)	1.08			17	B	69
	malononitrile	2.18			27	B	69
	malononitrile (2)	1.04			27	B	69
	malononitrile	1.89			36	B	69
	malononitrile (2)	0.95			36	B	69
	malononitrile	2.2	-59.4	-154	25	B	70,71
	malononitrile	1.49	-22.2	-46.3	25	C	70,71
	nitromethane	0.48			9	B	69
	nitromethane (2)	0.69			9	B	69
	nitromethane	0.26			17	B	69
	nitromethane (2)	0.60			17	B	69
	nitromethane	0.08			27	B	69
	nitromethane (2)	0.40			27	B	69
	nitromethane	-0.05			36	B	69
	nitromethane (2)	0.18			36	B	69
	t-$BuNH_3^+$	2.41			33.5	M	7
	t-$BuNH_3^+$	2.57	-19.23	-16.30	18	M	7
	t-$BuNH_3^+$	2.79			3.0	M	7
	t-$BuNH_3^+$	2.98			-12.5	M	7
	t-$BuNH_3^+$	3.65			33.5	A	7
	t-$BuNH_3^+$	3.90	-22.57	-2.93	18.0	A	7
	t-$BuNH_3^+$	4.15			3.0	A	7
	t-$BuNH_3^+$	4.32			-12.5	A	7
	t-$BuNH_3^+$	3.47			33.5	AN	7
	t-$BuNH_3^+$	3.54	-6.69	44.72	18.0	AN	7
	t-$BuNH_3^+$	3.63			3.0	AN	7
	t-$BuNH_3^+$	3.67			-12.5	AN	7
	nitromethane (2)		-31.8	-105	36	B	69
2	malononitrile	1.20	-26.4	-66.0	25	B	70
	malononitrile	1.04	-6.69	-2.81	25	C	70
3	malononitrile	1.04	-21.8	-53.4	25	C	70
	malononitrile	1.00	-19.7	-46.3	25	B	70
	nitromethane	-0.03			9	B	69
	nitromethane	-0.12			17	B	69
	nitromethane	-0.21			27	B	69
	nitromethane	-0.28			36	B	69
	nitromethane		-15.10	-54.40	9-36	B	69
	t-$BuNH_3^+$	0.58			33.5	M	7
	t-$BuNH_3^+$	0.76			18	M	7
	t-$BuNH_3^+$	0.93			3.0	M	7
	t-$BuNH_3^+$	1.09			-12.5	M	7
	t-$BuNH_3^+$	1.36			-33	M	7

Table 1 (cont.)

ligand [a]	guest [b]	log *K* [c]	ΔH kJ/mol	ΔS J/K.mol	T °C	solvent [d]	ref
	t-$BuNH_3^+$	1.71			33.5	A	7
	t-$BuNH_3^+$		-16.72	-43.80	-33-18	M	7
	t-$BuNH_3^+$	1.89			18.0	A	7
	t-$BuNH_3^+$	2.07			3.0	A	7
	t-$BuNH_3^+$	2.23			-12.5	A	7
	t-$BuNH_3^+$	2.38			-33.0	A	7
	t-$BuNH_3^+$	1.81			33.5	AN	7
	t-$BuNH_3^+$		-14.12	-12.54	-33-18	A	7
	t-$BuNH_3^+$	1.92			18.0	AN	7
	t-$BuNH_3^+$	2.02			3.0	AN	7
	t-$BuNH_3^+$	2.10			-12.5	AN	7
	t-$BuNH_3^+$	2.21			-33.0	AN	7
	t-$BuNH_3^+$		-8.36	8.36	-33-18	AN	7
4	malononitrile	1.04	-7.95	-7.02	25	B	70,71
5	malononitrile	1.59	-50.2	-139	25	B	70,71
6	malononitrile	0.70	-18.4	-47.7	25	B	70,71
	malononitrile	0.70	-18.8	-50.5	25	C	70,71
7	malononitrile	1.04	-19.2	-44.9	25	B	70,71
8	malononitrile	1.80	-36.0	-85.6	25	B	70,71
	malononitrile	1.63	-23.4	-46.3	25	C	70,71
9	malononitrile	1.48	-33.5	-82.8	25	B	70,71
	malononitrile	1.70	-22.6	-43.5	25	C	70,71
10	malononitrile	2.05	-19.7	-26.7	25	C	70,71
	2,4,6-trinitrotoluene	0.017	-12.5	-40.9	[e]	D	72
11	malononitrile	1.63	-34.7	-85.6	25	B	70
	malononitrile	1.49	-10.0	-4.21	25	C	70
12	malononitrile	1.53	-23.8	-50.5	25	B	70
	malononitrile	W			25	C	70
13	malononitrile	0.70	-16.3	-40.7	25	B	70,71
14	malononitrile	0.70	-21.8	-59.0	25	B	70
	malononitrile	0.85	-14.2	-30.9	25	C	70
15	tetrafluoro-1,4-benzoquinone	-0.25			31.6	C	73
16	malononitrile	0.48	-18.0	-50.5	25	B	70
	malononitrile	0.30	-7.95	-19.7	25	C	70
17	malononitrile	0.48	-14.6	-39.3	25	B	70
	malononitrile	W			25	C	70
18	2,4,6-trinitrotoluene	-0.77			[e]	D	72
19	malononitrile	0.48	-13.4	-35.1	25	B	70
20	malononitrile	0.60	-16.7	-44.9	25	B	70
21	*t*-$BuNH_3^+$	4.40			25	C	75
22	*t*-$BuNH_3^+$	3.88			25	C	75
23	*t*-$BuNH_3^+$	5.08			25	C	75
24	*t*-$BuNH_3^+$	6.23			25	C	75
25	*t*-$BuNH_3^+$	4.90			25	C	75
26	*t*-$BuNH_3^+$	5.18			25	C	75
27	*t*-$BuNH_3^+$	5.38			25	C	75
28	*t*-$BuNH_3^+$	5.86			25	C	75
29	*t*-$BuNH_3^+$	4.65			25	C	75
30	malononitrile	1.49	-33.9	-85.6	25	B	50,76
	malononitrile	1.45	-35.1	-89.9	25	C	50,76
31	malononitrile	W			25	B	50
	malononitrile	0.90	-19.7	-49.1	25	C	50
32	malononitrile	1.49	-16.3	-26.7	25	B	50,76
	malononitrile	2.02	-16.3	-16.8	25	C	50,76
33	malononitrile	1.58	-23.8	-49.1	25	B	50
	malononitrile	W			25	C	50
34	malononitrile	1.20	-25.9	-63.2	25	B	50
	malononitrile	1.18	-7.35	-2.81	25	C	50
35	*t*-$BuNH_3$Picrate	5.36			25	A	77
36	*t*-$BuNH_3$Picrate	6.30			25	A	77
37	*t*-$BuNH_3$Picrate	6.67			25	A	77
38	*t*-$BuNH_3$Picrate	6.96			25	C	77

Table I (cont.)

ligand [a]	guest [b]	log *K* [c]	ΔH kJ/mol	ΔS J/K.mol	T °C	solvent [d]	ref
39	*t*-BuNH$_3$Picrate	9.34			25	C	77
40	*t*-BuNH$_3$Picrate	9.65			25	C	77
41	*t*-BuNH$_3$Picrate	7.17			25	C	77
42	NapEt$^+$	3.33	-44.4	-84.5	25	1M/1C	8

[a] See ligand structures in Chart I. [b] See guest structures in Chart II. The number in parentheses indicates the coordination number. [c] W = weak complexation. [d] A = $CO(CD_3)_2$; AN = CD_3CN; B = C_6D_6; C = $CDCl_3$; D = CD_2ClCD_2Cl; DM = CD_2Cl_2; DMSO = $SO(CD_3)_2$; E = C_2D_5OD; Ipr = $(CD_3)_2CDOD$; M = CD_3OD; N = CD_3NO_2; T = CCl_4; W = D_2O. [e] No temperature was listed.

mechanics calculations [52]. T1 changes showed that the (*S*,*S*)-ligand formed a more stable complex with (*R*)-NapEt$^+$ than with (*S*)-NapEt$^+$ as already proved by the log *K* values [32]. Because of the flexibility of the ligand, tripod hydrogen bonding to the guest allowed the ^{13}C nmr T1 values of all periphery carbons of the complex to decrease without significant selectivity. Similarly, the presence of π-π stacking in the complex was proved by the NOESY ^1H nmr spectra for the complexation of (*S*,*S*)-**63** with NapEt$^+$ [66].

Echegoyen and coworkers [81] have examined chiral recognition by chiral dialkyl-substituted triazolo-18-crown-6 ligands **64**-**66** for the enantiomers of primary organic ammonium salts. In these complexes, the host molecules are more rigid in the chiral portion of the molecule. The significant spectral difference for the interaction of hosts (*S*,*S*)-**65** and (*S*,*S*)-**66** with guests (*R*)-NapEt$^+$ (downfield shift for methyl hydrogen atoms on chiral centers) and (*S*)-NapEt$^+$ (upfield shift for the same methyl hydrogens) strongly suggests that the structure in the region of the chiral centers is fairly rigid.

C. Thermodynamic Values for the Interaction of Cyclophanes and Other Macrocycles with Organic Cations and Anions.

Table II

Log *K* Values for Interactions of Chiral Crown Ethers with the Enantiomers of Primary Ammonium Cations

ligand [a]	guest [b]	log *K* [c]	Δlog *K*	T °C	Solvent [d]	ref
(*S*,*S*)-43	(*R*)-NapEt$^+$	3.96		25	1M/1C	32
	(*S*)-NapEt$^+$	3.42	0.54	25	1M/1C	32
	(*R*)-NapEt$^+$	N/R		25	DMSO	32
	(*S*)-NapEt$^+$	N/R		25	DMSO	32
	(*R*)-NapEt$^+$	3.12		25	M	32
	(*S*)-NapEt$^+$	2.72	0.40	25	M	32
	(*R*)-NapEt$^+$	4.64		25	AN	78
	(*S*)-NapEt$^+$	4.10	0.54	25	AN	78
	(*R*)-NapEtBuSO$_3$	3.48		25	1M/1C	32
	(*S*)-NapEtBuSO$_3$	3.02	0.46	25	1M/1C	32
	(*R*)-NapEtTs	3.61		25	1M/1C	32
	(*S*)-NapEtTs	3.17	0.44	25	1M/1C	32
	(*R*)-NapEtTs	3.46		25	DM	32
	(*S*)-NapEtTs	3.20	0.26	25	DM	32
	(*R*)-NapEtPicrate	3.73		25	1M/1C	32
	(*S*)-NapEtPicrate	3.38	0.35	25	1M/1C	32
	(*R*)-NapEt$^+$	4.18		10	1M/1C	32
	(*S*)-NapEt$^+$	3.58	0.60	10	1M/1C	32
	(*R*)-NapEt$^+$	3.65		40	1M/1C	32
	(*S*)-NapEt$^+$	3.24	0.41	40	1M/1C	32
	(*R*)-NapEt$^+$	3.38		50	1M/1C	32
	(*S*)-NapEt$^+$	3.17	0.21	50	1M/1C	32
	(*R*)-PhEt$^+$	3.62		25	1M/1C	78
	(*S*)-PhEt$^+$	3.29	0.33	25	1M/1C	78
	(*R*)-PhEt(OH)$^+$	3.21		25	1M/1C	78
	(*S*)-PhEt(OH)$^+$	3.27	-0.06	25	1M/1C	78
	(*R*)-PheMe$^+$	3.02		25	1M/1C	78
	(*S*)-PheMe$^+$	3.11	-0.09	25	1M/1C	78
(*R*,*R*)-44	(*R*)-NapEt$^+$	2.92		25	M	79
	(*S*)-NapEt$^+$	3.10	0.18	25	M	79
	(*R*)-PhEt$^+$	2.91		25	M	79
	(*S*)-PhEt$^+$	3.05	0.14	25	M	79

Table II (cont.)

ligand [a]	guest [b]	log *K* [c]	Δlog *K*	T °C	Solvent [d]	ref
(*S,S*)-45	(*R*)-NapEt	1.33		25	1M/9C	79
	(*S*)-NapEt$^+$	0.62	0.71	25	1M/9C	79
(*R,R*)-46	(*R*)-NapEt$^+$	3.00		25	M	79
	(*S*)-NapEt$^+$	2.94	-0.06	25	M	79
(*R,R,R,R*)-47	(*R*)-PhEt$^+$	3.58		25	1M/9C	43
	(*S*)-PhEt$^+$	3.31	-0.27	25	1M/9C	43
(*R,R,R,R*)-48	(*R*)-NapEt$^+$	1.55		25	M	43
	(*S*)-NapEt$^+$	1.56	0.01	25	M	43
	(*R*)-PhEt$^+$	2.98		25	1M/9C	43
	(*S*)-PhEt$^+$	2.87	-0.11	25	1M/9C	43
(*R,R*)-49	(*R*)-NapEt$^+$	2.08		25	M	8
	(*S*)-NapEt$^+$	2.50	0.42	25	M	8
	(*R*)-NapEt$^+$	2.20		25	1M/1C	78
	(*S*)-NapEt$^+$	2.80	0.60	25	1M/1C	78
	(*R*)-NapEt$^+$	2.97		25	1M/9C	78
	(*S*)-NapEt$^+$	3.41	0.44	25	1M/9C	78
	(*R*)-NapEt$^+$	2.98		25	A	78
	(*S*)-NapEt$^+$	3.40	0.42	25	A	78
	(*R*)-NapEt$^+$	3.80		25	AN	78
	(*S*)-NapEt$^+$	4.24	0.44	25	AN	78
	(*R*)-NapEt$^+$	N/R		25	DMSO	78
	(*S*)-NapEt$^+$	N/R		25	DMSO	78
	(*R*)-NapEt$^+$	5.5		25	N	78
	(*S*)-NapEt$^+$	>6	>0.5	25	N	78
	(*R*)-NapEt$^+$	2.55		25	1M/1B	78
	(*S*)-NapEt$^+$	2.99	0.44	25	1M/1B	78
	(*R*)-NapEt$^+$	2.08		25	1E/1C	78
	(*S*)-NapEt$^+$	2.78	0.70	25	1E/1C	78
	(*R*)-NapEt$^+$	2.17		25	1Ipr/1C	78
	(*S*)-NapEt$^+$	2.77	0.60	25	1Ipr/1C	78
	(*R*)-PhEt$^+$	1.88		25	M	78
	(*S*)-PhEt$^+$	2.33	0.45	25	M	78
(*S,S*)-50	(*R*)-NapEt$^+$	2.15		25	7M/3C	79
	(S)-NapEt$^+$	<1.30	>0.85	25	7M/3C	79
	(*R*)-PhEt$^+$	2.62		25	1M/1C	79
	(*S*)-PhEt$^+$	2.06	0.56	25	1M/1C	79
	(*R*)-PhEt(OH)$^+$	2.24		25	1M/1C	79
	(*S*)-PhEt(OH)$^+$	2.95	-0.71	25	1M/1C	79
	(*R*)-BzEt(OH)$^+$	2.18		25	1M/1C	79
	(*S*)-BzEt(OH)$^+$	1.76	0.42	25	1M/1C	79
	(*R*)-PheMe$^+$	1.60		25	1M/1C	79
	(*S*)-PheMe$^+$	1.28	0.32	25	1M/1C	79
(*S,S*)-51	(*R*)-NapEt$^+$	N/R		25	1M/9C	79
	(*S*)-NapEt$^+$	N/R		25	1M/9C	79
(*S,S*)-52	(*R*)-NapEt$^+$	3.34		25	1M/1C	78
	(*S*)-NapEt$^+$	2.54	0.80	25	1M/1C	78
	(*R*)-PhEt(OH)$^+$	3.14		25	1M/1C	78
	(*S*)-PhEt(OH)$^+$	3.08	0.06	25	1M/1C	78
(*S,S*)-53	(*R*)-NapEt$^+$	N/R		25	1M/9C	79
	(*S*)-NapEt$^+$	N/R		25	1M/9C	79
(*S,S*)-54	(*R*)-NapEt$^+$	1.51		25	M	79
	(*S*)-NapEt$^+$	1.49	0.02	25	M	79
(*S,S*)-55	(*R*)-NapEt$^+$	1.58		25	1M/1C	43
	(*S*)-NapEt$^+$	1.54	0.04	25	1M/1C	43
(*S,S*)-56	(*R*)-NapEt$^+$	3.17		25	1M/1C	43,80
	(*S*)-NapEt$^+$	3.30	-0.13	25	1M/1C	43,80
(*S,S*)-57	(*R*)-NapEt$^+$	<1.0		25	1M/1C	43,80
	(*S*)-NapEt$^+$	N/R		25	1M/1C	43,80
(*S,S*)-58	(*R*)-NapEt$^+$	N/R		25	1M/1C	43,80
	(*S*)-NapEt$^+$	N/R		25	1M/1C	43.80
(*S,S*)-59	(*R*)-NapEt$^+$	N/R		25	1M/1C	43,80
	(*S*)-NapEt$^+$	N/R		25	1M/1C	43,80
(*S,S*)-60	(*R*)-NapEt$^+$	1.39		25	1M/1C	43,80
	(*S*)-NapEt$^+$	1.02	0.37	25	1M/1C	43,80
(*S,S*)-61	(*R*)-NapEt$^+$	N/R		25	1M/9C	80
	(*S*)-NapEt$^+$	N/R		25	1M/9C	80

Table II (cont.)

ligand [a]	guest [b]	log K [c]	Δlog K	T °C	Solvent [d]	ref
(*S*,*S*)-62	(*R*)-NapEt$^+$	<1.0		25	1M/1C	43
	(*S*)-NapEt$^+$	<1.0		25	1M/1C	43
(*S*,*S*)-63	(*R*)-NapEt$^+$	3.47		25	2DMSO/8M	66
	(*S*)-NapEt$^+$	3.36	0.11	25	2DMSO/8M	66
	(*R*)-NapEt$^+$	4.05		25	M	66
	(*S*)-NapEt$^+$	3.88	0.17	25	M	66
	(*R*)-NapEt$^+$	4.31		25	7M/3C	66
	(*S*)-NapEt$^+$	3.97	0.34	25	7M/3C	66
	(*R*)-NapEt$^+$	4.56		25	1M/1C	66
	(*S*)-NapEt$^+$	4.16	0.40	25	1M/1C	66
	(*R*)-NapEt$^+$	5.18		25	3M/7C	66
	(*S*)-NapEt$^+$	4.66	0.52	25	3M/7C	66
	(*R*)-NapEt$^+$	S		25	A	66
	(*S*)-NapEt$^+$	S		25	A	66
	(*R*)-PhEt$^+$	4.00		25	1M/1C	66
	(*S*)-PhEt$^+$	3.78	0.22	25	1M/1C	66
	(*R*)-PhEt$^+$	4.33		25	3M/7C	66
	(*S*)-PhEt$^+$	4.12	0.21	25	3M/7C	66
	(*R*)-PheMe$^+$	3.34		25	1M/1C	66
	(*S*)-PheMe$^+$	3.38	-0.04	25	1M/1C	66
	(*R*)-PheMe$^+$	3.53		25	3M/7C	66
	(*S*)-PheMe$^+$	3.64	-0.11	25	3M/7C	66
	(*R*)-PhEt(OH)$^+$	3.52		25	1M/1C	66
	(*S*)-PhEt(OH)$^+$	3.57	-0.05	25	1M/1C	66
(*S*,*S*)-64	(*R*)-NapEtCl	2.70		21	C	81
	(*S*)-NapEtCl	W		21	C	81
(*S*,*S*)-65	(*R*)-NapEtCl	2.32		21	C	81
	(*S*)-NapEtCl	W		21	C	81
	(*R*)-PhEtCl	2.22		21	C	81
	(*S*)-PhEtCl	1.75	0.47	21	C	81
(*S*,*S*)-66	(*R*)-NapEtCl	2.91		21	C	81
	(*S*)-NapEtCl	2.38	0.53	21	C	81
	(*R*)-PhEtCl	2.67		21	C	81
	(*S*)-PhEtCl	2.21	0.46	21	C	81

[a] See ligand structures in Chart I. [b] See guest structures in Chart II, the anion is perchlorate unless otherwise noted. [c] N/R = No reaction, S = Too strong to get accurate values, W = Weak complexation. [d] See footnote [d] in Table I.

Macrocyclic compounds of the cyclophane-type can have large cavities with well-defined sizes, shapes and regions of very pronounced hydrophobicity as potential binding sites for organic guests. A large amount of work has been done on the complexation of cyclophanes with neutral organic molecules in aqueous and organic solutions. This work has been reviewed [5,6]. Thermodynamic and kinetic data concerning cyclophane interactions with neutral molecules, including those obtained through nmr methods, have been collected [4-6]. This review does not repeat those data. Only the thermodynamic data for the interaction of cyclophanes with cations and anions are collected in this review. The log K, ΔH, and ΔS values for the interactions of cyclophanes **67-83** with some cations and anions are collected in Table III.

Saigo and coworkers have investigated the interactions of macropolycyclic ligand **67** having a cyclophane subunit with (ω-phenylalkyl)ammonium picrates (PAAP) [83]. Host **67** formed strong complexes with guest PAAP-5 (n = 5, see compound in Chart II) and PAAP-6 (n = 6). Selectivity could result from a cooperative phenomenon involving electrostatic and hydrophobic interactions. The superstructure of the complexes can be deduced from the values of the maximum chemical shift changes ($\Delta\delta_{max}$). The $\Delta\delta_{max}$ values of the protons on the methylene next to the ammonium cation for the complexes of the host and all guests were almost the same. This means that the environment around the methylene moiety next to the NH_3^+ is almost independent of the length of the methylene chains of PAAP. By contrast, the $\Delta\delta_{max}$ values of the benzyl protons of the PAAP depends greatly on the length of the methylene chain of PAAP. These phenomena indicate that the PAAP is bound in a 1/1 stoichiometry within the central cavity of the host by anchoring the primary ammonium group to the crown ether subunit, independent of the length of its methylene chain.

Koga and coworkers [83,84] and Schneider and coworkers [85,86,92] have shown by nmr spectral studies that cyclophane compounds **68-77** formed inclusion complexes with aliphatic and aromatic anion guests (see anion structures in Chart II). Dougherty and coworkers [87,88] have examined the interactions of cyclophane

Table III

Log K, ΔH and ΔS Values for the Interactions of Cyclophanes and Other Macrocycles with Organic Cations and Anions

ligand [a]	guest [b]	log K [c]	ΔH kJ/mol	ΔS J/K.mol	T °C	Solvent [d]	ref
67	PAAP-3	2.52			20	4C/1M	82
	PAAP-3	2.43			40	4C/1M	82
	PAAP-3	2.34			60	4C/1M	82
	PAAP-3		-8	22	20-60	4C/1M	82
	PAAP-4	2.64			20	4C/1M	82
	PAAP-4	2.57			40	4C/1M	82
	PAAP-4	2.45			60	4C/1M	82
	PAAP-4		-11	15	20-60	4C/1M	82
	PAAP-5	3.24			20	4C/1M	82
	PAAP-5	2.94			40	4C/1M	82
	PAAP-5	2.66			60	4C/1M	82
	PAAP-5		-28	-32	20-60	4C/1M	82
	PAAP-6	3.23			20	4C/1M	82
	PAAP-6	2.91			40	4C/1M	82
	PAAP-6	2.62			60	4C/1M	82
	PAAP-6		-29	-37	20-60	4C/1M	82
	PAAP-7	2.79			20	4C/1M	82
	PAAP-7	2.67			40	4C/1M	82
	PAAP-7	2.48			60	4C/1M	82
	PAAP-7		-18	-5	20-60	4C/1M	82
	PAAP-8	2.70			20	4C/1M	82
	PAAP-8	2.61			40	4C/1M	82
	PAAP-8	2.48			60	4C/1M	82
	PAAP-8		-10	19	20-60	4C/1M	82
	PAAP-9	2.41			20	4C/1M	82
	PAAP-9	2.32			40	4C/1M	82
	PAAP-9	2.20			60	4C/1M	82
	PAAP-9		-9	16	20-60	4C/1M	82
68	anion-1	N/R			[f]	1M/4W	83
	anion-2	N/R			[f]	1M/4W	83
	anion-3	N/S			[f]	1M/4W	83
	anion-4	2.48			[f]	1M/4W	83
	anion-5	2.30			[f]	1M/4W	83
69	anion-1	N/R			[f]	W	83
	anion-2	N/R			[f]	W	83
	anion-3	N/R			[f]	W	83
	anion-4	3.52			[f]	W	83
	anion-5	2.95			[f]	W	83
70	anion-1	N/R			28	W	84
	anion-2	N/R			28	W	84
	anion-4	3.04			28	W	84
	anion-5	3.28			28	W	84
	anion-6	1.35			[f]	8W/2M	85
	TMNA	0.68			[f]	8W/2M	85
	anion-7	2.40			[f]	6W/4M	86
	anion-8	2.35			[f]	2W/8M	86
	anion-8	2.10			[f]	4W/6M	86
	anion-9	3.18			25	1M/1W	92
	anion-9	2.41			25	8M/2W	92
	anion-10	5.18			25	3M/7W	92
	anion-10	4.49			25	1M/1W	92
	anion-10	3.23			25	8M/2W	92
71	anion-7	2.03			[f]	4M/6W	86
72	anion-1	1.30			[f]	1M/4W	83
	anion-2	N/S			[f]	1M/4W	83
	anion-3	N/S			[f]	1M/4W	83
	anion-4	1.48			[f]	1M/4W	83
	anion-5	1.90			[f]	1M/4W	83
73	anion-1	1.90			[f]	W	83
	anion-2	2.78			[f]	W	83
	anion-3	3.60			[f]	W	83
	anion-4	2.70			[f]	W	83

Table III (cont.)

ligand [a]	guest [b]	log *K* [c]	ΔH kJ/mol	ΔS J/K.mol	T °C	Solvent [d]	ref
	anion-5	2.48			[f]	W	83
	anion-1	1.88			28	W	84
	anion-2	2.78			28	W	84
	anion-4	2.67			28	W	84
	anion-5	2.52			28	W	84
74	anion-1	2.54			28	W	84
	anion-2	2.60			28	W	84
	anion-4	3.15			28	W	84
	anion-5	3.30			28	W	84
75	anion-1	2.38			28	W	84
	anion-2	2.28			28	W	84
	anion-4	3.00			28	W	84
	anion-5	2.95			28	W	84
76	anion-6	0.95			[f]	8W/2M	85
	TMNA	1.20			[f]	8W/2M	85
77	anion-6	0.85			[f]	8W/2M	85
78	MQ(s) [e]	3.09			-39	C	87
	MQ(s) [e]	2.58			23	C	87
	MQ(s) [e]	2.28			61	C	87
	MQ(c) [e]	3.09			-39	C	87
	MQ(c) [e]	2.61			23	C	87
	MQ(c) [e]	2.28			61	C	87
79	MQ	5.60 (*p*H 9.0)			22	W	88
	MIQ	5.30 (*p*H 9.0)			22	W	88
80	MQ	4.67 (*p*H 9.0)			22	W	88
	MIQ	4.43 (*p*H 9.0)			22	W	88
81	$(CH_2)_2(CO_2^-)_2$	3.15 (*p*H 6.0)			20	W	89
	$(CH_2)_3(CO_2^-)_2$	3.36 (*p*H 6.0)			20	W	89
	$(CH_2)_3(CO_2^-)_2$	3.72 (*p*H 5.5)			20	W	89
	$(CH_2)_4(CO_2^-)_2$	3.41 (*p*H 6.0)			20	W	89
	$(CH_2)_4(CO_2^-)_2$	3.77 (*p*H 5.5)			20	W	89
	$(CH_2)_5(CO_2^-)_2$	3.32 (*p*H 6.0)			20	W	89
	$(CH_2)_5(CO_2^-)_2$	3.51 (*p*H 5.5)			20	W	89
	$(CH_2)_6(CO_2^-)_2$	3.28 (*p*H 6.0)			20	W	89
	$(CH_2)_7(CO_2^-)_2$	3.15 (*p*H 6.0)			20	W	89
	$(CH_2)_8(CO_2^-)_2$	3.18 (*p*H 6.0)			20	W	89
	fumarate	3.61 (*p*H 6.0)			20	W	89
	maleate	3.38 (*p*H 6.0)			20	W	89
	terephthalate	3.40 (*p*H 6.0)			20	W	89
	terephthalate	4.78 (*p*H 5.5)			20	W	89
	$(CH_2)_2(CO_2^-)_2$	4.85 (*p*H 6.0)			[f]	W	91
	terephthalate	4.0 (*p*H 6.0)			[f]	W	91
82	$(CH_2)_2(CO_2^-)_2$	2.8 (*p*H 5.8)			[f]	W	90
83	$^+NEt_4Br^-$	3.53			25	W	92
	$^+NEt_4Br^-$	3.41			25	2M/8W	92
	$^+NEt_4Br^-$	3.04			25	1M/1W	92
	$^+NEt_4Br^-$	2.65			25	9M/1W	92

[a] See ligand structures in Chart I. [b] See guest structures in Chart II. [c] N/R = No reaction, N/S = Not soluable. [d] See footnote [d] in Table I. [e] s = single point complexation, c = complete complexation. [f] No temperature was listed.

compounds **78-80** with methylquinolinium (MQ) and methylisoquinolinium (MIQ) iodide. Their results indicated that donor/acceptor π-π interactions and ion-dipole attractions can contribute significantly to the binding in aqueous solution.

Lehn and coworkers [89-91] have investigated the interactions of polyaza macrocycles of the cyclophane-type **81, 82** with dicarboxylate guests. The cyclophanes exhibited recognition for linear guest molecules. For example, compound **81** complexed adipate dianion more strongly than either a shorter or the longer dicarboxylate. This linear recognition probably corresponds to the size of the molecular cavity.

D. Kinetic Parameters for the Interaction of Macrocycles with Organic Guests.

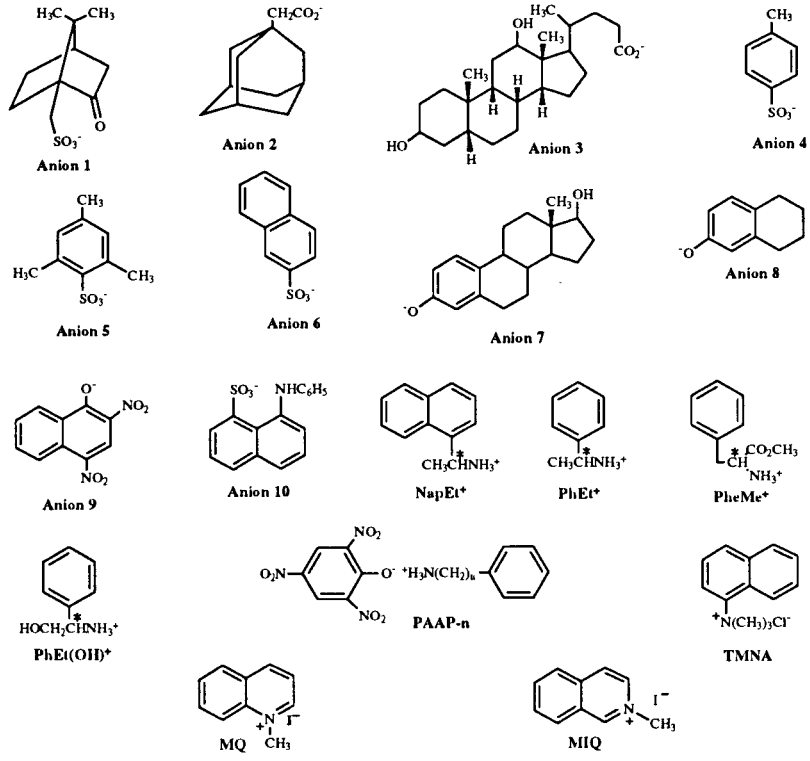
Measurements of free energies of activation ($\Delta G_c^{\ddagger}$) for complex dissociation at the ^1H nmr spectral coales-

cence temperature have been made using the variable temperature technique discussed above. The data are collected in Table IV. Since previous work was summarized in a review in 1981 [41], only new data after 1981 are given in Table IV.

Bradshaw and coworkers [66,79,80,93-98,100] have measured $\Delta G_c^{\ddagger}$ values for the interactions of 18-crown-6 ligands **42-45**, **56**, **57**, **59**, **62**, **63**, **84-95**, **97-111**, including temperature nmr procedure [101]. The results showed that their chiral macrocycles exhibited moderate enantiomeric selectivity.

Bauer and Gutsche [102] have studied the complexation of calixarenes **118-120** with neutral aliphatic amines using the variable temperature nmr spectral technique. The results indicated that the major factor accounting for the different $\Delta G_c^{\ddagger}$ values was the basicity of the amine.

Chart II



many chiral crown ethers, with several organic primary amines or ammonium salts. These crown ethers vary by having different subcyclic units including pyridine, phenanthroline and triazole, different substituents on chiral carbon atoms and by having the chiral centers in different positions. In chiral recognition studies, most of the complexes of the (*R*,*R*)[(*S*,*S*)]-ligands with (*S*)[(*R*)] guests had higher coalescence temperatures and greater $\Delta G_c^{\ddagger}$ values than those with (*R*)[(*S*)]-guests. Although the $\Delta G_c^{\ddagger}$ values have no direct relationship to ΔG values, these results have proven useful to identify the presence or absence of chiral recognition in host-guest pairs. A review covering most of this work has been published [95].

Sutherland and coworkers have investigated the enantioselectivity of the interaction of chiral diaza-15-crown-5 and diaza 18-crown-6 derivatives **112-117** with chiral phenylethylammonium (PhEt+) salts using the variable

Those amines that exhibited strong complexation have basicities on the order of 10^5 times greater than that of aniline. Steric factors also played a role. For example, neopentylamine and *t*-butylamine have very similar basicities, but the latter formed more stable complexes.

Collet and coworkers [103] have examined the complexation of dichloromethane and dibromomethane by cryptophanes **121** and **122**. The results showed that dibromomethane formed stronger complexes than did dichloromethane.

In conclusion, there is increasing interest in the application of nmr spectral methods to the interactions of macrocyclic organic ligands. Particularly, the development of modern nmr techniques makes possible more accurate information about the comformations of host-guest complexes in solution which allows for a better understanding of molecular recognition.

Table IV

$\Delta G_c^{\ddagger}$ and T_c Values for Interactions of Macrocyclic Ligands with Organic Guests

ligand [a]	guest [b]	$\Delta G_c^{\ddagger}$ (KJ/mol) [c]	T_c(K)	Solvent [d]	ref
42	$PhCH_2NH_3^+$	54.3	283.2	DM	93
(*S*,*S*)-43	(*R*)-NapEt$^+$	43.1	217.2	DM	93
	(*S*)-NapEt$^+$	36.4	187.2	DM	93
	(*R*)-PheMe$^+$	47.3	233.2	DM	93
	(*S*)-PheMe$^+$	41.8	200.2	DM	93
	$PhCH_2NH_3^+$	48.9	244.2	DM	93
(*R*,*R*)-44	(*R*)-NapEt$^+$	59.4	279.2	DM	79
	(*S*)-NapEt$^+$	46.9	239.2	DM	79
(*S*,*S*)-45	(*R*)-NapEt$^+$	47.3	235.2	DM	79
	(*S*)-NapEt$^+$	36.9	178.2	DM	79
(*R*,*R*)-46	(*R*)-NapEt$^+$	62.3	301.2	DM	79
	(*S*)-NapEt$^+$	61.1	303.2	DM	79
(*R*,*R*,*R*,*R*)-47	(*R*)-NapEt$^+$	56.0	276.2	DM	94
	(*S*)-NapEt$^+$	59.8	300.2	DM	94
	(*R*)-PhEt$^+$	50.6	252.2	DM	94
	(*S*)-PhEt$^+$	59.8	298.2	DM	94
(*R*,*R*,*R*,*R*)-48	(*R*)-NapEt$^+$	43.9	221.2	DM	94
	(*S*)-NapEt$^+$	46.9	230.2	DM	94
	(*R*)-PhEt$^+$	46.9	235.2	DM	94
	(*S*)-PhEt$^+$	44.4	227.2	DM	94
(*R*,*R*)-49	(*R*)-NapEt$^+$	52.3	260.2	DM	93
	(*S*)-NapEt$^+$	56.1	286.2	DM	93
	(*R*)-PheMe$^+$	49.4	237.2	DM	93
	(*S*)-PheMe$^+$	50.6	248.2	DM	93
	$PhCH_2NH_3^+$	52.7	252.2	DM	93
(*S*,*S*)-49	(*R*)-NapEt$^+$	56.1	285.2	DM	93
	(*S*)-NapEt$^+$	51.5	254.2	DM	93
	(*R*)-PheMe$^+$	50.6	248.2	DM	93
	(*S*)-PheMe$^+$	49.4	237.2	DM	93
	$PhCH_2NH_3^+$	51.8	248.2	DM	93
(S,*S*)-50	(*R*)-NapEt$^+$	55.6	284.2	DM	94
	(*R*)-NapEt$^+$	54.3	283.2	DM	97
	(*S*)-NapEt$^+$	50.2	238.2	DM	94
	(*S*)-NapEt$^+$	51.2	247.2	DM	97
	(*R*)-PheMe$^+$	49.8	252.2	DM	94
	(*S*)-PheMe$^+$	45.2	228.2	DM	94
	$PhCH_2NH_3^+$	53.9	278.2	DM	97
(*S*,*S*)-51	(*R*)-NapEt$^+$	43.1	219.2	DM	79
	(*S*)-NapEt$^+$	<35.5	<183.2	DM	79
(*S*,*S*)-52	(*R*)-PheMe$^+$	51.8	247.2	DM	93
	(*S*)-PheMe$^+$	53.0	262.2	DM	93
	$PhCH_2NH_3^+$	56.0	265.2	DM	93
(*S*,*S*)-56	(*R*)-NapEt$^+$	50.2		DM	80
	(*S*)-NapEt$^+$	50.6		DM	80
(*S*,*S*)-57	(*R*)-NapEt$^+$	N/O		DM	80
	(*S*)-NapEt$^+$	N/O		D	80
(*S*,*S*)-59	(*R*)-NapEt$^+$	47.2		DM	80
	(*S*)-NapEt$^+$	46.8		DM	80
(*S*,*S*)-62	(*R*)-NapEt$^+$	>58.5		DM	80
	(*S*)-NapEt$^+$	>58.1		DM	80
(*S*,*S*)-63	(*R*)-NapEt$^+$	51.2	264.0	DM	66
	(*S*)-NapEt$^+$	49.3	245.0	DM	66
	(*R*)-PheMe$^+$	59.2	295.0	DM	66
	(*S*)-PheMe$^+$	57.1	286.5	DM	66
	(*R*)-PhEt$^+$	>62.9	>303	DM	66
	(*S*)-PhEt$^+$	>62.3	>303	DM	66
	(*R*)-PhEt(OH)$^+$	51.9	272.0	DM	66
	(*S*)-PhEt(OH)$^+$	53.1	261.0	DM	66

Table IV (cont.)

ligand [a]	guest [b]	$\Delta G_c^{\ddagger}$ (KJ/mol) [c]	T_c(K)	Solvent [d]	ref
(*R*,*R*)-84	(*R*)-NapEt$^+$	52.3	253.2	DM	94
	(*S*)-NapEt$^+$	55.6	278.2	DM	94
	(*R*)-PhEt$^+$	45.2	223.2	DM	94
	(*S*)-PhEt$^+$	50.6	258.2	DM	94
	(*R*)-PheMe$^+$	47.3	231.2	DM	94
	(*S*)-PheMe$^+$	45.6	225.2	DM	94
	(*R*)-PhEt(OH)$^+$	52.7	243.2	DM	94
	(*S*)-PhEt(OH)$^+$	46.0	234.2	DM	94
(*S*,*S*)-85	(*R*)-NapEt$^+$	59.4	302.2	DM	94
	(*S*)-NapEt$^+$	55.6	283.2	DM	94
(*S*,*S*)-86	(*R*)-NapEt$^+$	54.4	273.2	DM	93,95
	(*S*)-NapEt$^+$	49.4	243.2	DM	93,95
	(*R*)-PheMe$^+$	47.7	235.2	DM	93,95
	(*S*)-PheMe$^+$	46.1	212.2	DM	93,95
	$PhCH_2NH_3^+$	50.6	240.2	DM	93
(*S*,*S*)-87	(*R*)-PheMe$^+$	48.1	240.2	DM	93
	(*S*)-PheMe$^+$	48.5	245.2	DM	93
	$PhCH_2NH_3^+$	53.9	283.2	DM	93
(*S*,*S*)-88	(*R*)-NapEt	51.8	254.2	DM	96
	(*S*)-NapEt	52.3	265.2	DM	96
	$PhCH_2NH_2$	53.1	267.2	DM	96
89	$PhCH_2NH_2$	58.5	288.2	DM	96
	$PhCH_2NH_3^+$	43.5	219.2	DM	96
(*S*,*S*)-90	(*R*)-PheMe$^+$	46.4	225.2	DM	93
	(*S*)-PheMe$^+$	48.4	239.2	DM	93
	$PhCH_2NH_3^+$	51.0	243.2	DM	93
91	$PhCH_2NH_3^+$	56.8	298.2	DM	98
(*S*,*S*)-92	(*R*)-NapEt$^+$	60.6	304.2	DM	98
	(*S*)-NapEt$^+$	54.7	280.2	DM	98
93	$PhCH_2NH_3^+$	58.9	308.2	DM	98
	$PhCH_2NH_2$	51.4	263.2	DM	98
(*S*,*S*)-94	(*R*)-NapEt$^+$	60.6	305.2	DM	98
	(*S*)-NapEt$^+$	56.0	265.2	DM	98
	(*R*)-NapEt	46.0	227.2	DM	98
	(*S*)-NapEt	43.1	202.2	DM	98
	$PhCH_2NH_3^+$	59.4	279.2	DM	98
	$PhCH_2NH_2$	46.0	221.2	DM	98
(*R*,*R*)-95	(*R*)-NapEt$^+$	56.0	272.2	DM	98
	(*S*)-NapEt$^+$	57.3	300.2	DM	98
	(*R*)-NapEt	43.1	213.2	DM	98
	(*S*)-NapEt	47.2	241.2	DM	98
	$PhCH_2NH_3^+$	57.3	296.2	DM	98
	$PhCH_2NH_2$	47.7	247.2	DM	98
96	$PhCH_2NH_3^+$	47.0	239.2	DM	99
97	$PhCH_2NH_3^+$	38.9		DM	100
98	$PhCH_2NH_3^+$	40.6		DM	100
	$PhCH_2NH_3^+$(0.5)	38.0		DM	100
	PhEt$^+$	39.7		DM	100
	t-$BuNH_3^+$	36.4		DM	100
99	$PhCH_2NH_3^+$	44.7		DM	100
	PhEt$^+$	43.5		DM	100
	t-$BuNH_3^+$	<33		DM	100
100	$PhCH_2NH_3^+$	45.1		DM	100
	$PhCH_2NH_3^+$(0.5)	43.9		DM	100
	PhEt$^+$	43.1		DM	100
	t-$BuNH_3^+$	<33		DM	100
101	$PhCH_2NH_3^+$	42.6		DM	100
	$PhCH_2NH_3^+$(0.5)	40.1		DM	100
	PhEt$^+$	40.1		DM	100
	t-$BuNH_3^+$	37.6		DM	100
102	$PhCH_2NH_3^+$	45.1		DM	100
	PhEt$^+$	43.9		DM	100
	t-$BuNH_3^+$	<33		DM	100

Table IV (cont.)

ligand [a]	guest [b]	$\Delta G_c^{\ddagger}$ (KJ/mol) [c]	T_c(K)	Solvent [d]	ref
103	$PhCH_2NH_3^+$	46.0		DM	100
	$PhEt^+$	43.1		DM	100
	t-$BuNH_3^+$	<33		DM	100
104	$PhCH_2NH_3^+$	<33		DM	100
105	$PhCH_2NH_3^+$	<33		DM	100
106	$PhCH_2NH_3^+$	<33		DM	100
107	$PhCH_2NH_3^+$	35.5		DM	100
108	$PhCH_2NH_3^+$	38.9		DM	100
	t-$BuNH_3^+$	<33		DM	100
109	$PhCH_2NH_3^+$	43.9		DM	100
	$PhCH_2NH_3^+$(0.5)	43.1		DM	100
	t-$BuNH_3^+$	<33		DM	100
110	$PhCH_2NH_3^+$	38.0		DM	100
111	$PhCH_2NH_3^+$	42.2		DM	100
112	$PhCH_2NH_3^+$	48.1	241.2	DM	101
	(*S*)-$PhEt^+$	48.1	238.2	DM	101
	(*R*)-$PhEt^+$	48.5	238.2	DM	101
	(*S*)-$PhEt(OH)^+$	47.2	228.2	DM	101
	(*R*)-$PhEt(OH)^+$	48.1	233.2	DM	101
113	$PhCH_2NH_3^+$	48.1	238.2	DM	101
	(*S*)-$PhEt^+$(0.5)	47.2	235.2	DM	101
	(*R*)-$PhEt^+$(0.5)	49.7	251.2	DM	101
114	$PhCH_2NH_3^+$	50.2	251.2	DM	101
	(*R*)-$PhEt^+$	46.4	233.2	DM	101
	(*S*)-$PhEt^+$	46.0	231.2	DM	101
115	(*S*)-$PhEt^+$	50.6	245.2	DM	101
	(*R*)-$PhEt^+$	51.0	263.2	DM	101
116	$PhCH_2NH_3^+$	53.5	271.2	DM	101
	(*S*)-$PhEt^+$	52.7	273.2	DM	101
	(*R*)-$PhEt^+$	50.6	243.2	DM	101
	t-$BuNH_3^+$	49.3	242.2	DM	101
117	(*S*)-$PhEt^+$	47.7	245.2	DM	101
	(*R*)-$PhEt^+$	47.2	235.2	DM	101
118	*t*-butylamine	60.2	301.2	AN	102
119	*t*-butylamine	64.4	323.2	AN	102
120	*t*-butylamine (2)		301.2	A	102
	t-butylamine (2)		305.2	AN	102
	t-butylamine (4)	61.3	308.2	A	102
	t-butylamine (4)	61.5	309.2	AN	102
	t-butylamine (4)	61.4	303.2	C	102
	t-butylamine (20)		308.2	A	102
	neopentylamine (4)	56.7	288.2	A	102
	neopentylamine (4)	56.8	292.2	AN	102
	neopentylamine (20)		301.2	A	102
	neopentylamine (20)		306.2	AN	102
	neopentylamine (40)		306.2	A	102
	t-amylamine (4)		311.2	A	102
	n-butylamine (4)		306.2	A	102
	n-butylamine (4)		306.2	AN	102
	undecylamine (4)	63.1	315.2	A	102
	undecylamine (4)		317.2	AN	102
	adamantylamine (4)		309.2	A	102
	diethylamine (4)		297.2	AN	102
	triethylamine (4)		296.2	A	102
	quinuclidine (4)		302.2	AN	102
	aniline (10)		284.2	A	102
121	CH_2Cl_2	49.5		C	103
122	CH_2Cl_2	45.2		C	103

[a] See ligand structures in Chart I. [b] See footnote [b] in Table I. [c] N/O = Not observable. [d] See footnote [d] in Table I.

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