Evaluation of a Direct ^{1}H NMR Method for Determining log K and ΔH Values for Crown Ether–Alkylammonium Cation Complexation [#]

C. Y. ZHU, J. S. BRADSHAW, J. L. OSCARSON, and R. M. IZATT*
Departments of Chemistry and Chemical Engineering, Brigham Young University, Provo, Utah 84602, U.S.A.

Abstract. A direct ^{1}H NMR method for determining log K and ΔH values for crown ether–ammonium cation complexation using milligrams of sample was tested and evaluated for accuracy and precision by comparing the results with those obtained using a titration calorimetric method. Log K values for the interactions of a non-chiral crown ether, diketopyridino-18-crown-6 (K$_2$P18C6), with α-phenylethylammonium (PhEt$^+$) perchlorate in 50%–50% and 90%–10% (v/v) mixtures of deuterated methanol (CD$_3$OD) and deuterated chloroform (CDCl$_3$) at four temperatures and, with α-(1-naphthyl)ethylammonium (NapEt$^+$) perchlorate in 50%CD$_3$OD–50%CDCl$_3$ (v/v) at 25°C were determined by a direct ^{1}H NMR method. Values of ΔH for the interactions of K$_2$P18C6 with PhEt$^+$ in the two solvents were calculated from the temperature dependence of log K. Log K values for the interactions of a chiral crown ether, dimethyldiketopyridino-18-crown-6 (M$_2$K$_2$P18C6), with (R) and (S) enantiomers of NapEt$^+$ in pure CD$_3$OD at 25.0°C were also determined by the NMR method. The results were compared with those determined by a calorimetric method at 25.0°C in 50%–50% and 90%–10% (v/v) mixtures of plain methanol and chloroform, in 100% plain methanol, and in a 50%–50% mixture of partially deuterated methanol (with deuterium substitution on the methanol OH group, CH$_3$OD) and deuterated chloroform. The log K values determined by both methods were found to be in good agreement, but the standard deviations associated with the NMR log K values were two to three times greater. The agreement of the ΔH values determined by the two methods was poor, differing by approximately 10 kJ/mol with the NMR method giving more negative values. The standard deviations associated with the NMR ΔH values were approximately ten times greater than those for the calorimetric values. Ion-pairing was observed for the interaction of perchlorate ion with both free and bound PhEt$^+$ in 50%methanol–50%chloroform mixture. It is concluded that the NMR procedure is satisfactory for the determination of log K, but not ΔH values.

Key words.   Crown ether-ammonium cation complexation, formation constants (K) and enthalpy changes (ΔH), direct ^{1}H NMR method, titration calorimetric method.

1. Retrospect

In February 1968, the late Professor James J. Christensen and one of us (RMI) visited Charlie Pedersen and Karl Frensdorf in their du Pont laboratory. This visit resulted from a conversation concerning Charlie's work on alkali metal coordination which we had had with George Eisenman (then at the University of Chicago). We had become interested in alkali metal coordination as a result of a post-doctoral stay by Jim at R. J. P. William's laboratory at Oxford two years earlier. Charlie

[#] This paper is dedicated to the memory of the late Dr C. J. Pedersen.
* Author for correspondence.

kindly provided us with a sample of dicyclohexano-18-crown-6 (mixed isomers) which became the basis for our first study of log K, ΔH, and ΔS values for cyclic polyether–alkali metal binding, *Science* **164**, 443–444 (1969).

This contact changed the direction of our research and, through collaboration at BYU with Jerald S. Bradshaw and N. Kent Dalley, led to extensive studies of factors determining cation selectivities by a large number of new cyclic polyethers and their derivatives. We at BYU owe much to Charlie for the direction and impetus he gave to our research program. Our associations with him after 1968 were limited, but always cordial. He was invited each year to the symposia on macrocyclic chemistry which were held at BYU beginning in 1977. Unfortunately, he was unable to attend due to the illness of his wife. In May 1989, one of us (RMI) visited him at his home in Salem, New Jersey. At the entrance to the city, a sign proclaimed Salem to be the home of Charles J. Pedersen, Nobel Prize Laureate. Charlie was not well, but took great interest in providing a guided tour of his home and garden.

2. Introduction

Crown ethers form complexes with inorganic and organic cations [1–4] and with neutral molecules [5, 6]. It is important to know the values of the equilibrium constant (K) and enthalpy change (ΔH) for the formation of these complexes. Large numbers of log K and ΔH values for crown ether–cation interactions determined by various methods have been reported [7, 8] since Pedersen described the synthesis of these macrocycles [9].

Among the various methods that have been used to determine log K and ΔH values, calorimetry is useful in being able to determine both of these quantities from a single experiment provided that log K values lie within a certain range [10–12]. Log K values determined in this way are comparable in accuracy and precision to those obtained by conventional potentiometric procedures [13, 14]. Calorimetry is the preferred method for ΔH determination since the heat of reaction is measured directly. For many systems, a major disadvantage of the calorimetric method is that a large amount of sample, usually tens or hundreds of milligrams, is required for the determination. This requirement is not easily met in the case of many crown ether compounds which are difficult to prepare.

NMR methods have been used for the determination of K values for the interaction of crown ethers with metal cations [15, 16], organic cations [17, 18], and neutral molecules [19]. Among the various NMR methods available, that involving ¹H NMR [18] is the simplest and, probably, the most accurate if it is applicable to the system under study and is used properly. Advantages of the direct ¹H NMR method are that a small amount (usually milligrams) of sample is required, useful structural information can often be obtained, and the experiment is much less time consuming than any of the other NMR methods. Despite the advantages that the ¹H NMR method has, its accuracy and precision in determining K and ΔH values relative to those of the calorimetric or other conventional methods have not been examined.

It has been common to obtain ΔH values from the temperature dependence of K using the Van 't Hoff equation. Various indirect methods [20–22] including the ¹H

NMR method [19] have been used to determine ΔH values. In these determinations, the temperature dependence of ΔH is assumed to be negligible. It is expected that ΔH values obtained through indirect methods should have larger standard deviations than those determined by calorimetric measurements. Also, the temperature dependence of ΔH is not always negligible [23, 24]. Thus, the accuracy of ΔH values obtained from indirect methods is open to question. A major objective of the present work was to provide an evaluation of our ^{1}H NMR method for determining log K and ΔH values by comparing these values with those obtained using the calorimetric method under experimental conditions which are identical except for deuterium substitution in the solvent.

The direct ^{1}H NMR method provides a desirable means for the determination of log K values for the interaction of chiral crown ethers with chiral alkylammonium cations or protonated amino acids. Those systems showing significant chiral recognition [25] are of particular interest. It is desirable to characterize these interactions and ^{1}H NMR provides a promising means to do this since only a few milligrams of each crown ether compound are used for each log K determination. In the present work, our ^{1}H NMR method was evaluated by determining log K and ΔH values for the interactions of diketopyridino-18-crown-6 (K_2P18C6) with α-phenylethylammonium (PhEt$^+$) and α-(1-naphthyl)ethylammonium (NapEt$^+$) cations in two deuterated methanol-chloroform mixtures with different volume ratios. In addition, log K values were determined for the interactions of (R,R)-dimethyldiketopyridino-18-

Diketopyridino-
18-Crown-6 (K_2P18C6)

(R,R)-Dimethyldiketopyridino-
18-Crown-6 (M_2K_2P18C6)
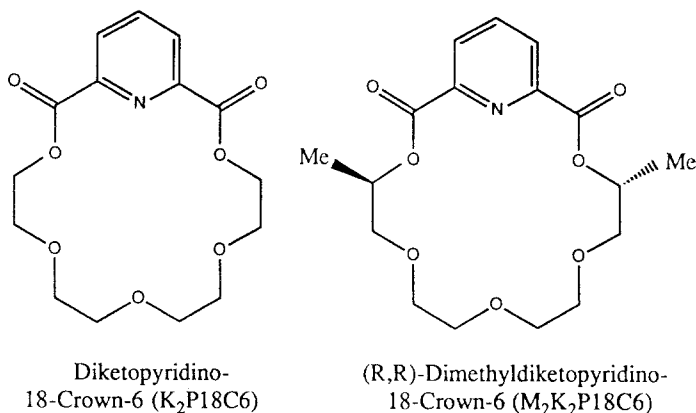
crown-6 (M_2K_2P18C6) with both the (R) and (S) enantiomers of NapEt$^+$ in pure CD$_3$OD. The method was evaluated by comparing the results with those determined by a titration calorimetric method in analogous non-deuterated and partially deuterated solvents.

3. Experimental

3.1. MATERIALS

K_2P18C6 and M_2K_2P18C6 were prepared as reported earlier [26, 27]. Each compound was purified by recrystallization in hot diisopropyl ether and drying *in vacuo*.

(R) and (S) enantiomers of PhEt$^+$ClO$_4^-$ and NapEt$^+$ClO$_4^-$ were prepared according to Zhu *et al.* [28]. The purities of K$_2$P18C6, M$_2$K$_2$P18C6, PhEt$^+$ClO$_4^-$ and NapEt$^+$ClO$_4^-$ were better than 99% as evidenced by their ^{1}H NMR spectra. CDCl$_3$, CH$_3$OD and CD$_3$OD (Aldrich, 98%) were used as purchased. CHCl$_3$ and CH$_3$OH (Fisher, HPLC grade) were used without further publication.

3.2. ^{1}H NMR EXPERIMENTS

All ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz apparatus with a temperature accessory.

For each log K determination at a given temperature, a sample containing a few milligrams of a macrocycle in a known volume of solvent was first loaded into the probe and a spectrum was taken. The sample was then unloaded, added to the sample tube with a small amount of the solid ammonium salt, reloaded into the probe, and another spectrum was taken. This process was repeated until no significant change was observed in successive ^{1}H NMR spectra. Usually eight to twelve spectra were taken for each log K determination. The crown ether concentrations were about 0.01–0.015M and the ammonium salt concentrations varied from 0.0M to approximately 0.06M for each of the experiments. In each experiment, an accurately weighed quantity of the crown ether was dissolved in a known volume of solvent at 25.0°C. The analytical balance used was calibrated for accuracy using a standard weight from the National Institute of Standards and Technology. The salt concentrations were calculated based on the integral ratio of a particular ammonium salt signal to a particular crown ether signal in the spectra. In order to obtain a quantitative integration, the time delay between the two pulses for each NMR acquisition was set long enough to allow sufficient relaxation of the signals of interest. The NMR parameter settings were kept the same for all of the experiments and Me$_4$Si (TMS) was used as the internal standard for all of the samples.

Under conditions of fast exchange on the NMR time scale, the average chemical shift of a crown ether signal is the weighted average of the chemcial shifts of the same signals for the free and complexed crown ether

$$\delta_{ave} = X_f \delta_f + (1 - X_f)\delta_c \tag{1}$$

where δ_{ave} = average chemical shift of the crown ether signal of interest, δ_f = chemical shift of the same signal for the free crown ether, and X_f = the mole fraction of free crown ether. By using a non-linear least-squares treatment, the best fit of the expermental data points can be achieved through the minimization of the function

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

where δ_{obs} = observed average chemical shift of the crown ether signal of interest. Since X_f is a function of log K, U is a function of log K also. The log K value that results in the minimum U value is taken to be the correct value. The log K values were calculated this way using the program EQDD on a VAX 11/780 computer. The ΔH values for the interactions were obtained from the temperature dependence of log K according to the relationship

$$2.303 \log K = -\Delta H/RT + C \tag{3}$$

which is obtained from the integration of the Van 'tHoff equation assuming that ΔH is a constant over the temperature range, where C is an integration constant. Linear least-squares treatment of the $\log K - T^{-1}$ data pairs based on Equation 3 gives the following expression for ΔH

$$\Delta H = (2.303R) \frac{\Sigma[(T_{av}^{-1} - T_i^{-1})(\log K_i - \log K_{av})]}{\Sigma(T_i^{-1} - T_{av}^{-1})^2} \tag{4}$$

where T_{av}^{-1} and $\log K_{av}$ = the averages of T_i^{-1} values and $\log K_i$ values, respectively.

3.3. CALORIMETRIC EXPERIMENTS

Calorimetric determinations were carried out on a Tronac model 450 isoperibol calorimeter using procedures described elsewhere [29]. The calorimeter was calibrated and tested according to Christensen et al. [10]. The calculations were done on a VAX 11/780 computer using the programs developed earlier in our laboratory [11].

4. Results and Discussion

K_2P18C6 forms complexes with $PhEt^+$ and $NapEt^+$ in 90%MeOH–10%H_2O [28]. These complexes are expected to be more stable in methanol–chloroform mixtures because of the decreased solvent polarity. The use of methanol–chloroform mixtures as the solvents in this work was based on solubility considerations since the complexes of K_2P18C6 with either $PhEt^+ClO_4^-$ or $NapEt^+ClO_4^-$ did not dissolve in methanol at concentrations larger than approximately 0.01M. However, the use of these mixed solvents increases the likelihood that ion-pair formation is present due to the decreased solvent polarity. In order to evaluate the contribution of ion-pairing to the overall complexation reaction, the interactions of K_2P18C6 with $PhEt^+ClO_4^-$ in two methanol-chloroform mixtures with different volume ratios were studied and compared.

The ^1H NMR spectra of the samples containing K_2P18C6 and either $PhEt^+$ or $NapEt^+$ showed that the pyridine signals of the macrocycle were a doublet and a triplet. Both of these signals were well resolved in the range 8.10–8.40 ppm, and were well separated from the phenyl signals of $PhEt^+$ or the naphthyl signals of $NapEt^+$. Therefore, the pyridine signals of K_2P18C6 were used as the probe for monitoring the complexation. The methyl signal of either $PhEt^+$ or $NapEt^+$ was found to be a well isolated sharp doublet at about 1.5 ppm. The integral of the methyl signal was used for the calculation of the ammonium salt concentrations. In the presence of $PhEt^+$, downfield shifts of up to 0.17 ppm (34 Hz) for the pyridine signals of K_2P18C6 were observed. However, in the presence of $NapEt^+$, upfield shifts of up to 0.19 ppm (38 Hz) for the same signals were observed. This difference in the direction of the chemical shift change is understood by considering the difference between the proposed structures of the K_2P18C6–$PhEt^+$ and K_2P18C6–$PhEt^+$ complexes [28] as illustrated in Figures 1A and 1B, respectively. The orientation of the phenyl group of $PhEt^+$ opposite to that of the pyridine ring of K_2P18C6 is the cause for the downfield shift of the pyridine signals in the case of K_2P18C6–$PhEt^+$ complexation since the deshielding zone of the phenyl group

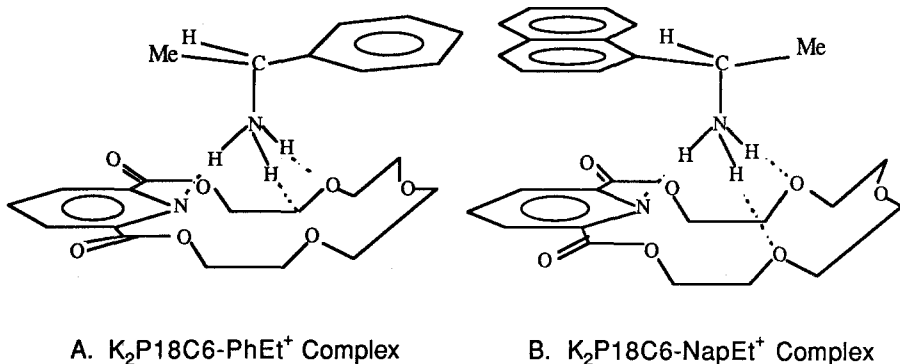**A. K$_2$P18C6-PhEt$^+$ Complex**   **B. K$_2$P18C6-NapEt$^+$ Complex**

Fig. 1. A schematic representation of the molecular structures of the diketopyridino-18-crown-6 complexes with α-phenylethylammonium cation (A) and with α-(1-naphthyl)ethylammonium cation (B) [28].
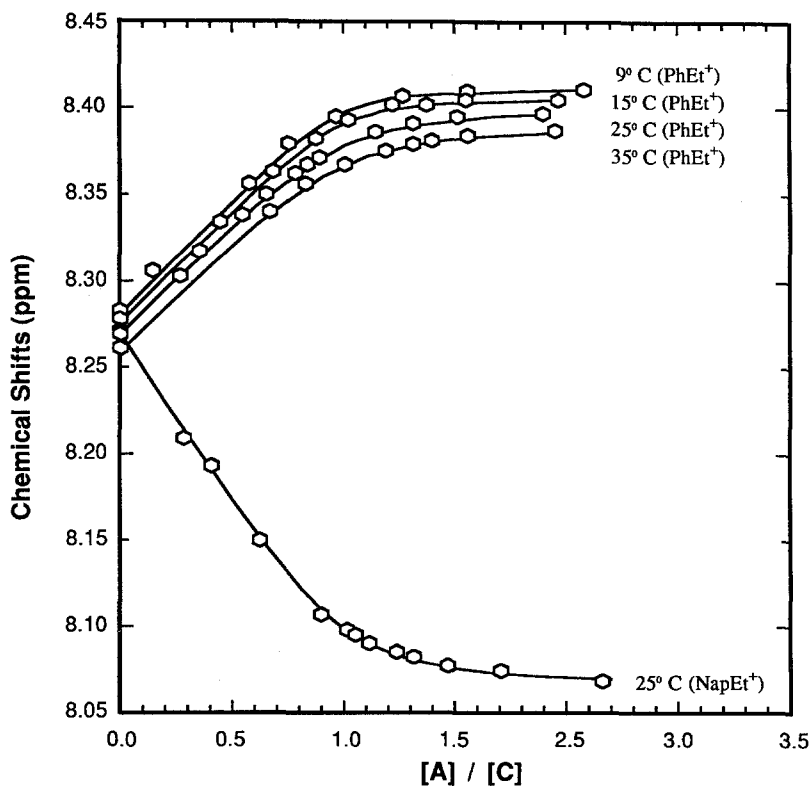

Fig. 2. Observed chemical shifts of the 3,5 protons on the pyridine moiety of diketopyridino-18-crown-6 (K$_2$P18C6) in 50%CD$_3$OD–50%CDCl$_3$ at different temperatures as a function of the molar ratio, [A]/[C], of the α-phenylethylammonium (PhEt$^+$) or α-(1-naphthyl)ethylammonium (NapEt$^+$) perchlorate to K$_2$P18C6, where [A] and [C] represent the concentrations of PhEt$^+$ (or NapEt$^+$) and K$_2$P18C6, respectively.

covers the pyridine ring. The overlap between the naphthyl group of NapEt$^+$ and the pyridine ring is the cause for the upfield shift of the pyridine signals in the case of K$_2$P18C6–NapEt$^+$ complexation since the shielding zone of the naphthyl group covers the pyridine ring. The plots of the observed and simulated pyridine chemical shifts of K$_2$P18C6 vs. the molar ratios of either PhEt$^+$ or NapEt$^+$ to K$_2$P18C6 in 50%CD$_3$OD–50%CDCl$_3$ (v/v) at different temperatures are shown in Figure 2.

(S,S)-M$_2$K$_2$P18C6 shows good chiral recognition toward chiral NapEt$^+$ by favorably complexing the (R) rather than the (S) enantiomer [30]. (R,R)-M$_2$K$_2$P18C6 is expected to show equal recognition towards chiral NapEt$^+$, but in favor of the (S) rather than the (R) enantiomer. The calorimetrically determined log K values for the interactions of (S,S)–M$_2$K$_2$P18C6 with both (R) and (S) enantiomers of NapEt$^+$ in methanol have been reported [30]. In the present work, the log K values for the interactions of (R,R)–M$_2$K$_2$P18C6 with (R)- and (S)-NapEt$^+$ in CD$_3$OD were determined by the ^{1}H NMR method, and compared with those for (S,S)–M$_2$K$_2$P18C6 determined by calorimetry. In the ^{1}H NMR spectrum of M$_2$K$_2$P18C6 with the presence of either the (R) or (S) form of NapEt$^+$, an upfield shift of the pyridine signals and a downfield shift of the methyl signal of M$_2$K$_2$P18C6 were observed. The methyl signal of M$_2$K$_2$P18C6 was a nice doublet and was well separated from the methyl signal of NapEt$^+$. The integral ratio of the two methyl signals was used to calculate the concentration of the salt. The plots of the observed and simulated pyridine chemical shifts of M$_2$K$_2$P18C6 vs. the molar ratios of either the (R) or (S) form of NapEt$^+$ to M$_2$K$_2$P18C6 in CD$_3$OD at 25.0°C are shown in Figure 3.

Analysis of the chemical shift–molar ratio plots showed that the maximum slope change of each curve happened where the molar ratio was about 1 : 1, indicating that 1 : 1 complexation dominated in each system studied. Similar analysis of the heat–molar ratio plots generated by calorimetry for the same systems in the corresponding non-deuterated and partially deuterated solvents also suggested the domination of 1 : 1 complexation. The simulation of the NMR or calorimetric data for each system by assuming 1 : 1 complexation was good with reasonably small statistical deviation. The log K, ΔH and ΔS values obtained by both ^{1}H NMR and calorimetric methods are listed in Tables I and II.

In Table I, the NMR ΔH values were calculated from the temperature dependence of log K according to Equation 3 where ΔH is assumed to be temperature independent. Values of ΔS at 25.0°C were calculated according to the relationship

$$2.303RT \log K = \Delta H - T\Delta S \tag{5}$$

Plots of log K vs. T^{-1} for K$_2$P18C6–PhEt$^+$ interactions in the two solvents are shown in Figure 4.

It is seen from Tables I and II that the log K values determined by the NMR method at 25.0°C are in good agreement with those determined by calorimetry at the same temperature. The method should prove useful in quantitating chiral recognition for new chiral systems in terms of Δ log K values determined by the NMR method. In addition, only very small amounts of valuable sample are used. However, as seen in Table I, the ΔH and ΔS values obtained by the NMR method are in poor agreement with those determined by calorimetry.
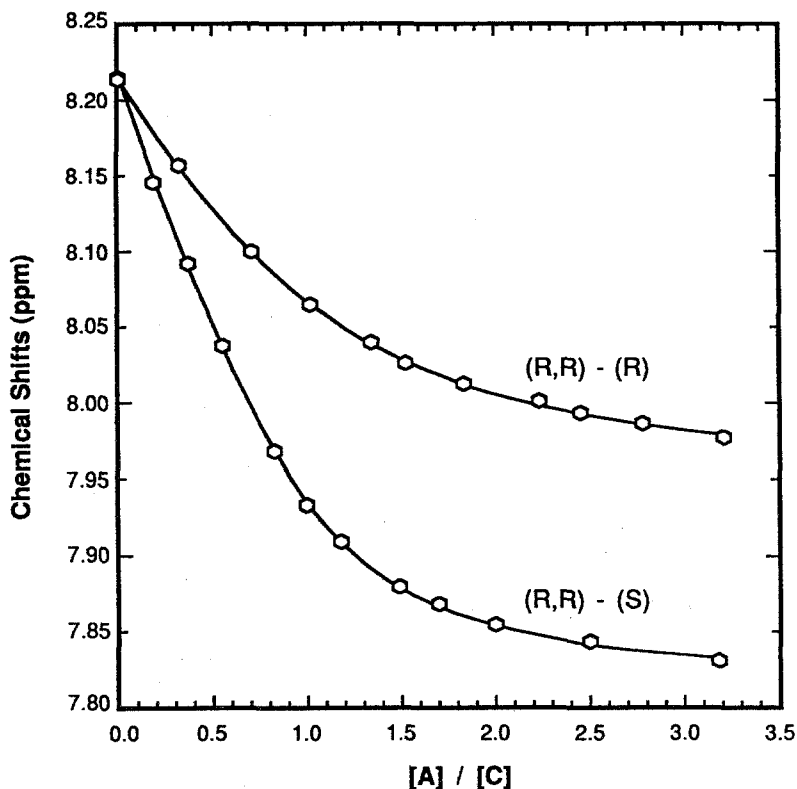
Fig. 3. Observed chemical shifts of the 3,5 protons on the pyridine moiety of (R,R)-dimethyldiketopy-ridino-18-crown-6 (M_2K_2P18C6) in pure CD_3OD at 25°C as a function of the molar ratio, [A]/[C], of the (R) on (S) enantiomer of α-(1-naphthyl)ethylammonium ($NapEt^+$) perchlorate of $NapEt^+$ and M_2K_2P18C6, respectively.

As mentioned earlier, one of the advantages of calorimetry is that the reaction heat is measured directly, and the $\log K$ and ΔH values are obtained simultaneously from a single experiment. Each of the calorimetrically determined $\log K$ and ΔH values listed in Tables I and II is the average of at least three values obtained from parallel experiments at the same conditions. The standard deviation of each $\log K$ or ΔH value is the standard deviation of the parallel values from the average. Each ΔS value is calculated from $\log K$ and ΔH values according to Equation 5, and the standard deviation of each ΔS value is the weighted sum of those of the $\log K$ and ΔH values.

In the case of the NMR method, only a $\log K$ value can be obtained from a single experiment and the ΔH value is calculated from the variation of $\log K$ with temperature according to Equations 3 and 4. Therefore, the standard deviation of each ΔH value is determined by, first, the standard deviation of the $\log K$ values used for the ΔH calculation, second, the number of $\log K - T^{-1}$ data pairs used and the temperature range that these data pairs cover, and third, the validity of the assumption that ΔH is independent of temperature in the temperature range covered. So, the standard deviations of the ΔH values obtained by the NMR

Table I. Log K, ΔH and ΔS values for the interactions of diketopyridino-18-crown-6 (K_2P18C6) with α-phenylethylammonium (PhEt$^+$) perchlorate in different solvents and at different temperatures.

Method	Solvent[a]	Temp.(°C)	Log K	ΔH(kJ/ mol)	ΔS(J/K mol)
NMR	1 : 1M/C(D)	9.0	3.73		
		15.0	3.62		
		25.0	3.33	-44.4[b]	-84.5[b]
		35.0	3.10		
Cal.[c]	1 : 1M/C	25.0	3.42 ± 0.01	-30.5 ± 0.5	-36.8 ± 1.6
NMR	9 : 1M/C(D)	15.0	3.18		
		25.0	2.99		
		35.0	2.76	-37.2[b]	-68.2[b]
		42.0	2.64		
Cal.[c]	9 : 1M/C	25.0	2.96 ± 0.01	-29.2 ± 0.5	-41.3 ± 1.6

[a] 1 : 1M/C(D) = 50%CD$_3$OD–50%CDCl$_3$ (v/v), 1 : 1M/C = 50%CH$_3$OH–50%CHCl$_3$ (v/v), 9 : 1M/C(D) = 90%CD$_3$OD–10%CDCl$_3$ (v/v), and 9 : 1M/C = 90%CH$_3$OH–10%CHCl$_3$ (v/v).
[b] The NMR ΔH values were calculated from the temperature dependence of log K according to the integrated form of the Van 'tHoff equation. The linear correlation coefficients for log K vs. $1/T$ were greater than 0.997.
[c] Cal. = Titration calorimetry.

method are expected to be greater than those of the ΔH values determined by calorimetry. As seen in Figure 4, each of the log K vs. T^{-1} plots is linear, indicating that no visible temperature dependence of ΔH exists. If the temperature dependence of ΔH is ignored, the standard deviation of an NMR ΔH value can be evaluated based on the following equation

$$\delta \Delta H = (2.303 R) \frac{\Sigma |T_{av}^{-1} - T_i^{-1}| \, |\delta \log K_i|}{\Sigma (T_{av}^{-1} - T_i^{-1})^2} \tag{6}$$

where $\delta \log K_i$ = the standard deviation of each log K value.

In evaluating the standard deviation of the NMR log K values, the reproducibility of these values determined for the same system by separate experiments was examined. The log K values obtained from six parallel experiments for K_2P18C6–PhEt$^+$ complexation at 25°C in 50%CD$_3$OD–50%CDCl$_3$ (3.33, 3.31, 3.39, 3.42, 3.40, and 3.36, respectively) were in good agreement with each other, and the standard deviation was ± 0.04. This standard deviation is a little greater than that of a calorimetric log K value which is typically ± 0.01–0.02. In comparison with the calorimetric results, the greater standard deviation of an NMR log K value is expected since the deviations of the sample concentrations are greater due to the use of very small amounts of sample and to the limitation of the balance precision. In addition, the smaller number of data points used for an NMR log K calculation may also increase the standard deviation of the result. The standard deviation of an NMR log K value is also affected by the magnitude of the maximum chemical shift change for the signal of interest induced by the complexation reaction and the standard deviations of the chemical shift values for the same signal at different ammonium salt-crown ether molar ratios. The larger the maximum chemical shift change and the smaller the standard deviation of each

Table II. Log K, ΔH and ΔS values for the interactions of diketopyridino-18-crown-6 (K$_2$P18C6) with α-(-naphthyl)ethylammonium (NapEt$^+$) perchlorate, and of (R,R)- and (S,S)-dimethyldiketopyridino-18-crown-6 (M$_2$K$_2$P18C6) with (R) and (S) enantiomers of NapEt$^+$ClO$_4^-$ at 25.0°C.

Ligand	Cation	Method	Solvent[a]	Log K	ΔH(kJ/mol)	ΔS(J/K mol)
K$_2$P18C6	NapEt	NMR	1:1M/C(D)	3.35		
		Cal.[b]	1:1M/C	3.49 ± 0.01	−29.8 ± 0.5	−33.3 ± 1.5
M$_2$K$_2$P18C6	NapEt					
(RR)	(R)	NMR	CD$_3$OD	2.08		
(SS)	(S)	Cal.[b]	CH$_3$OH	2.06 ± 0.01[c]	−26.4 ± 0.5[c]	−49.8 ± 1.2[c]
(RR)	(S)	NMR	CD$_3$OD	2.50		
(SS)	(R)	Cal.[b]	CH$_3$OH	2.47 ± 0.01[c]	−27.6 ± 0.5[c]	−45.2 ± 1.1[c]

[a] See footnote [a] of Table I.
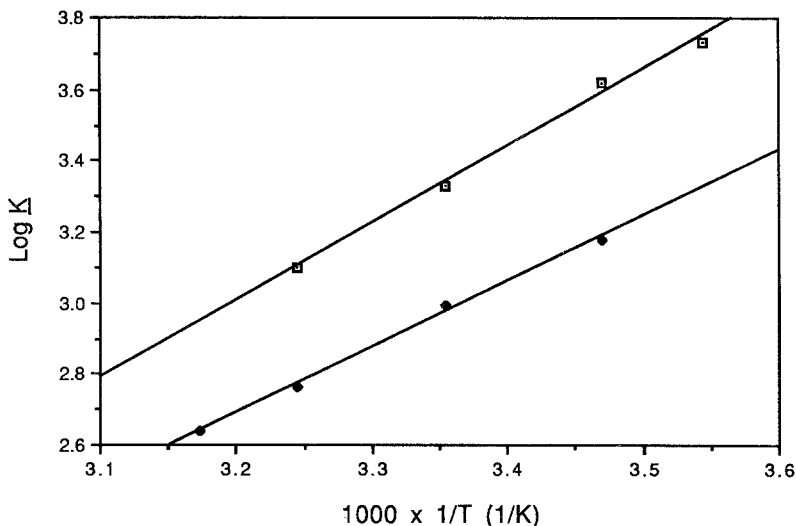[b] See footnote [c] of Table I.
[c] Ref. [30].

Fig. 4. Plot of log K for the interaction of diketopyridino-18-crown-6 with α-(1-naph-thyl)ethylammonium (NapEt$^+$) perchlorate in 50%CD$_3$OD–50%CDCl$_3$ (solid circles) and in 90%CD$_3$OD–10%CDCl$_3$ (solid triangles).

chemical shift value, the smaller the standard deviation of the NMR log K value. Since the maximum chemical shift changes induced by the complexation reactions for all of the systems studied are of a comparable magnitude (0.17–0.35 ppm) and are much greater than the standard deviation of each chemical shift value (0.001 ppm), it is expected that the standard deviations of all of the NMR log K values reported in the present work are similar to that found for the K$_2$P18C6–PhEt$^+$ interaction, i.e., ± 0.04 log K unit.

As mentioned earlier, the standard deviation of an NMR ΔH value is dependent on those of the log K values used. If the standard deviation of each log K value in Table I for the K$_2$P18C6–PhEt$^+$ interaction in 50%CD$_3$OD–50%CDCl$_3$ is taken to be ± 0.04, the standard deviation of the ΔH value will be ± 8.4 kJ/mol according to Equation 6. The standard deviation of ΔS (± 17 J/K mol) is even greater than that of ΔH. It is also interesting to note that the standard deviation of each calculated ΔH value is dependent on the number of log $K-T^{-1}$ data pairs used and the temperature range covered by these data pairs. Calculations based on Equation 6, where ΔH is assumed to be temperature independent, showed that the wider the temperature range, the smaller the standard deviation of the ΔH value. In a given temperature range, the more the number of data pairs, the smaller the standard deviation of the ΔH value.

Since it is difficult to differentiate experimental data accurately, the poor agreement between the NMR and calorimetric ΔH values is not surprising. Even small, random experimental errors in the log K values can lead to large errors in calculating the slope of the curve going through the log K values when plotted versus T^{-1}. The slope of the log K vs. T^{-1} plot is usually evaluated by assuming some functional relationship between log K and T^{-1}. The assumption made about

this functionality influences the answer obtained. In this work, it was assumed that ΔH was constant, hence the slope of $\log K$ versus T^{-1} was constant. This appears to be a reasonable assumption from observation of the data, but if it were assumed that the relationship was quadratic, a different ΔH value would be obtained. The researcher must decide which function is the best. Including too many terms in the function can lead to a curve which is somewhat wavy resulting in unreasonable ΔH values at some temperatures. Inclusion of too few terms does not allow enough temperature dependence in the ΔH term. This problem can be overcome somewhat by taking many $\log K$ values over a wide temperature range and fitting the data to a smooth curve with the fewest possible parameters in the fitting equation. Even with great care the ΔH values obtained from $\log K$ values will not usually be as good as those obtained from calorimetric data.

Our conclusion is that the direct ^{1}H NMR method can produce acceptable $\log K$ values in comparison with those determined by the calorimetric method. However, the ΔH and ΔS values obtained by the NMR method have large standard deviations and care must be taken before discussing any chemical reactions in terms of these values. The standard deviation problem for ΔH and ΔS exists in other indirect methods [20–22] also.

It is important to mention a possible limitation of the ^{1}H NMR method. Since the proton of interest whose signal is used as a probe for the complexation is, in most cases, not directly involved in the bond breaking and forming processes and is far from the reaction center, the proton chemical shift change induced by the complexation reaction is not necessarily proportional to the stability of the complex. The formation of a stable complex may result in only a very small chemical shift change due to the special structural feature of the complex in which the proton of interest remains basically unaffected upon complexation. If this happens, the NMR method will fail to provide the $\log K$ value for the particular system. However, if the formation of a complex does induce a significant chemical shift change for a proton signal of interest, the NMR method will provide a reliable $\log K$ value no matter how far the proton of interest is from the reaction center. The factor that reflects the complex stability is not the maximum chemical shift change induced by the complexation reaction, but the curvature of the chemical shift vs. molar ratio plot (Figures 2 and 3), provided the conditions of fast exchange on the NMR time scale are met, i.e., Equation 1 is valid.

It is seen from Table I that the $\log K$ values for the interactions of K_2P18C6 with PhEt$^+$ in 50%methanol–50%chloroform are greater than those in 90%methanol–10%chloroform at corresponding temperatures, respectively. This is expected since the 50%–50% methanol–chloroform mixture has the smaller solvent polarity and dielectric constant. Both NMR and calorimetric ΔH values for the same interaction in 50%methanol–50%chloroform are more negative than those in 90%methanol–10%chloroform. The calorimetric ΔS value for the same interaction in 50%methanol–50%chloroform is less negative than that in 90%methanol–10%chloroform, but the relative magnitudes of the two NMR ΔS values are reversed. Since the NMR ΔH and ΔS values have much greater standard deviations than the calorimetric values, the poor agreement between the NMR and calorimetric ΔH or ΔS values is not surprising. However, the use of deuterated solvent in the NMR measurements may account for part of this difference. Since the hydrogen on

Table III. Log K, ΔH and ΔS values for the interaction of K_2P18C6 with α-phenylethylammonium perchlorate in 50%–50% (v/v) CH_3OH–$CHCl_3$, CH_3OD–$CDCl_3$, and CD_3OD–$CDCl_3$ at 25.0°C.

Solvent	Method	Log K	ΔH(kJ/mol)	ΔS(J/K mol)
CH_3OH–$CHCl_3$	Cal.[a]	3.42 ± 0.02	-30.5 ± 0.5	-36.8 ± 1
CH_3OD–$CDCl_3$	Cal.[a]	3.42 ± 0.02	-33.2 ± 0.8	-45.9 ± 2
CD_3OD–$CDCl_3$	NMR	3.33 ± 0.04	-44.4[b]	-84.5[b]

[a] See footnote [c] of Table I.
[b] The estimated deviations of the NMR ΔH and ΔS values are ± 8.4 kJ/mol and ± 17 J/K mol, respectively.

the solvent methanol OH group is capable of fast exchange with those on an ammonium cation, the substitution of deuterium for hydrogen on the methanol OH group may affect the interaction of an ammonium cation with a crown ether ligand. In order to evaluate the difference that deuterium substitution on the methanol OH group could make, the calorimetric measurement of log K and ΔH values for the K_2P18C6–$PhEt^+$ interaction in $50\%CH_3OD$–$50\%CDCl_3$ was made and the results are compared with those in $50\%CH_3OH$–$50\%CHCl_3$ (Table III). It is found that the log K values for the reaction in the two solvents are in excellent agreement, while the ΔH and ΔS values are different. The ΔH and ΔS values in $50\%CH_3OD$–$50\%CDCl_3$ are about 2.7 kJ/mol and 9.1 J/K mol more negative than those in $50\%CH_3OH$–$50\%CHCl_3$ (Table III), respectively. Apparently, the substitution of deuterium for the hydrogen on the methanol hydroxy group has an appreciable effect on the interaction of K_2P18C6 with $PhEt^+$. Since the deuterium on the hydroxy group of a deuterated methanol molecule can be involved in a fast exchange with the hydrogens of an ammonium cation [31], this fast exchange will result in deuterium substitution for part or all of the protons in the N^+—H—N or N^+—H—O hydrogen bonds formed between a crown ether ligand and an ammonium cation. The substitution of deuterium for hydrogen in a hydrogen bond was found to increase the bond strength [32]. This is consistent with our observation of a more negative ΔH value for the K_2P18C6–$PhEt^+$ interaction in $50\%CH_3OD$–$50\%CDCl_3$ than that in $50\%CH_3OH$–$50\%CHCl_3$. The substitution of protons from N^+—H—N or N^+—H—O hydrogen bonds by deuterium atoms may be an entropy reducing process, as we observed a more negative ΔS value for the same interaction in $50\%CH_3OD$–$50\%CDCl_3$ than in $50\%CH_3OH$–$50\%CHCl_3$.

The use of methanol–chloroform mixtures as solvents in the present work increases the likelihood of ion-pairing due to the reduced solvent polarity and dielectric constant in comparison with pure methanol. Therefore, care has been taken in the analysis of both the NMR and calorimetric data to look for the possibility of ion-pairing. It was found that the fit of either the NMR or the calorimetric data assuming 1 : 1 complexation for the reactions in the 50%methanol–50%chloroform mixture generally gave larger statistical deviations than in the 90%methanol–10%chloroform mixture. NMR spectra of $PhEt^+ClO_4^-$ in deuterated 50%methanol–50%chloroform showed that the methyl chemical shift changed as the concentration of the salt changed. Since the extent of ion-pairing

depends on the salt concentration, the weighted average of the chemical shifts for the free and ion-paired cations will also depend on the salt concentration. Therefore, the observed chemical shift change as a result of the salt concentration change provided clear evidence for the presence of ion-pairing. A similar phenomenon was not observed in deuterated 90%methanol–10%chloroform. The ion-pairing constant for $PhEt^+ClO_4^-$ (log K_{ip}) in the 50%–50% mixture was found to be 2.08 using a ^1H NMR method similar to the one used for log K determination. The calculation of the ion-pairing constant from the ^1H NMR chemical shift data of the salt as a function of the salt concentration used a basic equation similar to Equation (1)

$$\delta_{ave} = X_f \delta_f + (1 - X_f)\delta_{ip} \tag{7}$$

where δ_{ave} = average chemical shift of the ammonium cation signal of interest, δ_f = chemical shift of the same signal for the free, non ion-paired ammonium cation, and X_f = the mole fraction of free ammonium cation. The δ_f value is known by extrapolating δ_{ave} values at zero salt concentration, where X_f is assumed to be equal to 1.

By incorporating the calculated ion-pairing constant of $PhEt^+ClO_4^-$ into the calculation of log K, the fit of both the NMR and calorimetric data for the 50%–50% mixture was significantly improved, while no significant effect was found for the 10%–90% mixture. This indicates the presence of ion-pairing in the 50%–50% mixture, but not in the 90%–10% mixture. By taking ion-pairing into account, the log K value for the K_2P18C6–$PhEt^+$ interaction and the ion-pairing constant, log K'_{ip} for the (K_2P18C6–$PhEt^+$)–ClO_4^- interaction were calculated. The log K value thus calculated was very close to that calculated assuming 1 : 1 complexation only and the log K'_{ip} value, 2.04, was also very close to that (log K_{ip} = 2.08) for the $PhEt^+$–ClO_4^- interaction. The log K_{ip} and log K'_{ip} values are the same within their expected standard deviations. During the interaction of K_2P18C6 with $PhEt^+$, the contribution from ion-pair dissociation of $PhEt^+ClO_4^-$ is mostly cancelled out by the contribution from ion-pair formation of the complexed ammonium cation with the anion. Therefore, the ion-pairing effect does not affect the observed complexation constant when 1 : 1 complexation is assumed.

Acknowledgement

References

1. F. de Jong and D. N. Reinhoudt: *Adv. Phys. Org. Chem.* **17**, 279 (1980).
2. C. J. Pedersen in *Synthetic Multidentate Macrocyclic Compounds* (R. M. Izatt and J. J. Christensen, eds.); Academic Press, New York (1978).
3. J. D. Lamb, R. M. Izatt, J. J. Christensen, and J. D. Eatough in *Coordination Chemistry of Macrocyclic Compounds* (G. A. Melson, ed.); Plenum Press, New York (1979).
4. J. P. Behr, J. M. Lehn, and P. Vierling: *J. Chem. Soc. Chem. Commun.* 621 (1976).
5. J. A. A. de Boer, D. N. Reinhoudt, S. Harkema, G. J. Van Hummel, and F. de Jong: *J. Am. Chem. Soc.* **104**, 4073 (1982).

6. F. Vogtle, H. Sieger, and W. M. Muler: *Top. Curr. Chem.* **98**, 107 (1981).
7. R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, and J. J. Christensen: *Chem. Rev.* **85**, 271 (1985).
8. R. M. Izatt, K. Pawlak, J. S. Bradshaw, and R. L. Bruening: *Chem. Rev.* in press.
9. C. J. Pedersen: *J. Am. Chem. Soc.* **89**, 2495 (1967).
10. J. J. Christensen, J. Ruckman, D. J. Eatough, and R. M. Izatt: *Thermochim. Acta* **3**, 203 (1972).
11. D. J. Eatough, J. J. Christensen, and R. M. Izatt: *Thermochim. Acta* **3**, 219 (1972).
12. J. J. Christensen, D. P. Wrathall, J. L. Oscarson, and R. M. Izatt: *Anal. Chem.* **40**, 1713 (1968).
13. H. K. Frensdorf: *J. Am. Chem. Soc.* **93**, 606 (1971).
14. T. Yamabe, K. Hori, and K. Akagi: *Tetrahedron* **35**, 1065 (1979).
15. M. Shamsipur, G. Rounaghi, and A. I. Popov: *J. Solution Chem.* **9**, 701 (1980).
16. C. Erk: *J. Mol. Liquids* **40**, 143 (1989).
17. F. de Jong, D. N. Reinhoudt, C. J. Smit, and R. Hius: *Tetrahedron Lett.* 4783 (1976).
18. J. A. A. de Boer and D. N. Reinhoudt: *J. Am. Chem. Soc.* **107**, 5347 (1985).
19. H. S. Gold and M. R. Rice: *Anal. Data* **29**, 637 (1982).
20. F. Wada, Y. Wada, K. Kikukawa, and H. Matsuda: *Bull. Chem. Soc. Jpn.* **54**, 458 (1981).
21. H. Shizuka, K. Kameta, and T. Shinozaki: *J. Am. Chem. Soc.* **107**, 3956 (1985).
22. R. A. Alberty, R. M. Smith, and R. M. Bock: *J. Biol. Chem.* **193**, 425 (1951).
23. R. M. Izatt, D. P. Nelson, J. H. Rytting, B. L. Haymore, and J. J. Christensen: *J. Am. Chem. Soc.* **93**, 1619 (1971).
24. R. M. Izatt, H. D. Johnston, and J. J. Christensen: *J. Chem. Soc. Dalton Trans* 1152 (1972).
25. J. S. Bradshaw, P. Huszthy, C. W. McDaniel, C. Y. Zhu, N. K. Dalley, R. M. Izatt, and S. Lifson: *J. Org. Chem.* **55**, 3129 (1990).
26. R. M. Izatt, J. D. Lamb, R. E. Asay, G. E. Maas, J. S. Bradshaw, J. J. Christensen, and S. S. Moore: *J. Am. Chem. Soc.* **99**, 6134 (1977).
27. B. A. Jones, J. S. Bradshaw, and R. M. Izatt: *J. Heterocycl. Chem.* **19**, 551 (1982).
28. C. Y. Zhu, R. M. Izatt, J. S. Bradshaw, and N. K. Dalley: *J. Incl. Phenom.* in press.
29. R. M. Izatt, J. D. Lamb, N. E. Izatt, B. E. Rossiter, Jr., J. J. Christensen, and B. H. Haymore: *J. Am. Chem. Soc.* **101**, 6273 (1979).
30. R. B. Davidson, J. S. Bradshaw, B. A. Jones, N. K. Dalley, J. J. Christensen, and R. M. Izatt: *J. Org. Chem.* **49**, 353 (1984).
31. J. W. Akitt: in *Multinuclear NMR* (J. Mason, ed.); Plenum Press, New York (1987).
32. H. Wolff: in *The Hydrogen Bond* (P. Schuster, G. Zundel, and C. Sandorfy, eds.); North-Holland Publishing Company, Amsterdam (1976).