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Gibbs Free Energies of Transfer of Cryptand (2,2,2) and Ag(2,2,2)ClO_4 from Water to Acetonitrile–Water Mixtures

B. G. Cox,[†] **C. Guminski,**[‡] **and H. Schneider***

Contribution from the Department of Chemistry, University of Stirling, Stirling, FK9 4LA Scotland, Institute of Fundamental Problems of Chemistry, University of Warsaw, Warsaw, Poland, and Max-Planck-Institut für Biophysikalische Chemie, D-3400 Göttingen, West Germany. *Received June 22, 1981*

Abstract: The stability constants (log K_s) of the cryptate salt Ag(2,2,2)ClO_4 have been determined by pH and pAg measurements in acetonitrile (AN)–water mixtures at 25 °C. There is an abrupt decrease in log K_s when acetonitrile is added to water as might be expected from the preferential solvation of Ag^+ in the mixture. However, it is shown by comparison of Gibbs free energies of transfer, ΔG_{tr}, of $AgClO_4$, (2,2,2), and Ag(2,2,2)ClO_4 in the mixtures that although the solvation of Ag^+ is an important factor, its effect is partially cancelled by ΔG_{tr} values of (2,2,2), which increase with increasing mol fraction $\chi_{AN} > 0.2$, and those of Ag(2,2,2)ClO_4 which decrease with increasing x_{AN}. The Gibbs free energies of transfer of Ag(2,2,2)ClO_4, which have been determined directly from solubility measurements, show that the stability of the cryptate ion Ag(2,2,2)$^+$ is decreased on addition of acetonitrile to water.

A variety of thermodynamic and extrathermodynamic studies suggest strongly that alkali-metal ions are more strongly solvated in water than in acetonitrile (AN), which means that the ionic Gibbs free energies of transfer are positive for transfer from water to acetonitrile.[1,2] The silver ion, to the contrary, interacts more strongly with acetonitrile, mainly because of the partially covalent bonding between Ag^+ and one or two acetonitrile molecules.[3,4] Mixtures of acetonitrile and water have been used frequently in order to study the preferential solvation of ions by various methods,[5–7] and the results confirm a behavior consistent with the solvation energies of the ions in the pure solvents.

The macrocyclic and macropolycyclic ligands which either partially or completely envelope cations on complexation offer a further possibility to study ionic solvation.[8–11] In particular cryptands,[12] which are macrobicyclic diaza polyethers with a three-dimensional cavity, should be very suitable for such studies. Magnetic resonance experiments on the nuclei of encapsulated cations (cryptates) showed a zero or insignificant dependence of the resonance frequencies on the solvent involved[13,14] and suggest a complete shielding of the ions from the solvent by the ligand. However, the Gibbs free energies of transfer of alkali-metal cryptate complexes between pure solvents are by no means constant and in general are characterized by values typical for large organic ions.[10,15] In addition there are specific interactions of cryptates with the medium which depend not only on the solvent but also on the nature of the encapsulated ion,[16] particularly with respect to the size of the ion in relation to that of the cavity of the ligand and the mode of interaction between the cation and ligand binding sites.[17,18]

In this paper we present results on the solvation of cryptand (2,2,2)—$N\{(CH_2CH_2O)_2CH_2CH_2\}_3N$—and of the perchlorates of K^+, Ag^+, and Ag(2,2,2)$^+$ in mixtures of water and acetonitrile. The Gibbs free energies of transfer of the cryptand molecule itself from water change from negative to positive around $\chi_{AN} = 0.65$, probably a result of the strong hydration of the ligand donor atoms, particularly the nitrogen atoms with their electron lone pairs in an exo conformation.[12] On complexation, the strongly negative Gibbs transfer free energies of $AgClO_4$ are reduced by a factor of approximately $^2/_3$ to give the values for the complex salt Ag(2,2,2)ClO_4. In the water–acetonitrile mixtures the selective solvation of Ag^+ is largely removed when the ion is enveloped in an organic sheath by the ligand, but both the free cryptand and the cryptate ion interact specifically with the different solvent components.

Experimental Section

Materials. Acetonitrile (Merck Uvasol) was used as purchased, since the water content was always less than 100 ppm, as determined by Karl Fischer titration, and experiments with freshly distilled AN showed the same results. The mixtures of water and AN were prepared by volume. The cryptand (2,2,2) (Merck) was used as purchased, since its purity was tested in the course of pK_a and pK_s determinations and found to be sufficient. $KClO_4$ (Merck p.a.) was recrystallized from water and dried in vacuo over P_2O_5 at 50 °C for 20 h. Tetraethylammonium picrate was the same as used in ref 19.

Solubility Determination of $KClO_4$ and Ag(2,2,2)ClO_4 in the Water–Acetonitrile System at 25 °C. An Ingold p*K* 201-K7 K^+ ion-sensitive glass electrode was used for the determination of the solubility product of $KClO_4$. The electrode response was pracitically Nernstian (±1 mV), and the potentials were stable after 10 min and reproducible to ±1 mV. A silver wire in a 0.10 M $AgNO_3$ solution served as reference electrode, and the salt bridge was filled with a 0.1 M tetraethylammonium picrate solution. The arrangement was similar to that used before,[9] and the solvent composition was the same in all three compartments of the cell.

The solubilities of solid Ag(2,2,2)ClO_4 were determined in at least two solutions of given mole fraction with different concentrations of $AgClO_4$ in order to prevent protonation of the cryptand. Crystalline Ag(2,2,2)ClO_4 was prepared from solutions of (2,2,2) and $AgClO_4$ in dried ace-

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[†] University of Stirling.

[‡] University of Warsaw.

* Max-Planck-Institut für Biophysikalische Chemie.

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Table I. Solubility Products (pK_{sp} = −log K_{sp}) and Gibbs Free Energies of Transfer of $KClO_4$ and Ag(222)ClO_4 in the Water–Acetonitrile System at 25 °C

$x_{AN} = 1 - x_{H_2O}$	pK_{sp}($KClO_4$)	pK_{sp}(Ag(2,2,2)ClO_4)	ΔG_{tr}($KClO_4$), kJ mol^{-1}	ΔG_{tr}(Ag(2,2,2)ClO_4), kJ mol^{-1}
0.0	1.95 ± 0.03, 1.94[a]	4.56 ± 0.03	0.00	0.0
0.05	1.88 ± 0.03	3.83 ± 0.02	−0.40	−4.2 ± 0.1
0.1	1.73 ± 0.03	3.26 ± 0.06	−1.26	−7.4 ± 0.3
0.2	1.65 ± 0.03	2.64 ± 0.03	−1.71	−11.0 ± 0.2
0.3	1.70 ± 0.03	2.39 ± 0.02	−1.43	−12.4 ± 0.1
0.4			−0.91[e]	
0.5	1.94 ± 0.03	2.43 ± 0.02	−0.06	−13.2 ± 0.1
0.6			+1.54[e]	
0.7	2.57 ± 0.03	2.34 ± 0.04	+3.54	−12.7 ± 0.2
0.8			+5.77[e]	
0.9	3.48 ± 0.04, 3.40[b]	2.59 ± 0.02	+8.74	−11.3 ± 0.1
0.95	3.86 ± 0.04, 3.71[b]	2.74 ± 0.02	+10.92	−10.4 ± 0.1
1.00	4.18 ± 0.05, 4.21[b]	2.84 ± 0.02	+12.72	−9.8 ± 0.1

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tonitrile. The concentration of Ag(2,2,2)$^+$ in saturated solution was determined by pAg titrations with 0.1 M HCl (Ag(2,2,2)$^+$ + 2H$^+$ + 2Cl$^-$ → AgCl↓ + (2,2,2)H_2^{2+} + Cl$^-$). These values, in conjunction with the known original concentrations of $AgClO_4$ and (2,2,2), were used to calculate the solubilities of Ag(2,2,2)ClO_4.

For both $KClO_4$ and Ag(2,2,2)ClO_4 the solubility products, K_{sp}, corrected to infinite dilution in the mixture concerned, were calculated from the experimental concentrations of saturated solution and mean ionic activity coefficients calculated from the Davies equation.[20]

Stability Constant Measurements. The stability constant, K_s, for Ag(2,2,2)$^+$ (eq 1) was measured by the simultaneous determination of

$$K_s = [\mathrm{Ag}(2,2,2)^+]/[\mathrm{Ag}^+][2,2,2] \tag{1}$$

pH and pAg metric titration curves, when a 5.25 × 10^{-3} M (2,2,2) solution was added to a 2.25 × 10^{-3} M $AgClO_4$ solution. The ionic strength was held constant at 0.1 M with Et_4NClO_4. Since in aqueous solution the ligand may exist in both singly and doubly protonated forms,[17,21] the acid–base equilibria, eq 2 and 3, also have to be taken into

$$(2,2,2)\mathrm{H_2}^{2+} \overset{K_1}{\rightleftharpoons} \mathrm{H}^+ + (2,2,2)\mathrm{H}^+ \tag{2}$$

$$(2,2,2)\mathrm{H}^+ \overset{K_2}{\rightleftharpoons} \mathrm{H}^+ + (2,2,2) \tag{3}$$

account together with the ionic product K_w of water.[19] [Ag$^+$] and [H$^+$] represent the actual equilibrium concentrations of the silver ion and the proton, as calculated from the measured electrode potentials, and K_S was obtained by using eq 4. In eq 4 C_{AG} and $C_{2,2,2}$ represent the total

$$K_s = \frac{C_{\mathrm{Ag}} - [\mathrm{Ag}^+]}{[\mathrm{Ag}^+]\dfrac{C_{2,2,2} - C_{\mathrm{Ag}} + [\mathrm{Ag}^+] + [\mathrm{H}^+] - K_w/[\mathrm{H}^+]\gamma_+^2}{1 - [\mathrm{H}^+]^2\gamma_+^2/(K_1K_2\gamma_{2+})}} \tag{4}$$

concentrations of silver salt and ligand, respectively. K_s values determined from eq 4 are assumed to be identical with the thermodynamic stability constant, with the unknown activity of (2,2,2) being taken to be unity and a single ion activity coefficient, γ_+, being used for all univalent cations including the proton and the monoprotonated ligand. γ_+ and the activity coefficient γ_{2+} of (2,2,2)H_2^{2+} have been calculated from the Davies equation.[20]

Results

The solubility products, K_{sp}, of $KClO_4$ and Ag(2,2,2)ClO_4 in Table I were used to calculate (eq 5) the Gibbs free energies of

$$\Delta G_{tr} = -RT \ln [K_{sp}(\mathrm{S})/K_{sp}(\mathrm{H_2O})] \tag{5}$$

transfer, ΔG_{tr}, of the salts between water and acetonitrile mixtures or acetonitrile (S). However, the solubility of $AgClO_4$, which is also required for calculations further on, is much too high in the solvent system studied to enable a direct experimental determination in a manner analogous to that used, for example, for $KClO_4$. The $AgClO_4$ values have been determined indirectly by using recently published transfer free energy data[7] for KX and AgX, with X$^-$ = Br$^-$ and I$^-$, in the water–acetonitrile system. The data were obtained from the solubilities of the silver salts and from emf measurements of galvanic cells with a K$^+$-sensitive glass electrode and a Ag/AgX, X$^-$ electrode. We were able to perform measurements in mixtures containing up to 85 vol % of acetonitrile, and solubility data for all of the salts are also available in pure acetonitrile. The effect of the anion has been eliminated by plotting the difference ΔG_{tr}(Ag$^+$–K$^+$) = ΔG_{tr}(AgX) − ΔG_{tr}(KX), with X = Br and I, vs. the volume fraction of the mixtures. As the data for the two anions are in good agreement, a mean curve for all of the data has been drawn, which could be interpolated in a smooth and monotonic manner between 85 vol % and pure acetonitrile. An alternative plot using a mole fraction scale requires a much longer interpolation (0.6 ≤ x_{AN} ≤ 1.0) and seems therefore to be more uncertain. In this paper ΔG_{tr}(Ag$^+$–K$^+$) values taken from the volume fraction plot have been transformed to the mole fraction scale and are reported in Table II. ΔG_{tr} data are also available for AgCl, $AgBPh_4$[22] and KCl, $KBPh_4$[7] in the solvent mixtures but have not been used because a combination of these data from two different laboratories leads to values differing from those of Br$^-$ and I$^-$.

Table II. Stability Constants (log K_S) for Ag(2,2,2)ClO_4 and Gibbs Free Energies of Transfer of $AgClO_4$ and (2,2,2) in the Water–Acetonitrile System at 25 °C

x_{AN} = 1 − x_{H_2O}	ΔG_{tr}-(Ag$^+$–K$^+$), kJ mol^{-1}	ΔG_{tr}-($AgClO_4$), kJ mol^{-1}	log K_S	ΔG_{tr}-(2,2,2), kJ mol^{-1}
0.0	0.0	0.0	9.53 ± 0.12	0.0
0.05	-7.3_2	-7.7_2	8.55 ± 0.07	−2.1 ± 0.4
0.1	−10.9	−12.2	8.21 ± 0.04	−2.8 ± 0.5
0.2	−14.6	−16.3	8.03 ± 0.06	−3.3 ± 0.5
0.3	−16.7	−18.1	8.03 ± 0.06	−2.9 ± 0.4
0.4	−18.4	−19.3	8.08[a]	
0.5	−19.9	−20.0	8.15 ± 0.05	−1.1 ± 0.3
0.6	−21.6	−20.1	8.22[a]	
0.7	−23.4	−19.9	8.30 ± 0.07	+0.2 ± 0.6
0.8	−25.3	−19.5	8.45[a]	
0.9	−27.4	−18.7	8.75 ± 0.07	+3.0 ± 0.4
0.95	−28.9	−18.0	8.87 ± 0.07	+3.8 ± 0.4
1.0	−30.5	−17.8	8.99 ± 0.07	+4.9 ± 0.5

[a] Interpolated values.

Scheme I

$$\begin{tikzcd}
\mathrm{H_2O:}\ \mathrm{Ag}^+ \arrow[d, "\Delta G_{tr}(\mathrm{Ag}^+)"] & + & (2,2,2) \arrow[d, "\Delta G_{tr}(2,2,2)"] \arrow[r, "\Delta G(\mathrm{H_2O}) = -RT \ln K_s(\mathrm{H_2O})"] & \mathrm{Ag}(2,2,2)^+ \arrow[d, "\Delta G_{tr}(\mathrm{Ag}(2,2,2)^+)"] \\
\mathrm{S:}\ \mathrm{Ag}^+ & + & (2,2,2) \arrow[r, "\Delta G(\mathrm{S}) = -RT \ln K_s(\mathrm{S})"'] & \mathrm{Ag}(2,2,2)^+
\end{tikzcd}$$

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The cycle shown in Scheme I has been used to establish a relationship (eq 6) between the Gibbs free energies of transfer

$$\Delta G_{tr}(2,2,2) = \Delta G_{tr}(Ag(2,2,2)^+ClO_4^-) - \Delta G_{tr}(AgClO_4) + RT \ln [K_s(S)/K_s(H_2O)] \quad (6)$$

of the species involved in the complexation equilibrium (eq 1) and the stability constants K_s in H_2O and S. The transfer free energies of (2,2,2) have been calculated from eq 6 and are also listed in Table II.

In the following discussion, the Gibbs free energies of transfer of $Ag(2,2,2)ClO_4$ and $AgClO_4$ have been used rather than estimated single ion values of ΔG_{tr} for Ag^+ and $Ag(2,2,2)^+$. This is because ClO_4^- is an inert anion with insignificant specific solvation[2] and the use of whole electrolyte values avoids the necessity of deciding between the various extrathermodynamic assumptions used to determine $\Delta G_{tr}(Ag^+)$ as a function of $\chi_{AN} = 1 - x_{H_2O}$.[3,6,22,23] All determinations give negative values for $\Delta G_{tr}(Ag^+)$ as expected but differ significantly in magnitude.

Discussion

The cryptand (2,2,2) is a rigid ligand which discriminates strongly between cations in cryptate formation and within the alkali-metal cations displays peak selectivity toward K^+. This cation fits optimally in the cavity of the ligand which has an estimated mean cavity diameter of 2.8 Å.[12] The ionic radius of Ag^+ ($r_{Ag^+} = 1.26$ Å) is very close to that of K^+ ($r_{K^+} = 1.33$ Å),[24] but in water the stability constant of $Ag(2,2,2)^+$ ($\log K_s = 9.6$[17]) is 4 orders of magnitude larger than that of $K(2,2,2)^+$ ($\log K_s = 5.58$[18]). This is despite the fact that the hydration energy of Ag^+ is much larger than that of K^+,[25,26] from which an opposite trend would be expected. Thus the difference in magnitude of the log K_s values depends mainly upon differences in the interaction of these cations with the binding sites of the cryptand. In addition to the charge–dipole type of interaction between the cations and the oxygen and nitrogen atoms of (2,2,2), Ag^+ has a much stronger and partially covalent interaction with the nitrogen lone pairs than does K^+. This interaction shows up as a considerably shortened Ag^+–nitrogen distance.[12,27]

In acetonitrile, however, the order of complex stability is reversed. The stability constant of $Ag(2,2,2)^+$ in acetonitrile ($\log K_s = 8.99$) is more than 2 orders of magnitude smaller than that of $K(2,2,2)^+$ ($\log K_s = 11.3$[15]). This large change depends mainly upon the different solvation behavior of the ions in the two solvents, as K^+ is more strongly solvated by water than by acetonitrile ($\Delta G_{tr}(H_2O \rightarrow AN) = 7.9$ kJ mol^{-1}),[2] whereas the preferential solvation of Ag^+ by acetonitrile ($\Delta G_{tr}(H_2O \rightarrow AN) = -21.8$ kJ mol^{-1})[2] is so marked that the existence of a linear complex of Ag^+ with two acetonitrile molecules has been confirmed by various methods,[3-5,28,29] even in dilute aqueous solutions of acetonitrile. The net result is a difference of some 30 kJ mol^{-1} in the free energies of transfer of the two ions between water and acetonitrile. The competition between the interactions of the nitrogen lone pairs of acetonitrile and (2,2,2) is predominantly responsible for the lower stability of $Ag(2,2,2)^+$ in acetonitrile than in water and its lower stability compared to that of $K(2,2,2)^+$ in acetonitrile.

To date we have not considered interactions of either the free cryptand (2,2,2) or the cryptate complex itself with the solvent, and the energies of any conformational changes in the various species have also been neglected. In order to gain more information on the role of the solvent in the formation of cryptate complexes, we have studied the stabilities of $Ag(2,2,2)^+$ in mixtures of acetonitrile and water, in which preferential solvation of uncomplexed Ag^+ by acetonitrile is particularly marked. This solvation may be seen in the variation of the Gibbs free energy of transfer of $AgClO_4$ with the mole fraction of acetonitrile (Table II). The abrupt decrease in $\Delta G_{tr}(AgClO_4)$ on addition of acetonitrile to water (Figure 1) is a measure of the strength of the solvation of Ag^+ by acetonitrile. The contribution of ClO_4^- to $\Delta G_{tr}(AgClO_4)$ is small compared with that of Ag^+ and shows up in Figure 1 as a small increase in ΔG_{tr} as x_{AN} approaches 1.

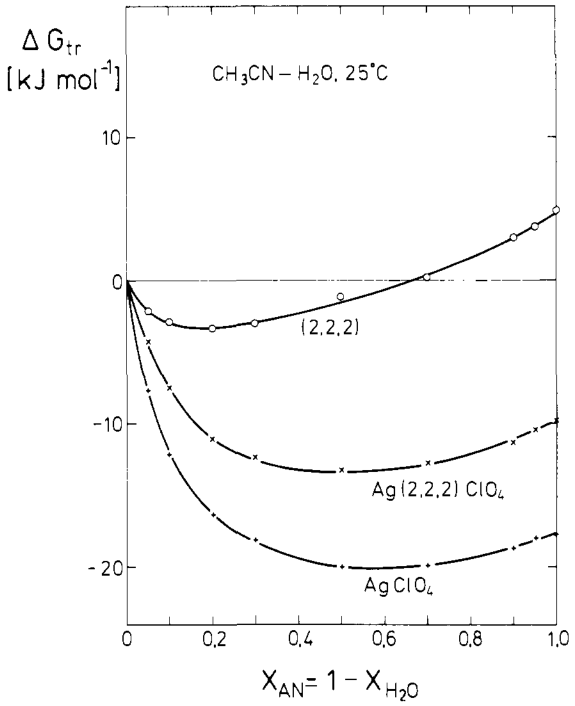

Figure 1. Gibbs free energy of transfer (ΔG_{tr}) of $AgClO_4$, (2,2,2), and $Ag(2,2,2)ClO_4$ from water to mixtures of water and acetonitrile at 25 °C.

The decrease of the transfer free energy of (2,2,2) on addition of acetonitrile to water (Table II, Figure 1) and the increase of $\Delta G_{tr}(2,2,2)$ at higher mole fractions may follow from a competition of a more favorable solvation of the ether groups by acetonitrile and a specific hydration of the nitrogen atoms. Solutions of (2,2,2) in water are very basic with pH values around 11, depending on the concentration of (2,2,2), and the present data show that the unprotonated (2,2,2) molecule is also strongly hydrated. At higher mole fractions of acetonitrile the interaction of (2,2,2) with water is reduced and is replaced by a weaker interaction with acetonitrile. Although the interaction with water presumably involves all donor atoms of the ligand, a detailed interpretation requires information on the conformations of (2,2,2) prevailing in solution. These results are considered in more detail along with a ^1H NMR study of the chemical shifts of the various protons of (2,2,2) in the free and complexed state.[30]

In the complex, where Ag^+ is enveloped by the cryptand, the organic sheath of the ligand separates the ion from the solvent and prevents the specific solvation of Ag^+ by acetonitrile. The metal ion is thus transformed into a large organic cation with reduced charge–solvent dipole interactions. These interactions as estimated by the Born equation,[31] using an cryptate radius of 5.40 Å, change only insignificantly on transfer from water to acetonitrile. However, although complexation by the cryptand reduces the $\Delta G_{tr}(AgClO_4)$ values, the free energy of transfer of the corresponding cryptate salt is still negative and, in particular, decreases quite sharply with x_{AN} in the initial stages (Figure 1). That this is not due to any residual specific interaction between the cryptated Ag^+ itself and acetonitrile is confirmed by a qualitatively similar behavior of $K(2,2,2)^+$.[30] In fact the behavior

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is similar to that of other typical "organic" cations and, for example, the Gibbs free energy difference between water and acetonitrile, $\Delta G_{tr} = -9.8$ kJ mol^{-1}, of Ag(2,2,2)ClO_4 is comparable to that of Et_4NClO_4 ($\Delta G_{tr} = -4.2$ kJ mol^{-1}).[2] It is also noticeable that there is a minimum in ΔG_{tr} for Ag(2,2,2)ClO_4 around $x_{AN} = 0.6$, which presumably can be attributed to a slight preferential hydration of ClO_4^- as mentioned for $\Delta G_{tr}(AgClO_4)$, as the increase in ΔG_{tr}(Ag(2,2,2)ClO_4) on going from $x_{AN} = 0.5$ to pure acetonitrile is as large as that for $AgClO_4$. An extension of these studies to other cations and cryptands may lead to a more detailed explanation of the behavior of cryptates in solution.

Registry No. Ag(2,2,2)ClO_4, 80434-44-2; $KClO_4$, 7778-74-7; $AgClO_4$, 7783-93-9; (2,2,2), 23978-09-8.

Kinetic and Thermodynamic Control in Group Transfer Reactions

Joseph R. Murdoch* and Douglas E. Magnoli

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received April 10, 1980*

Abstract: The concept of kinetic and thermodynamic control is basic to an understanding of chemical reactivity. In the present paper, a theory of nuclear substitution, developed in other work, is used to show that under certain conditions kinetic and thermodynamic factors can be rigorously separated for group transfer reactions (A–B + C → A + B–C). These factors can be evaluated from $\Delta E°$ for the overall reaction and from the barriers of two related "identity" reactions (A–B + A → A + B–A and C–B + C → C + B–C). For large values of $\Delta E°$, no rigorous separation is yet possible. However, using the virial theorem and the fact that the kinetic energy can be decomposed into orbital contributions, it is shown for proton-transfer reactions that the total energy expression at *stationary points* on the A–H–C potential surface (e.g., reactants, transition states, products) can be divided into two terms. In the limit of reactants (or products), one term reduces to the total energy of A–H (or A) and the other term corresponds to the total energy of C (or H–C). At other stationary points (viz., a transition state), it is shown that the two terms have altered values, but *no new terms are necessary to describe the interaction between the reacting molecules*. This convenient property is used to derive a simple empirical equation for the barrier of a group transfer reaction which takes the interplay of kinetic and thermodynamic factors into account. The general equation allows $\Delta E^{\ddagger}$ to approach $\Delta E°$ for sufficiently large, positive values of $\Delta E°$ (either finite or infinite), and special cases of the general expression can account for the SCF barriers of certain proton-transfer reactions to within 0.4 kcal over a range for $\Delta E°$ of 108 kcal.

The fact that rates and equilibria for chemical reactions often respond in similar fashion to changes in substituents has attracted considerable attention over the years. In the past, this connection has been approached from many different angles, and before introducing a new treatment, it would be instructive to examine some common elements which have emerged.

I. Introduction

A. Thermodynamic Factor—The Bronsted Relationship. In a large number of cases, a change in substituent which makes the reaction less favorable thermodynamically will also make the reaction proceed to equilibrium at a slower rate. This idea has a certain appeal and forms the basis for extensive theoretical and experimental work by a number of workers, including Bronsted,[1] Bell,[2] Evans and Polanyi,[3] Hammond,[4] Leffler,[5] Eigen,[6] and many others.[7]

At the transition state, it is commonly expected that the structural changes connecting reactants and products are at some intermediate stage of completion. Leffler[5] showed how this idea could lead to the quantitative form of Bronsted's catalysis law

$$\log k = \alpha \log K_{eq} + C \qquad (1)$$

The central theme of Leffler's proposal is that if a substituent change destabilizes the products relative to the reactants, then some of this destabilization should carry over into the transition state since the transition state bears a partial, structural resemblance to the products. One implication of this hypothesis is that as a transition state approaches the products in structure, the destabilization of the transition state should approach the destabilization of the products, and α should approach unity.[7] The parameter α is regarded as a measure of the relative sensitivities of the transition state and the products to structural perturbations.[6,7] Equation 1 provides quantitative substance to the prevalent belief that the barrier of a reaction is dependent, in part, on the thermodynamics of the reaction. This dependence could be thought of as the thermodynamic component of the barrier.

B. Kinetic Factor. (1) Kinetic Acidity vs. Thermodynamic Acidity. Even though relationships such as the Bronsted equation (eq 1) tend to focus attention on the thermodynamic factor, it is widely recognized that other considerations are important as well. A simple example involves the deprotonation of a 2-methylcyclohexanone derivative by tritryllithium.[8] Proton abstraction from the less hindered side is faster and results in initial formation of II, which slowly rearranges to the more stable enolate I. Similar "paradoxes" of the less stable product forming faster than the more stable product are well-known.[9]

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