intermolecular contacts. It can be seen in the *ac* projection of the structure, Figure 3, that $\alpha_1{}^1$ lies along the mean projection of a set of bent C—H··O contacts. $\alpha_2{}^1$ lies along the mean direction of a set of linear C-H···O contacts. Perhaps significantly, this $\alpha_1{}^{\mathrm{L}}$-$\alpha_2{}^{\mathrm{I}}$ plane also lies approximately normal to a network of Cl···Cl intermolecular contacts.

One explanation for the two-dimensional nature of the contraction below the transition is that when the molecules become ionic, the lattice tends to contract because of the attractive Coulomb forces now present. However, in the direction of α_3, an array of already close Cl··Cl intermolecular contacts prevents contraction, thereby limiting molecular movement to the plane perpendicular to α_3 (α_1-α_2, *ac*).

Another, and more probable, model is that when the molecules become ionic, the C-H groups of TTF^+ become slightly activated, while at the same time the oxygen atoms on the chloranil anion become more negative. This should lead to an increase in the strength of the C-H··O interaction and bring about a contraction in the plane defined by the C-H··O network. The fact that the observed contraction in this plane is large is evidence that these C-H··O interactions are significant in the ionic phase of TTF-chloranil and are responsible for the structural phase transition that accompanies the neutral-ionic transition.

The issue of C-H··O hydrogen bonding is controversial. However, investigators[12] are becoming increasingly less reluctant to postulate its existence in those materials in which the C-H group is activated in some way. The C-H bonds are certainly activated in the ionic phase of TTF-chloranil, and the neutral-ionic transition offers a unique opportunity to examine the phenomenon. Whether or not C-H··O interactions are strong enough to properly be termed hydrogen bonding, it is clear that they are common and perhaps a structural-determining feature in some materials. TTF-chloranil is a particularly clear example of this and, in fact, the sudden strengthening of these interactions induced by the neutral-ionic transition appears to be responsible for the structural distortion at 84 K.

In summary, what we have been able to show solely from powder-diffraction data is that (1) a structural phase transition accompanies the neutral-ionic electronic phase transition and (2) molecular movement at the transition is limited to a plane defined by a network of C-H··O intermolecular contacts. This brings up the possibility that the contraction of the lattice below 84 K is caused by the onset of what, at best, is usually considered to be weak hydrogen bonding.

Acknowledgment. We thank Dr. J. Pannetier of the Institute Laue-Langevin for helpful discussions. P.B. is grateful to IBM for an IBM World-Trade Postdoctoral Fellowship.

---

(12) D. J. Sutor, *J. Chem. Soc.*, 1105 (1963); D. Schomberg, *J. Am. Chem. Soc.*, **102**, 1055 (1980); W. S. Sheldrick, *J. Chem. Soc., Dalton Trans.*, 943 (1975).

Kinetics of Lithium(+) and Calcium(2+) Complexation by 211 Cryptand Using a Stopped-Flow Calorimeter

Gerard W. Liesegang

National Heart, Lung, and Blood Institute
National Institutes of Health
Laboratory of Technical Development
Bethesda, Maryland 20205

Received July 15, 1980

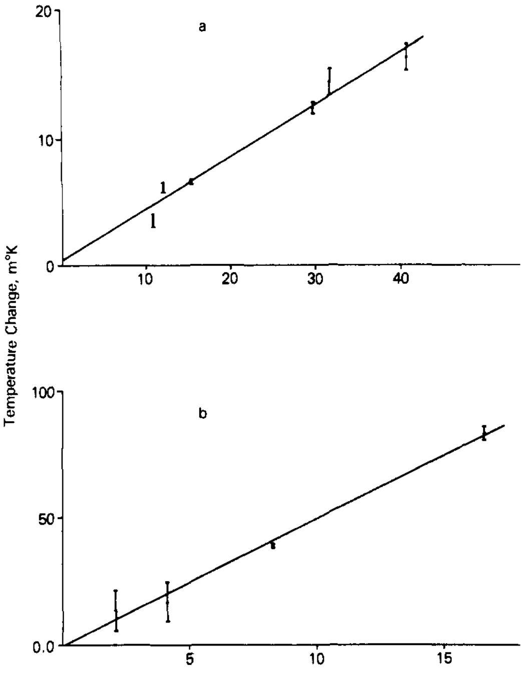


Figure 1. Plot of overall temperature change vs. product concentration for (a) Ca^{2+}-211 and (b) Li^+-211. The straight line is a linear least-squares fit of the experimental data points. The vertical length of the data points corresponds to the precision of the data.

Synthetic multidentate ligands are employed in numerous chemical applications.[1] Two prominent features of these macrocyclic ligands are abilities to selectively complex metal ions[1b] and act as phase-transfer agents.[1c] Upon these basic properties several laboratories have "tailor-made" multidentate molecules which selectively bind organic and bioorganic ions.[2] In a continuing effort to elucidate the mechanism by which these multidentate ligands complex ions, a number of kinetic techniques have been employed. However, the general problem posed, to a kineticist, is finding a suitable probe to monitor the reactions. In a number of these kinetic investigations metal ion or pH indicators have been used. Though effective, the use of an indicator is a competitive technique and hence susceptible to a number of complications. This note discusses the application of a recently developed rapid thermal stopped-flow (TSF) system[3] to monitor the progress of ion complexation reactions. This stopped-flow system is unique in its ability to monitor the intrinsic heats of reaction, thereby allowing measurements not only of rate constants but also of enthalpy changes, ΔH, of the individual reaction steps. The dead time of the apparatus is 10 ms, with a detection sensitivity of 2 mK.

The binding of lithium(+) and calcium(2+) ions to the cryptand 211 (4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]eicosane)[4] was investigated in aqueous media at 25.0 °C. The solutions were buffered at pH 11.4 (piperidine-hydrochloric acid buffer system) where effects from the acid-catalyzed decomplexation are minimal and a high precentage concentration of the cryptand is in the unprotonated form.[5] The ionic strength was maintained (with

---

(1) (a) C. J. Pederson and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); (b) J. M. Lehn, *Struct. Bonding (Berlin)*, **16**, 1 (1973); (c) G. W. Gokel and H. D. Hurst, *Aldrichim. Acta*, **9**, 3 (1976).

(2) (a) D. J. Cram, *Pure Appl. Chem.*, **43**, 327 (1976); (b) J. M. Lehn, *ibid.*, **49**, 857 (1977).

(3) P. Bowen, B. Balko, K. Blevens, R. L. Berger, and H. P. Hopkins, Jr., *Anal. Biochem.*, **102**, 434 (1980).

(4) See ref 1b for a discussion of the short-form (numerical) cryptand nomenclature.

(5) (a) V. M. Loyola, R. Pizer, and R. G. Wilkins, *J. Am. Chem. Soc.*, **99**, 2809 (1977); (b) B. G. Cox and H. Schneider, *ibid.*, **99**, 2809 (1977); (c) J. M. Lehn and J. Sauvage, *ibid.*, **97**, 6700 (1975); (d) E. Kauffmann, J. M. Lehn, and J. P. Sauvage, *Helv. Chim. Acta*, **59**, 1099 (1976); (e) B. G. Cox, D. Knop, and H. Schneider, *J. Am. Chem. Soc.*, **100**, 6002 (1978); (f) a difference exists in the reported pK_a values for the 211 cryptand [$(211\ H)^+ = 211 + H^+$]. Reference 5c reports a value of 10.64 while ref 5e reports a pK_a of 11.17, giving no explanation for the difference. The impact of this difference on the present study is to possibly increase the concentration of protonated to unprotonated cryptand. In either case, however, the pH is maintained well above the pK_a. In lieu of a possible higher pK_a, the first-order transition could be considered due to proton loss from the cryptand; however, if true, one should not observe such a large difference in amplitude for this first-order reaction when comparing Li^+ and Ca^{2+} (see Figure 1).

Table I. Kinetic and Thermodynamic Parameters for Li^+ and Ca^{2+} Complexation with Cryptand 211 in Water (pH 11.4, Piperidine-HCl Buffer, $I = 0.1$ M, 25 °C)

ion	$\Delta H_{ov}{}^a$, kcal mol^{-1}	ΔH_{ov}, kcal mol^{-1}	k_1, M^{-1} s^{-1}	$k_2 + k_{-2}$, s^{-1}	K_{ov},^{e} M^{-1}	ΔH_1, kcal mol^{-1}
Li^+	-5.2 ± 0.26	-5.1 ± 0.2^c	f	3.2 ± 0.16	3.2×10^5	-2.8
Ca^{2+}	-0.41 ± 0.06	-0.1 ± 0.2^c -0.3^b	$4.1 (\pm 0.6) \times 10^{2\,d}$	2.3 ± 0.3	3.1×10^2	0.27

[a] Obtained from this study (see text). [b] Reference 5a. [c] Reference 5d. [d] Reference 5a cites 1.6×10^2. [e] Reference 5b. [f] Occurs within deadtime of TSF.

the buffer) at 0.1 M. Concentration ranges of metal ion and cryptand were from 3.5 to 50 mM, after mixing. Over this concentration range both Li^+ and Ca^{2+} exhibited a minum of two relaxations. It is of interest to note the large difference in the overall temperature changes for the two systems (see Figure 1), with this difference being reflected in the enthalpies of complexation (Table I).[5a,d] For Li^+ complexation, a fast reaction occurred within the dead time of the apparatus, followed by a slower reaction and measurable heat change. In the case of Ca^{2+} there is a biphasic reaction occurring after stopping with near equal but opposite temperature changes. For both ions no reaction was observed when either metal ion or 211 was absent. A test for a concentration dependency of these reactions revealed that (for both ions) the slower reaction was strictly first order, while for Ca^{2+} the faster (endothermic) reaction best fit a second-order concentration dependency. It would appear therefore that a possible mechanism is

$$M^{n+} + L \xrightarrow{k_1} (M^{n+}L)_1 \xrightarrow{k_2} (ML)_2{}^{n+} \qquad (1)$$

reaction 1 being similar to that proposed by others[5a,b] but including a subsequent conformational rearrangement of the ligand following ion complexation.

A measurement of the overall enthalpy change (ΔH_{ov}) observed in the thermal stopped-flow procedure was made (i.e., $\Delta H_{ov} = \Delta T_{ov}[\text{prod}]$) and compared with other observations.[5a,d] It should be noted that in so doing one need not postulate a mechanism, since only the beginning and final temperatures are being measured. Figure 1 is a plot of ΔT_{ov} vs. concentration for both ions. By using a calibration factor of 38 mV/mK[6] ΔH may be evaluated from the slopes (see Table I for listings of the ΔH_{ov} so obtained). The agreement for Li^+ is very good whereas for Ca^{2+} there is a slight discrepancy in the ΔH_{ov} values. This difference may be due to measuring such small reaction enthalpies or because more than two reactions are contributing to the overall ΔH.

The kinetic analysis of the relaxation spectrum was undertaken by using the simplest possible mechanistic scheme. As stated earlier, Li^+–211 complexation exhibited a large positive temperature change, within the dead time of the TSF, followed by what best fits a first-order exothermic reaction. At the lowest concentrations, this fit deviated during the initial time course of the reaction. If the value 8×10^3 M^{-1} s^{-1} [5b] for Li^+ complexation by 211 is correct, the influence of this bimolecular step would be observed only at the lowest concentration ranges. This observation is in full agreement with this study. Analysis of the calcium ion complexation required deconvolution of a coupled reaction system. Since the heats of reaction, for Ca^{2+}–211, were only slightly above the sensitivity limits of the instrument, a rigorous kinetic analysis was difficult; however, best fits were obtained by using reaction 1. Again the slower reaction was found to be first order with a composite rate constant ($k_2 + k_{-2}$) approximately equal to that of Li^+. The second-order complexation rate (k_1) for Ca^{2+}–211 is in fair agreement with that observed in other studies.[5a]

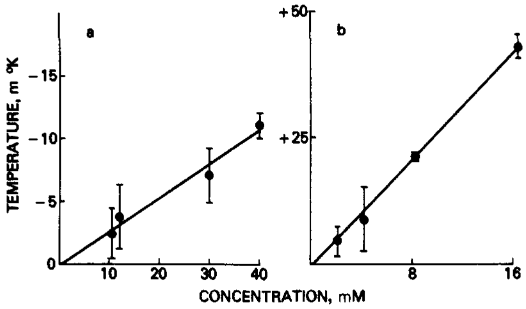


Figure 2. Plot of reaction temperature vs. product concentration ($[M^{n+}L]_1 + [M^{n+}L]_2$) for (a) Ca^{2+}–211 fast reaction and (b) Li^+–211 fast reaction. The straight line is a linear least-squares fit of the experimental data points. The vertical length of the data points corresponds to the precision of the data.

When reaction 1 is employed, it is also possible to unravel the reaction enthalpies of the individual reaction steps. To do this requires a knowledge of the amount of material reacted in each step, that is, K_1 ($=k_1/k_{-1}$) and K_2 ($=k_2/k_{-2}$). Since this is the first study to observe a biphasic reaction for 211-ion complexation, it becomes apparent that values for K_1 and K_2 have not been reported. However, for the fast complexation step the amount of material reacted may be evaluated from the stability constant:

$$K_{ov} = \frac{([ML^{n+}]_1 + [ML^{n+}]_2)}{[M^{n+}][L]} \qquad (2)$$

By use of the above equilibrium constant and the amplitude for the bimolecular reaction (at a given concentration), ΔH_{rxn} may be tabulated ($\Delta H_{rxn} = \Delta T_{rxn}[\text{prod}]$). Figure 2 is the plot of ΔT_{rxn} as a function of concentration for both Li^+ and Ca^{2+} ions and Table I contains the resultant values of ΔH for the bimolecular step. It is interesting to note that the bimolecular complexation for Ca^{2+}–211 is entropy driven (ΔH_1 = +), which is in contrast to that for Li^+. A thorough compilation of $\Delta H_{1,2}$ and $\Delta S_{1,2}$ for a series of ions would prove quite informative in attempting to understand the elementary forces governing metal ion complexation and selectivity by the cryptands.

In a study of metal ion complexation by sterically hindered cryptands, Maass et al.[7] observed a biphasic reaction: metal ion complexation followed by a slower ligand rearrangement. Additionally the ^{133}Cs NMR studies of Cs^+ complexation by several cryptands[8] present evidence for the existence of exclusive and inclusive complexes. Due to the multifaceted structure of a cryptand and the topographical arrangement of the ion within the bicyclic ligand cavity,[9] it appears that complexation occurs first to one face of the bicyclic ligand, with the ion partially complexed by ligand and solvent (exclusive complex denoted by $M^{n+} \cap L$), with subsequent rearrangement of the complex to a more stable conformation, with the ion totally encapsulated within the macrocycle (inclusive complex denoted by $M^{n+} \subset L$). If the nomenclature of Mei et al. is used, complexation occurs through the following steps:

$$M^{n+} + L = \underset{\text{exclusive}}{M^{n+} \cap L} = \underset{\text{inclusive}}{M^{n+} \subset L} \qquad (3)$$

On the basis of the above NMR observations, the biphasic reaction observed in this study would appear to be metal ion complexation to an exclusive complex followed by complex rearrangement to the inclusive form of the complex.

However, the slowness of the complexation rate is much lower than that observed for other macrocyclic ligands,[10] suggesting some

---

(6) The value was obtained from a plot of the amplitude vs. concentration for the neutralization reaction of NaOH with HCl performed within the thermal stopped-flow calorimeter.

(7) B. Tümmler, G. Maass, E. Weber, W. Wehner, and F. Vögtle, *J. Am. Chem. Soc.*, **99**, 4683 (1977).

(8) E. Mei, A. I. Popov, and J. L. Dye, *J. Am. Chem. Soc.*, **99**, 6532 (1977).

(9) M. R. Truter, *Struct. Bonding*, **16**, 71 (1973).

ligand rate-limiting step rather than the usual rapid stepwise water loss or diffusion-controlled encounter. A plausible explanation is that the metal ion be required to lose a majority of its solvation shell, prior to formation of an exclusive complex. Such a process would be energetically unfavorable and so reflected in ΔH_1 and ΔS_1. A full accounting of the unsually slow complexation rates would require monitoring several other ions as well as the larger cryptands and the monocyclic cryptands (e.g., 220).

Finally this study raises the exciting applications of monitoring an intrinsic reaction parameter, such as heat, in revealing the overall dynamical processes of molecules on the stopped-flow time scale. Another area of particular application would be protein–protein interactions, most specifically *lac* repressor–operator interactions.[11]

---

(10) G. W. Liesegang and E. M. Eyring, "Synthetic Multidentate Macrocyclic Compounds", R. M. Izatt and J. J. Christensen, Eds., Academic Press, New York, 1978, Chapter 5.

(11) A. D. Riggs, S. Bourgeois, and M. Cohn, *J. Mol. Biol.*, **51**, 303 (1970).

Mechanism of the Benzidine Rearrangement. Kinetic Isotope Effects and Transition States. Evidence for Concerted Rearrangement[1,2]

Henry J. Shine,*[†] Henryk Zmuda, and Koon Ha Park

Department of Chemistry, Texas Tech University
Lubbock, Texas 79409

Harold Kwart*[§] and Ann Gaffney Horgan

Department of Chemistry, University of Delaware
Newark, Delaware 19711

Clair Collins* and Brian E. Maxwell

Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Received August 4, 1980

The name "benzidine rearrangement" refers to a class of rearrangements of hydrazo aromatics, among which are the benzidine rearrangement itself (i.e., the rearrangement of hydrazobenzene), and the diphenyline, *o*-semidine, *p*-semidine, and *o*-benzidine rearrangements. These names describe the types of product given by rearrangement of particular hydrazo aromatics. Although an extraordinarily large amount of work has been devoted to these rearrangements and their products and kinetics have been described in ample detail,[3] a decisive answer to one question has always been elusive: namely, how do the rearrangements occur? Concerning this question, three major theories have been proposed in recent years. One of these, calling for a rate-determining ring protonation,[4] was shown subsequently to be inconsistent with the kinetic nitrogen isotope effect in the rearrangement of hydrazobenzene.[2] The two remaining ones are the polar-transition-state theory, which says in essence that the benzidine rearrangements are concerted and go through polar transition states,[3a] and the π-complex theory, which says that the rearrangements go through π-complex intermediates, and, in essence, are not concerted.[5] The major remaining unanswered question about the benzidine rearrangements may thus be stated quite simply: are they or are they not concerted? More specifically, does the transition state of a rearrangement involve concerted bond breaking and bond making? We are now able to answer that question as it applies to the rearrangement of hydrazobenzene to benzidine. We hope, in time, to answer the question as it applies to the several types of benzidine rearrangement.

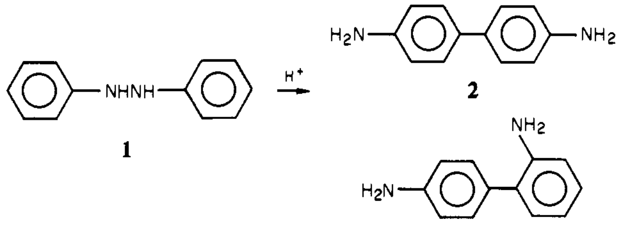
Table I. Experimental and Calculated Kinetic Isotope Effects for the Benzidine and Diphenyline Rearrangements

		kinetic isotope effect, $k_{\text{light}}/k_{\text{heavy}}$		
			calcd (model)	
rearrangement	isotope	obsd	concerted	dissociative
benzidine	$^{14}N^{15}N$	1.0222[a]	1.025	1.055
diphenyline	$^{14}N^{15}N$	1.063[b]	1.027	1.055
benzidine/ diphenyline	H/D	0.962[c]	<1.0	>1.0[e]
benzidine	$^{12}C^{14}C$	1.050[d]	1.0367	

[a] Mean value for 5% (1.0229 ± 0.0009), 10% (1.0222 ± 0.0034), and 15% (1.0214 ± 0.0001) conversions. [b] Mean value for 5% (1.0634 ± 0.0037), 10% (1.0630 ± 0.0009), and 15% (1.0635 ± 0.0007) conversions. [c] Mean value for 40% (0.9618), 50% (0.962), 60% (0.962), 70% (0.961), 80% (0.962), and 95% (0.062) conversions, all data equal to or better than 0.004 deviation. [d] Mean value for four runs, 5% (1.042), 5% (1.054), 5% (1.050), and 10% (1.055) conversions. [e] A hyperconjugative effect of deuterium at the 4,4′ positions for the charged structures formed in the dissociative mechanism would give rise to $k_H/k_D > 1.0$.[17–19]

The rearrangement of hydrazobenzene is second order in acid. We shall assume for the sake of simplicity that the second proton is fully transferred to nitrogen in the transition state, although this has been questioned,[2,6] and confine ourselves to the question of whether N–N bond breaking and C–C bond making are concerted.

When hydrazobenzene (**1**) rearranges in acid solution, two major products are formed: benzidine (**2**) and diphenyline (**3**).



The question of concertedness should, therefore, be asked for each product. Concerted rearrangement should result in a kinetic nitrogen isotope effect for bond breaking and a kinetic carbon isotope effect for bond making. Rate-determining C–C bonding should also result in a secondary deuterium isotope effect.

That N–N bond breaking is part of the transition state was, in fact, shown a few years ago by using ordinary **1** and isotope-ratio mass spectrometry after converting the products to N_2.[2] We have repeated the determination, but this time by using an enrichment with doubly labeled **1** and by measuring the relative abundances of the products, i.e., of masses 184 and 186. Also, the measurements were made for both of the separated products, **2** and **3**. The results are given in Table I. They show that the transition state for forming each product involves N–N bond breaking but

---

[†] Supported by the National Science Foundation, Grant CHE 78-00813, and the Robert A. Welch Foundation, Grant D-028.

[§] Supported by the National Science Foundation, Grant 79-11110.

(1) Benzidine Rearrangements, 15.

(2) Part 14: Shine, H. J.; Henderson, G. N.; Cu, A.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 3719.

(3) (a) Banthorpe, D. V.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1964**, 2864. (b) Shine, H. J. "Aromatic Rearrangements", Elsevier: New York, 1967; pp 126–179. (c) Shine, H. J. *MTP Int. Rev. Sci.: Org. Chem., Ser. 1* **1973**, *3*, 79–84. (d) *MTP Int. Rev. Sci.: Org. Chem., Ser. 2* **1976**, *3*, 100–110. (e) Cox, R. A.; Buncel, E. *Chem. Hydrazo, Azo, Azoxy Groups* **1975**, *2*, 777–805 and references therein.

(4) Olah, G. A.; Dunne, K.; Kelly, D. P.; Mo, Y. K. *J. Am. Chem. Soc.* **1972**, *94*, 7438.

(5) (a) Dewar, M. J. S. In "Molecular Rearrangements"; de Mayo, P., Ed.; Interscience: New York, 1963; Vol. 1, pp 323–343. (b) Dewar, M. J. S.; Marchand, A. P. *Annu. Rev. Phys. Chem.* **1965**, *16*, 338.

(6) Bunton, C. A.; Rubin, R. J. *Tetrahedron Lett.* **1975**, 59; *J. Am. Chem. Soc.* **1976**, *98*, 4236.

0002-7863/81/1503-955$01.25/0