been determined for any histidine derivative, so that in the present work the contributions to x of K_2 and of k_{HL}/k_L have not been separated.[23]

The experimental results are, however, satisfied by values of k_{HL}/k_L and K_2 that are chemically reasonable. As one example, if $k_{HL} = k_L$, then $pK_1 = 5.69$, $pK_2 = 7.11$, $pK_3 = 7.94$, $pK_4 = 6.51$, and (LH)/(HL) = 26. Thus it is unnecessary to invoke any special involvement of the unprotonated imidazole in the major species LH in order to explain the rate of decomposition of I at low pH values.

(23) An estimate of K_2 could obviously be obtained from the K_a of the (unknown) N,N'-dimethylimidazolium derivative of I.

Acknowledgment. Support of this research by the National Institutes of Health is gratefully acknowledged.

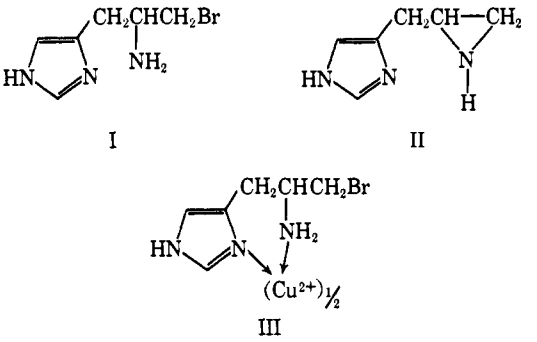
Inhibition of Neighboring-Group Participation by Chelation. The Effect of Cupric Ion on the Solvolysis of 4(5)-(2-Amino-3-bromopropyl)imidazole

D. A. Usher

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received August 9, 1967*

Abstract: The stability constants for complex formation between cupric ion and I and II were measured at 25° and the effect of cupric ion on the rate of the reaction of I to give II has been measured at pH 9.4. With a metal to ligand ratio of 0.6:1 a 50-fold decrease in the initial rate of reaction was found. With a metal-to-ligand ratio less than 0.5 complicated kinetic behavior was shown, which was quantitatively accounted for by the partitioning of the metal ion between the starting material and the product.

During a study, at present in progress, of the synthesis of some enzyme models related to ribonuclease, we wished to carry out a displacement of the bromide ion of the (aminobromopropyl)imidazole (I) by an external nucleophile at about pH 10. Unless the nucleophile were an unusually powerful one, an attempt to run this reaction would normally result[1,2] in a good yield of the substituted aziridine (II) and in little of the desired product. Standard methods of protecting one or both of the intramolecular nucleophiles (the amino and imidazole groups) could then be tried in the hope of allowing the bimolecular reaction to take precedence. However, in the case of I a rather different approach should be possible: formation of the complex of I with a metal ion (III) may be expected to slow down the unwanted intramolecular reaction on both electrostatic and steric grounds, and if the external nucleophile did not interfere with the formation of the complex, the required product may now be formed. Examination of literature values for the stability constants of complexes of histamine derivatives[3] suggested that the copper complex of I would be the most likely one to remain stable at pH 10. Homogeneous inhibition of a reaction by metal ions has been less well investigated than has catalysis, the



latter phenomenon obviously playing an important role in the action of many enzymes and enzyme models.[4] Cupric ion has been reported to inhibit the decarboxylation of nitroacetic acid[5] and the intermolecular reaction of imidazole and of glycylglycine with *p*-nitrophenyl acetate,[6] and has been used[7,8] to mask the α-amino group in some reactions of ornithine and lysine, thus allowing reaction (*e.g.*, acylation) to occur preferentially at the δ- and ϵ-amino groups, respec-

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(2) H. Freundlich and H. Kroepelin, *Z. Physik. Chem.*, **122**, 39 (1926); H. Freundlich and G. Salomon, *ibid.*, **166A**, 161 (1933), and earlier papers; P. D. Bartlett, S. D. Ross, and C. G. Swain, *J. Am. Chem. Soc.*, 71, 1415 (1949), and earlier papers; B. Cohen, E. R. Van Artsdalen, and J. Harris, *ibid.*, **74**, 1875, 1878 (1952); W. E. Hanby, G. S. Hartley, E. O. Powell, and H. N. Rydon, *J. Chem. Soc.*, 519 (1947); B. Hansen, *Acta Chem. Scand.*, **16**, 1945 (1962); C. C. Howard and W. Marckwald, *Ber.*, **32**, 2036 (1899).

(3) L. G. Sillén and A. E. Martell, Ed., "Stability Constants of Metal Ion Complexes," Special Publication No. 17, The Chemical Society, London, 1964.

(4) (a) See, for example: R. F. Gould, Ed., "Reactions of Coordinated Ligands," Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963; F. P. Dwyer and D. P. Mellor, Ed., "Chelating Agents and Metal Chelates," Academic Press Inc., New York, N. Y., 1964; T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 110–118; (b) H. L. Conley and R. B. Martin, *J. Phys. Chem.*, **69**, 2923 (1965); (c) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1889 (1957); (d) R. W. Hay and P. J. Morris, *Chem. Commun.*, 23 (1967).

(5) K. J. Pedersen, *Acta Chem. Scand.*, **3**, 676 (1949).

(6) W. L. Koltun, R. N. Dexter, R. E. Clark, and F. R. N. Gurd, *J. Am. Chem. Soc.*, **80**, 4188 (1958); W. L. Koltun and F. R.N. Gurd, *ibid.*, **81**, 301 (1959).

(7) A. C. Kurtz, *J. Biol. Chem.*, **122**, 477 (1937–38).

(8) A. Neuberger and F. Sanger, *Biochem. J.*, **37**, 515 (1943); **38**, 125 (1944).

tively. The effect of cupric ion on phenylalanylglycine amide was to catalyze the hydrolytic reactions, but to inhibit slightly the intramolecular reaction that gave the diketopiperazine.[9]

Metal complexes of aziridines have been investigated by Jones, *et al.*,[10] and more recently by Jackson and Edwards,[11] Kiser and Lapp,[12] and Scherzer, *et al.*[13]

This paper describes the inhibitory effect of cupric ion on the rate of the reaction of I to give II.

Experimental Section

Materials. The preparation of 4(5)-(2-amino-3-bromopropyl)-imidazole bishydrobromide and the standardization of the other reagents were as described previously.[1] Cupric nitrate and cupric sulfate were Mallinckrodt Analytical Reagent grade. The water used in the preparation of solutions was obtained by passage of distilled water through a mixed-bed, ion-exchange column (Barnstead Red Dot) and had a specific resistance of greater than 3 Mohms as measured with a Barnstead PM4 meter.

The cupric nitrate solution (1.028 *M*) was standardized by the potassium iodide–thiosulfate method, using the starch–ammonium thiocyanate modification[14] to increase the accuracy of detection of the end point.

Apparatus. Kinetic studies and potentiometric titrations were carried out using the Radiometer titration assembly described previously.[1] The same precautions[1] were taken to exclude atmospheric carbon dioxide and to ensure good performance of the glass electrode. All experiments were carried out at 25.0°.

Kinetic Methods. The reaction of I to give II requires the addition of base to maintain a constant pH, and was conveniently followed in the pH-Stat. Reactions carried out in the presence of less than 0.5 equiv of cupric ion were allowed to go to completion and gave a final steady reading of 1 equiv of base taken up. Initial rates only were calculated for reactions carried out in the presence of more than 0.5 equiv of cupric ion.

A solution (2.0 ml) 0.01 *M* in I bishydrobromide was transferred by means of a pipet to the titration vessel. The required amount of cupric nitrate solution was added by means of a calibrated microliter syringe; the calibration was carried out by weighing the syringe before and after delivery of the cupric nitrate solution, the density of which was determined experimentally at the laboratory temperature.

The reaction was initiated by the rapid addition of base from the manual syringe microburet to give a pH of 9.4 or 9.5 (9.0 in the case of 0.6 equiv of added copper); the pH was then held constant at this value by the pH-Stat and associated syringe buret unit.

There was no evidence for the formation of a precipitate during any of the kinetic runs. The initial rate of the reaction was calculated in the usual way[15] from the slope of the line obtained by plotting ln $(B_{inf} - B_t)$ *vs.* time, where B_{inf} is the final uptake of base, and B_t that at time t. For reactions carried out in the presence of less than 0.5 equiv of copper the experimental value of B_{inf} was used; otherwise the calculated value was used. No swamping electrolyte was used in these runs; in the absence of added cupric nitrate the ionic strength changed from an initial 0.017 to 0.023 at the end of the reaction, but the rate was insensitive to this change.[1]

Determination of Stability Constants. Stability constants for complex formation between cupric ion and I and II were measured under the same conditions as were used in the kinetic experiments. No attempt was made to extrapolate to infinite dilution. Values of the first and second acid dissociation constants of I and II were taken from previous work.[1]

1. Cupric Ion Plus (Aminobromopropyl)imidazole (I). To 2.0 ml of a solution 0.01 *M* in the (aminobromopropyl)imidazole bishydrobromide (I) was added 0.5 equiv of cupric nitrate solution. The solution was titrated under carbon dioxide free nitrogen in the Radiometer TTA31 microtitration assembly. Two equivalents of base was added manually in 20 equal increments, and the pH of the solution was measured on the PHA 630T scale expander after each addition.

The cupric ion slowed down the reaction of I sufficiently that accurate titration figures were obtained up to about 1.9 equiv of added base.

In a separate experiment, using the Radiometer TTT1c automatic titrator, a good end point was observed when 2 equiv of base had been added; precipitation did not occur until the pH reached 9.8.

The first and second stability constants for complex formation were calculated from the titration data by the least-squares method of Irving and Rossotti;[16] values of $\bar{n}$ between 0.95 and 1.05 were ignored. The calculations were performed on a CDC1604 digital computer. Higher[4b] and polynuclear complexes[17] were not considered in the calculations, but are probably not significant under the conditions of the experiment. The results are given in Table I.

2. Cupric Ion Plus (Aziridinylmethyl)imidazole (II). To 2.0 ml of 0.01 *M* (aminobromopropyl)imidazole bishydrobromide was added 0.40 ml of 0.10 *N* potassium hydroxide, and the solution was maintained at pH 9.4 by the addition of further base until reaction was complete (30 min); a total of 3 equiv of base had then been added, and the solution volume was 2.6 ml. The pH of the solution was lowered to 3.80 by the addition of 0.10 *N* hydrochloric acid (0.40 ml), and 0.5 equiv of cupric nitrate solution was added. The resulting solution was titrated with standard base, and the stability constants were calculated[16] as above. In a separate experiment, using the automatic titrator, a good end point was observed when 2 equiv of base had been added. No precipitate formed, even when the pH was taken as high as 12. The ligand was shown to be stable under the conditions of the titrations (see below). The results are given in Table I.

Table I. Stability Constants for Formation of Complexes of I and II with Cupric Ion at 25°

Compd	Log K_1 and range[d]	Log β_2 and range[d]
I[a]	8.60 ± 0.02 (0.25–0.90)	14.40 ± 0.15 (0.71–1.83)
II[b]	9.28 ± 0.07 (0.36–1.60)	16.83 ± 0.07 (0.76–1.60)
II[b,c]	9.30 ± 0.03 (0.36–1.60)	17.09 ± 0.04 (0.51–1.60)

[a] pK_a values used[1] were 5.55 and 7.95. [b] pK_a values used[1] were 5.58 and 7.61. [c] Assuming a 90% yield of II (see text). [d] Range of $\bar{n}$ used in calculating the spread.

Stability of (Aminobromopropyl)imidazole in the Presence of Cupric Ion. To 2.0 ml of 0.01 *M* (aminobromopropyl)imidazole bishydrobromide was added 0.6 equiv of cupric nitrate and the pH of the solution was raised to 9.0 by the addition of potassium hydroxide. A slow reaction ensued that required the addition of further base to maintain a constant pH; after 20 min 0.1 equiv had been added. In the absence of copper, 20 min corresponds to about eight half-lives. Hydrochloric acid was then added to give a pH of 2.95, and the cupric ion was removed by treatment with hydrogen sulfide followed by filtration; excess hydrogen sulfide was removed from the solution under vacuum. The amount of unreacted I (0.9 equiv) was found by raising the pH rapidly to 9.3 and following the further addition of base at constant pH in the pH-Stat. The rate of this addition was that expected[1] for free I.

Stability of (Aziridinylmethyl)imidazole in the Presence of Cupric Ion. The aziridine II was generated from 2.0 ml of 0.01 *M* I in the usual way, then 0.5 equiv of cupric nitrate was added and the pH of the solution adjusted to 9.04. At the end of 10 min the pH had dropped to 9.03 and hydrochloric acid was added to give a pH of 2.80. After a further 10 min (the pH was still 2.80), the cupric ion was removed by treatment with hydrogen sulfide and the excess hydrogen sulfide removed under vacuum. The amount of II remaining was estimated[1] by reaction with thiosulfate at pH 3.7 and was found to be still 1.0 equiv.

(9) L. Meriwether and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 5119 (1956).
(10) R. G. Jones, E. Bindschadler, D. Blume, G. Karmas, G. A. Martin, Jr., J. R. Thirtle, and H. Gilman, *ibid.*, **78**, 6027 (1956).
(11) T. B. Jackson and J. O. Edwards, *ibid.*, **83**, 355 (1961); *Inorg. Chem.*, **1**, 398 (1962).
(12) R. W. Kiser and T. W. Lapp, *ibid.*, **1**, 401 (1962).
(13) J. Scherzer, P. K. Phillips, L. B. Clapp, and J. O. Edwards, *ibid.*, **5**, 847 (1966).
(14) A. I. Vogel, "Quantitative Inorganic Analysis," Longmans, Green and Co. Ltd., London, 1955, pp 343–344.
(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, p 38.
(16) H. Irving and H. S. Rossotti, *J. Chem. Soc.*, 3397 (1953); A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, Chapter 9.
(17) D. D. Perrin and V. S. Sharma, *J. Inorg. Nucl. Chem.*, **28**, 1271 (1966).

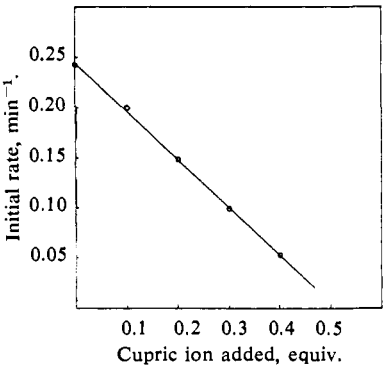

Figure 1. Initial rate of reaction of I to give II as a function of the number of equivalents of cupric ion (T = 25°).

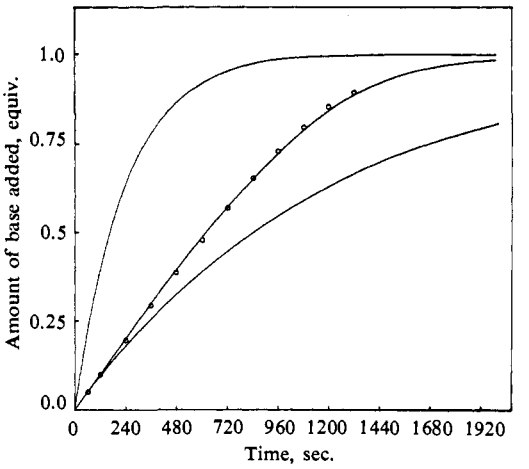

Figure 2. The reaction of I to give II at 25°; the amount of base added is proportional to the extent of reaction. Upper curve: no added cupric ion. Middle curve: experimental rate with 0.4 equiv of added copper. The circles are the points predicted from the calculations described in the text, with log K_1 = 8.60; log K_2 = 5.79; log K_3 = 9.28; log K_4 = 7.56; log K_5 = 7.31; and k = 4.2×10^{-3} sec^{-1}. At t = 0, 9.5% of the added I had already been converted to II (see text). Lower curve: a hypothetical first-order reaction with a rate constant equal to the starting rate of the middle curve.

Product of the Reaction of I in the Presence of Cupric Ion. To 2.0 ml of a 0.01 M solution of I was added 0.4 equiv of cupric nitrate, and the solution was held at pH 9.4 until reaction was complete. Hydrochloric acid was added to give a pH of 3.0, and the cupric ion was removed by treatment with hydrogen sulfide. Excess hydrogen sulfide was removed under vacuum. The pH of the solution was raised to 3.8 by the addition of sodium hydroxide (0.1 N), and the amount of aziridine II present in the solution was estimated[1] by reaction with thiosulfate at constant pH (3.8). The amount of aziridine present was found to be 1.00 equiv.

Results and Discussion

The stability constants for complex formation between cupric ion and I and II are given in Table I, and are similar to those found for other derivatives of histamine.[3] The amino group of II has the lower pK_a, yet II forms the stronger complex; a somewhat similar observation was made by Jackson and Edwards.[11] In the present work the precision and accuracy of the results would be expected to be affected by two main sources of error: in the case of I some decomposition occurs during the pK_a determination[1] (with a consequent inaccuracy in the stability constants), and in the case of II the compound was not isolated, but was produced in solution from I. A check on the probable limits of error was made for the second of these determinations by recalculating the stability constants from the same titration figures, but assuming that II was formed from I in 99, 98, 97... 80% yield (and that the remainder of the material was inert). The least spread in the values of log K_1 and log β_2 was obtained with the assumption of a 90% yield, but the actual least-squares values were little changed (see Table I), and since the yield of II has been shown[1] to be close to 100%, the original figures were used in the calculations given below. Both of the ligands were shown to be stable under the conditions of the titrations.

Obviously, much greater inhibition of the intramolecular reaction of I is possible if the experiments are carried out in the presence of more than 0.5 equiv of cupric ion, and this would be an advantage if the inhibition were to be used to allow an intermolecular nucleophilic displacement of the bromide ion to compete effectively with the intramolecular reaction. With 0.6 equiv of copper, a decrease in the initial rate by a factor of 50 was found. However, the situation is complicated by the ionization of water that is bound to the copper[18] and by the formation of polynuclear complexes,[17] and a detailed analysis of the kinetics was not attempted.

Kinetic Analysis

When less than 0.5 equiv of copper was used, the initial rate of reaction of I to give II was that expected if every metal ion chelated two molecules of I, and the complex so formed was unreactive.[19] This can be seen in Figure 1. However, when the reaction was followed past the initial stages, the first-order rate constant showed a gradual increase as the reaction progressed; this is shown for the case of 0.4 equiv of cupric ion in Figure 2. Consideration of the relative stability constants of I and of II with copper shows that this effect is to be expected, for as the reaction proceeds, more and more II is formed, and since II has a greater affinity for the inhibitor than has I, the inhibition is gradually reduced. This situation is the reverse of that found by Bender and Turnquest[4c] for cupric ion catalyzed hydrolysis of amino acid esters. In that case the product of the reaction (the free amino acid) again complexed more strongly with the copper than did the starting material, but thus gave a gradual *decrease* in the specific rate. In the present work, then, the specific rate at any time depends on the concentration of free I, which in turn depends on the relative amounts of I, II, and cupric ion present and on the relative affinities of I and of II for the copper. A quantitative analysis of this situation has been made.

It was assumed throughout that the reaction of I to give II is slow compared to the rate of establishment of equilibrium[20] among the various complexes present in solution.

In the calculations that follow consideration was restricted to the following species: M, ML, ML_2, ML′,

(18) R. Leberman and B. R. Rabin, *Nature*, 185, 768 (1960).

(19) "Unreactive" in the sense that I, when bound to the copper, does not undergo the reaction to form II.

(20) F. Basolo and R. C. Johnson, "Coordination Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, Chapter 6.

ML_2', L, L', and MLL', where M is the metal ion, L the (aminobromopropyl)imidazole, and L' the (aziridinylmethyl)imidazole. The concentrations of these species are related by the following equilibria (where the equilibrium constants are those applicable under the experimental conditions).

$$M + L \overset{K_1}{\rightleftharpoons} ML \qquad M + L' \overset{K_3}{\rightleftharpoons} ML'$$

$$ML + L \overset{K_2}{\rightleftharpoons} ML_2 \qquad ML' + L' \overset{K_4}{\rightleftharpoons} ML_2'$$

The fifth equilibrium expression was arbitrarily chosen to be

$$ML + L' \overset{K_5}{\rightleftharpoons} MLL'$$

In addition, by material balance we have

$$M_t = M + ML + ML_2 + ML' + ML_2' + MLL'$$

$$L_t = L + ML + 2ML_2 + MLL'$$

$$L_t' = L' + ML' + 2ML_2' + MLL'$$

where the subscript t represents "total." As the reaction proceeds the relative amounts of L_t and L_t' change according to the rate equation

$$L \overset{k}{\longrightarrow} L'$$

The first step, then, is to calculate the equilibrium concentrations of the species in solution (see Appendix), in particular that of free L (it was assumed that all bound forms of L were unreactive[19]).

The change of I into II is a first-order process, and thus in the small time interval δt, L_t decreases by the amount $L(1 - \exp(-k\delta t))$, and L_t' increases by the same amount. A new set of equilibrium values for all the species must then be calculated and the process repeated. Since this method assumes that the equilibria are "frozen" during each δt for each step of the reaction, it is necessary to choose a small enough δt that the predicted rate of reaction is independent of the actual choice. This procedure could be very wasteful of computer time since significant differences in the predicted rate of reaction were still discernible with δt values as low as 5 sec. Fortunately, it was found that even when quite large values of δt were employed, a surprisingly accurate linear relationship existed between the size of δt and the predicted amount of reaction at any given time. Thus extrapolation to a zero value for δt was easily made.

The only parameter in these calculations for which an independent measurement was not made and which therefore could be treated as a variable is K_5, the equilibrium constant for formation of the mixed complex MLL'.[21] If the assumption were made[22] of a purely statistical distribution of ligands in the equilibrium

$$ML_2 + ML_2' \overset{K_6}{\rightleftharpoons} 2MLL'$$

then K_6 would have the value 4.0, and since K_5 and K_6 are related by the equation

$$K_6 = \frac{(K_5)^2 K_1}{K_2 K_3 K_4}$$

K_5 would have the value 2.07×10^7. The use of this value for K_5 gave a calculated rate of take-up of base (Figure 2) that agreed somewhat more closely with the experimental rate than when values higher or lower by a factor of five were used, though in view of other possible perturbations on the predicted rate, it is unlikely that much confidence could be placed in a value of K_5 obtained in this way. The predicted result shows, as would be expected, more sensitivity to a change in K_5 toward the end of the reaction. Interestingly, when K_5 was given the value 4.73×10^6, the predicted amount of reaction at first slightly lagged behind, then overtook, the amount predicted by giving K_5 the value 2.06×10^7.

The amount of reaction with time (predicted and experimental) is shown in Figure 2 for the case of 0.4 equiv of added copper; an equally good fit was obtained for experiments run with less than 0.4 equiv.

It was mentioned in the introduction that one of the reasons for investigating the effect of cupric ion on the rate of formation of II from I was that inhibition of this intramolecular reaction may allow a slow intermolecular displacement of the bromide ion of I by an external nucleophile at high pH to compete effectively with the intramolecular reaction. A further bonus could arise from the use of copper for this purpose: any aziridine that does form would be activated by virtue of being bound to the cupric ion, and may be expected to undergo ring opening at high pH more readily than in the absence of copper.[23] Reaction would probably occur at the primary carbon atom.[1] A preliminary test of this possibility has been made by comparing the rate of reaction of II with thiosulfate at pH 9.5 in the presence and in the absence of 0.5 equiv of cupric ion. The former reaction took place at about 20 times the rate of the latter. The application of these effects to some synthetic reactions is now under investigation.

Acknowledgments. Support of this research by the National Institutes of Health is gratefully acknowledged. The author wishes to thank Dr. N. W. Ashcroft for a helpful discussion.

Appendix

Calculation of Equilibrium Composition. The method used here is based on previously published methods of Brinkley,[24] Browne,[25] Villars,[26] and Cruise,[27] but is adapted for the characteristics of this particular problem.

The system comprising: M, L, L', ML, ML_2, ML', ML_2', and MLL', is connected by the equilibrium constants K_1, K_2, K_3, K_4, K_5 and by the expressions for total M, total L, and total L'.

(21) A small amount of II is formed during the addition of base to bring the pH to 9.4; the predicted rate of reaction is reasonably sensitive to the value that is given to this "small amount." However, the actual amount can be obtained from the experimental total take-up of base and is not therefore an additional variable.

(22) The author wishes to thank Dr. R. C. Fay for a helpful discussion of this point.

(23) *Cf.* ref 11.

(24) S. Brinkley, *J. Chem. Phys.*, **15**, 107 (1947); H. Kandiner and S. Brinkley, *Ind. Eng. Chem.*, **42**, 850 (1950).

(25) H. Browne, Jr., "The Theoretical Computation of Equilibrium Compositions, Thermodynamic Properties and Performance Characteristics of Propellant Systems," U. S. Naval Ordnance Test Station, China Lake, Calif., NOTS TP 2434.

(26) D. Villars, *J. Phys. Chem.*, **63**, 521 (1959).

(27) D. R. Cruise, *ibid.*, **68**, 3797 (1964).

Three of the concentrations (L, ML_2, MLL′) were chosen (the "basis")[24] from which all the other concentrations could be considered to be derived. It has been shown[25] that increased speed of calculation results if the constituents present in greatest amount are chosen for the basis, and this is accomplished automatically in more general programs. Here it proved convenient to fix the basis at the start; as the reaction progressed the concentrations were never far from their equilibrium values. Rewriting the equilibria then

$$MLL' + L \overset{K_3/K_5}{\rightleftharpoons} L' + ML_2$$

$$ML_2 \overset{1/K_2}{\rightleftharpoons} ML + L$$

$$ML_2 \overset{1/K_1K_2}{\rightleftharpoons} M + 2L$$

$$2MLL' \overset{K_2K_3K_4/K_1K_5^2}{\rightleftharpoons} ML_2' + ML_2$$

$$MLL' \overset{K_3/K_1K_5}{\rightleftharpoons} ML' + L$$

At the start of the calculation, initial values are given to the basis species (and to the derived species if necessary) such that the total amounts of M, L, and L′ are correct and that none of the basis species is zero.[28] A check is then made to see if the equilibrium expressions are satisfied, using the present values of the concentrations. In general the ratio of concentrations for a particular equilibrium expression will yield a figure Q_n, different from the applicable equilibrium constant K_n. The relationship is considered satisfied only if $|1 - K_n/Q_n| < 10^{-4}$ (the condition used by Cruise[27] for "minor" species; 10^{-5} was initially used and found to be unnecessarily stringent here). If all equilibria are satisfied, then the system is considered to be at equilibrium, and a small amount of reaction is allowed, as given in the text, followed by an "updating" of the relative concentrations of L and of L′. If, however, an equilibrium expression is *not* satisfied, then the concentrations of the species that appear in that expression are changed stoichiometrically by an amount Δ, which is obtained by a linear approximation, *e.g.*, for the trivial case of

$$A + B \overset{K}{\rightleftharpoons} C$$

Suppose A, B, and C are the present nonequilibrium values, and A_e, B_e, C_e the true equilibrium values, which can be obtained from the former values by allowing a shift Δ to the right in the above expression. Then $A_e = A - \Delta$, $B_e = B - \Delta$, and $C_e = C + \Delta$, so that

$$K = \frac{C_e}{A_e B_e} = \frac{(C + \Delta)}{(A - \Delta)(B - \Delta)}$$

Thus by solving for Δ and ignoring terms in Δ^2 (Δ small) we get for this example

$$\Delta = (KAB - C)/(1 + K(A + B))$$

The present values of A and B would then be lowered, and that of C raised, by the amount Δ unless one of the reagents would be reduced to a negative concentration by this procedure, in which case an attempt is made to carry out the adjustment with a fraction of Δ, typically one-tenth. In neither case is this adjustment assumed to leave the concentrations of the reagents at their true equilibrium values, each expression must still pass the test given above, and all equilibria must be satisfied at once. (This "stoichiometric"[26] correction method leaves the total amounts of M, L, and L′ unchanged.) No convergence failures have yet been noted. The time taken for "reaction" to run to 94% completion using a δt of 20 sec (see text) was 4 min, 16 sec on the CDC 1604 computer; most of the computing time is taken up toward the end of the run, where the basis is no longer optimum.

(28) If at the start of the reaction the concentration of total L′ is considered to be zero, then MLL′ is also zero, and a very small number such as 10^{-20} would be used for its starting value. In practice, the starting concentration of total L′ is finite in these experiments.[21]