Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.58; O, 17.66. Found: C, 57.25; H, 4.53; N, 20.47; O, 17.68.

10-Ethyl-7-methylisoalloxazine. The crude diamine from 0.30 g (0.0015 mol) of *N*-ethyl-4-methyl-2-nitroaniline was converted to the isoalloxazine with 1.0 g of boric acid and 0.24 g (0.0016 mol) of alloxan as previously described. Evaporation of solvent yielded a brown oil which crystallized (yellow needles) from dimethylformamide to give 0.20 g (0.0008 mol) of 10-ethyl-7-methylisoalloxazine, 51.1% yield, mp 313–315° dec. Tlc gave one spot with an R_f 0.65; ir (KBr) 820 (s), 1190 (s), 1290 (s), 1410 (s), 1430 (m), 1480 (m), 1590 (m), 1660 (s), 1735 (s), 2870 (m), and 3490 cm^{-1} (s); uv_{max} (phosphate buffer pH 7) 218 (ϵ 26,450) and 265 nm (35,300); uv_{max} (6 *N* hydrochloric acid) 262 nm (ϵ 23,110); $visible_{max}$ (phosphate buffer pH 7) 350 (ϵ 7722) and 442 nm (10,160); $visible_{max}$ (6 *N* hydrochloric acid) 367 nm (ϵ 14,960); $fluorescence_{max}$ (glycine buffer pH 3.25) exc, 365 and anal, 515 nm; mass spectrum *m/e* 256 (M^+, 75), 228 (100), 157 (76), and 116 (15).

Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.95; H, 4.68; N, 21.87; O, 12.50. Found: C, 60.87; H, 4.77; N, 21.79; O, 12.51.

3,8-Dimethyl-10-ethyl-8α-histidylisoalloxazine. A three-necked, round-bottom flask equipped with a magnetic stirrer, reflux condenser protected with a calcium chloride drying tube, and dropping funnel was charged with 4.0 g (0.014 mol) of 10-ethyl-8-hydroxymethyl-3-methylisoalloxazine dissolved in 100 ml of dioxane and 10 ml of pyridine; 1.40 g (0.005 mol) of phosphorus tribromide was then added with stirring over a period of 2.0 hr. The reaction mixture was then stirred at room temperature for 3.0 hr, refluxed for 2.0 hr, cooled, and flash evaporated to a volume of 10 ml. The liquid residue was poured into 250 ml of chloroform and the chloroform solution was then washed twice with 250-ml portions of 1 *N* hydrochloric acid, and then twice with 250-ml portions of water. After drying over sodium sulfate, the chloroform was removed by flash evaporation (50°). Crude 8-bromomethyl-10-ethyl-3-methylisoalloxazine, 3.2 g (0.009 mol), 67.0% yield, mp 281–302°, was obtained. Tlc showed three yellow-green fluorescing spots (R_f 0.31, 0.44 and 0.68) and two orange spots (R_f 0.12 and 0.81) when visualized under ultraviolet light. All attempts to obtain pure 8-bromomethyl derivative were unsuccessful.

The crude 8-bromomethyl-10-ethyl-3-methylisoalloxazine was then converted to 3,8-dimethyl-10-ethyl-8α-histidylisoalloxazine by a modification of the method of Ghisla and coworkers,[9] 4.2 g (0.012 mol) of crude 8-bromomethyl-10-ethyl-3-methylisoalloxazine in 100 ml of dimethylformamide being treated at 90° for 24.0 hr with 7.75 g (0.03 mol) of N^{α}-benzoylhistidine. The reaction mixture was then flash evaporated (80°) to a brown oil and the product was isolated by chromatography on a 20 × 350 mm silica gel column, employing the upper phase of the butanol–acetic acid–water mixture and collecting 50-ml fractions. On evaporation, fractions 2–5 gave N^{α}-benzoylhistidine, 3.9 g (0.015 mol), mp 246–249° (lit.[25] mp 250°). The remaining fractions were pooled, and after the solvent was removed by flash evaporation, the brown residue was refluxed for 2.0 hr with 6 *N* hydrochloric acid. The solvent was removed *in vacuo* and the oily residue crystallized from formic acid–water to give 1.7 g (0.004 mol) of 3,8-dimethyl-10-ethyl-8α-histidylisoalloxazine, 33.5% yield, mp 337–344° dec. Several recrystallizations from formic acid–water yielded orange-brown needles, mp 338–344° dec. Tlc gave two close yellow-green fluorescing spots, R_f 0.36 and 0.38; (KBr) 820 (m), 1150 (m), 1420 (m), 1440 (w), 1500 (m), 1555 (w), 1620 (m), 1715 (m), 3050 (s), and 3450 cm^{-1} (s); uv_{max} (phosphate buffer pH 7) 217 (ϵ 28,690) and 263 nm (35,120); uv_{max} (6 *N* hydrochloric acid) 262 nm (ϵ 29,910); $visible_{max}$ (phosphate buffer pH 7) 344 (ϵ 9430) and 443 nm (11,100); $visible_{max}$ (6 *N* hydrochloric acid) 371 (ϵ 20,030) and 405 nm (shoulder, 10,800); fluorescence (glycine buffer pH 3.25) exc, 355 and anal, 522 nm; mass spectrum *m/e* 423 (M^+, 83), 395 (100), 310 (70), 296 (35), and 81 (25).

Anal. Calcd for $C_{20}H_{21}N_7O_4$: C, 56.74; H, 4.97; N, 23.17. Found: C, 56.96; H, 5.12; N, 22.97.

pH-Dependent Fluorescence. Variation of fluorescence with pH was determined for 1.00×10^{-7} *M* solutions of the isoalloxazines. The following buffer solutions were employed: pH 2.00–3.65, glycine–hydrochloric acid; pH 3.90–5.30, sodium acetate–acetic acid; pH 5.80–7.00, potassium dihydrogen phosphate–potassium hydroxide; pH 8.20–9.20, potassium monohydrogen phosphate–potassium hydroxide; pH 10.20 and greater, sodium carbonate–sodium hydroxide. Fisher reagent grade chemicals were used in all cases, and all buffers were stored at 5° prior to use.

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Kinetics of Reactions in Solutions under Pressure. XXVI. Fragmentation of Chloroacetylhydrazide[1]

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Abstract: The reaction of chloroacetylhydrazide with aqueous hydroxide ion to give chloride ion and products derived from ketene and diazene (diimide) is first order in each reagent up to a pH of 12. The activation volume for the reaction is negative. *N,N'*-Dimethyl substitution leads to a very much (10^{7-8}) slower rate of chloride production, whereas *N,N*-dimethyl substitution retards the reaction only moderately (10 times). A yellow, transient intermediate is observed in the reaction of the parent compound; stopped-flow experiments show that its formation rate becomes independent of base at a pH of 12. The uv-visible spectrum of the intermediate has been determined; the disappearance is first order and independent of base. Neither ketene nor diazene can account for it. These observations are interpreted in terms of rate controlling α-lactam formation rather than of a concerted fragmentation as described in the recent literature; the color is tentatively attributed to an anion of acetyldiazene.

Fragmentations are reactions of the general type A–B–C–D–X → A–B + C=D + :X. A wide variety of examples has been reported[2] and the general mechanism has been discussed.[3] One of the more

(1) Presented in part at the Symposium, "High Pressure Science and Technology," American Institute of Chemical Engineering Meeting, San Francisco, Calif., Dec 1971.

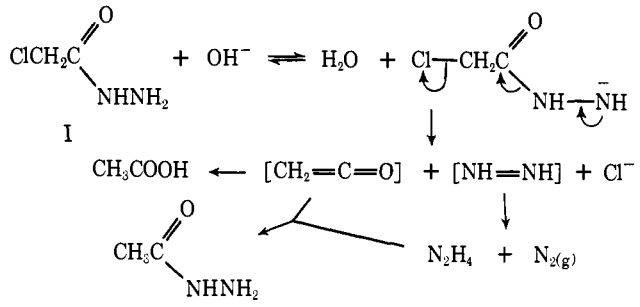
(2) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).

(3) C. A. Grob, *ibid.*, **8**, 535 (1969).

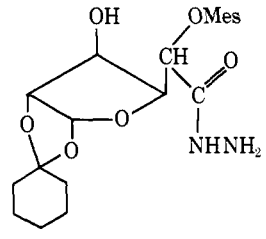
difficult questions to assess in each example is the concertedness of the two-bond cleaving processes, simultaneity being characteristic of true fragmentation whereas successive fission reactions *via* some intermediate add up to a process that belongs in this category only formally. The concertedness of these reactions has been extensively investigated by Grob,[2,3] whose primary tools were the sensitivity of the rate constant to the substituent effect, and to subtle conformational changes introduced in rigid polycyclic structures. Since such methods require a great deal of synthetic effort, we have been interested in developing the activation volume as a criterion: a reaction involving two simultaneously breaking bonds will obviously be affected by the application of pressure in a way different from those in which only one bond is cleaved. Thus, whereas decarboxylations are characterized by activation volumes of +6 to +10 cm³/mol,[4] the fragmentation of bromoangelate ion to bromide, 2-butyne and carbon dioxide has an activation volume of +17 cm³/mol.[5]

One example that attracted our attention was reported by Buyle,[6] who found that treatment of chloroacetylhydrazide (I) led to nitrogen, hydrazine, chloride, and acetate ions as well as a small amount of acetylhydrazide; this observation was rationalized by the sequence shown in Scheme I. By traversing a

Scheme I



similar sequence of events more than once, even trichloroacetylhydrazide can be reduced all the way to acetic acid.[6a] A related reaction was investigated by Paulsen,[7] who found that in the more complex hydrazide (II) *N,N'*-dimethyl substitution led to a qualitatively



II

somewhat slower reaction while *N,N*-dimethyl substitution stopped the reaction entirely, thus supporting the Buyle pathway.

Two features of these reactions appeared surprising to us. First of all, acetylhydrazide in 1 *N* base would be expected to be completely hydrolyzed. Its appearance among the products in this reaction seemed to us an indication that the C–N bond might not yet have been broken in the first intermediate and hence that the fragmentation might not be concerted. Secondly, the acidity of the β protons must be enormously less (by perhaps 10^{20}) than that of the amide hydrogen, yet the reaction is pictured as depending on β ionization. While neither of these aspects is fundamentally impossible, the combination seemed sufficiently unlikely to warrant a reinvestigation.

Results and Discussion

The reaction of I has a convenient rate at 25.0° in a sodium bicarbonate buffer and it can be followed readily by electrometric chloride titration. The pseudo-first-order rate constant was found to have a value of 3.48×10^{-5} sec^{-1} in a solution buffered at a pH of 7.85; the rate plot was linear for at least the first three half-lives. The activation volume was determined on the basis of rate measurements over a 4-kbar range.[8] The result was that $\Delta V^{\ddagger}_{app} = +3 \pm 2$ cm³/mol. Since pressure also affects the pH of buffer solutions the following correction is necessary (values in cm³/mol).[9]

$I + HCO_3^- \longrightarrow H_2O + CO_2 + Cl^- + \text{products}$	$+3 \pm 2$
$H_2O + CO_2 \longrightarrow H^+ + HCO_3^-$	-29.0
$OH^- + H^+ \longrightarrow H_2O$	$+21.3$
$I + OH^- \longrightarrow H_2O + Cl^- + \text{products}$	-5 ± 2

This negative value is very far indeed from what is expected on the basis of the Buyle–Paulsen pathway.

Two alternative rate-limiting steps are possible that would be in reasonable agreement with the observed pressure coefficient of the rate constant:[8] an internal displacement to give an α-lactam or a 1,2-diazetidinone or, following α ionization, a fragmentation to ketene and the zwitterionic aminonitrene, $^-N{=}N^+H_2$, with electrostriction due to the charges accounting for the volume decrease despite the breaking bonds.

Methyl substitution in our case had an effect on the rate of chloride release quite unlike that described by Paulsen[7] for II. The *N,N*-dimethyl homolog III produced chloride only 10 times more slowly than the parent compound; at 25.0° and a pH of 7.85, $k_1 = 3.46 \times 10^{-6}$ sec^{-1}. The deliquescence of salts of the *N,N'* isomer made it difficult to get precise information for the rate of chloride formation in that case; however, extrapolation of data obtained at higher pH clearly showed that the rate constant for the *N,N'* isomer IV was at least 10^7 times smaller than that of the parent compound. This effect of the methyl groups on the rate of chloride release strongly suggests that α ionization is required for the first step of reaction of I.

(4) K. R. Brower, B. Gay, and T. L. Konkol, *J. Amer. Chem. Soc.*, **88**, 1681 (1966).

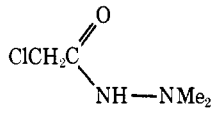
(5) W. J. le Noble, R. Goitien, and A. Shurpik, *Tetrahedron Lett.*, 895 (1969). For another recent application, see I. Fleming and C. R. Owen, *J. Chem. Soc. B*, 1293 (1971). The simultaneity of bond formation processes has also been scrutinized by means of the pressure coefficient of the rate constant; see for instance R. A. Grieger and C. A. Eckert, *J. Amer. Chem. Soc.*, **92**, 2918 (1970); C. A. Stewart, *ibid.*, **94**, 635 (1972).

(6) (a) R. Buyle, A. Van Overstraeten, and F. Eloy, *Chem. Ind. (London)*, 839 (1964); (b) R. Buyle, *Helv. Chim. Acta*, **97**, 2449 (1964).

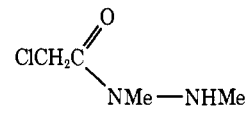
(7) H. Paulsen and D. Stoye, *Chem. Ber.*, **99**, 908 (1966); H. Paulsen, "The Chemistry of Amides," J. Zabicky, Ed., Wiley, New York, N. Y., 1970, Chapter X.

(8) For a review of this technique, see W. J. le Noble, *Progr. Phys. Org. Chem.*, **5**, 207 (1967).

(9) For a listing of ionization volumes, see S. D. Hamann, "High Pressure Physics and Chemistry," Vol. II, R. S. Bradley, Ed., Academic Press, New York, N. Y., 1963, p 150.



III



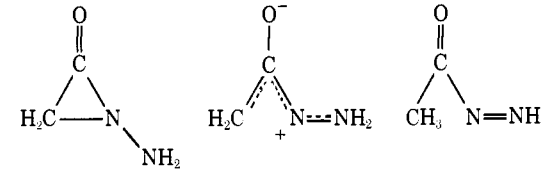
IV

The known pK_a's of acetic acid (4.8), chloroacetic acid (2.8), acetamide (15.1), hydrogen peroxide (11.7), methanol (16), and water (15.7) led us to estimate that the pK_a of I should be near 11. If this is correct and if the reaction of I depends on α ionization, one should be able to reduce the second-order rate law to base independence at high pH. We had noted early that the addition of the solid hydrochloride of I to concentrated base gave rise to a transient yellow color, and hence stopped-flow experiments were in order. Neither the initial nor the final solutions have any absorption above 280 nm, and measurement of the transmission of light above that wavelength *vs.* time revealed the theoretical curve indicating consecutive first-order formation and decay of an absorbing intermediate. The equations for analyzing such curves have been published by Wiberg,[10] and the following results were obtained. At a pH of 12.3, the pseudo-first-order rate constant for the formation of the intermediate is 1.05 sec^{-1}. The value calculated on the basis of the constant obtained in a bicarbonate buffer (pH 7.85) is 0.99 sec^{-1}, so that the reaction at $[OH^-] = 0.02$ is still second order. At still higher concentration the dependence on base strength rapidly decreases, however; at $[OH^-] = 0.062$, $k_1 = 1.20$ sec^{-1} and at $[OH^-] = 0.25$, $k_1 = 1.33$ sec^{-1}. The pK_a of the acid that produces the precursor of the intermediate is therefore about 12. This result rules out β ionization. Likewise, the reaction of III becomes independent of base at a pH of 11–12, but the relative rates of formation and of decomposition in this case were evidently such that the intermediate could not be directly observed.

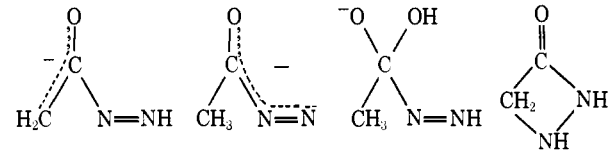
If α ionization is accepted, concerted fragmentation to ketene and aminonitrene is in principle still possible, but it can be ruled out on the following grounds. Ketene has been reported[11] to have a λ_{max} of about 325 nm in hexane solution with an ϵ_{max} of 14.5. Measurement of the transmittance *vs.* time curves at various wavelengths about 5 nm apart yielded the ultraviolet spectrum of the intermediate. After the optical densities have been corrected for incomplete generation and partial decay, we find that λ_{max} is 322 nm and ϵ_{max} equals 1500 ± 100; at 400 nm, ϵ equals about 100 and at 430 nm it equals 6, thus accounting for the yellow color. The ϵ values are based on the assumption that the yield of the intermediate is 100%, and thus they are minimum values. We conclude that the intermediate has the right λ_{max} to be ketene but its ϵ_{max} is much too high. It is conceivable of course that the much more polar medium is responsible for an increase in the extinction coefficient but it would seem odd that this change would not affect the wavelength. Furthermore, when known, pure ketene was injected into alkaline solutions, the transient yellow color is not observed.[12]

Aminonitrene likewise cannot account for it. Substituted aminonitrenes have been involved as intermediates elsewhere;[13] aminonitrene itself has been dismissed as a structure of N_2H_2 in favor of diazene, both the cis and trans forms having been observed in a low-temperature matrix.[14] This material is then present as a yellow deposit and has a λ_{max} at 350 nm;[15a] however, it rapidly and irreversibly disproportionates at −135° to colorless products which turn out to be nitrogen and hydrazine.[15] These observations are very different from our results: the intermediate has a half-life of approximately 1 sec at room temperature and disappears by a first-order rate law. Thus, at $[OH^-] = 0.02$–0.25 M, k_1 for this process equals 0.45 ± 0.02 sec^{-1} for at least three half-lives. Disproportionation would be expected to be a second-order decay. Furthermore, diazene has been used in preparative applications,[16] but no mention has ever been made of its direct observation in such reactions. We emphasize that there is no reason to doubt that diazene is an intermediate and that it is the source of the nitrogen and hydrazine; however, it is not the yellow intermediate described here.

The simple α and β anions can similarly be ruled out; apart from the fact that the β acid is much too weak, neither ion would be expected to be colored or to be generated as slowly as is observed, and quenching in acid of rapidly mixed solutions of I and base does not regenerate I. This leaves as the most likely initial product the *N*-amino-α-lactam V. The observed intermediate may have any one of a host of different structures, including the lactam itself (V), a ring-opened dipolar structure such as VI, a tautomer VII or anion such as VIII–X derived from any of these structures, or even rearranged structures such as XI. The possibility, if not likelihood, of equilibration among some of these structures may make it fruitless at this point to further



V VI VII



VIII IX X XI

(10) K. B. Wiberg and P. A. Lepse, *J. Amer. Chem. Soc.*, 86, 2612 (1964). The expression given for B (the concentration of the intermediate) is actually that for $-B$.

(11) G. C. Lardy, *J. Chim. Phys.*, **21**, 353 (1923).

(12) If ketene is injected in large doses into concentrated base, a permanent yellow color develops.

(13) D. M. Lemal and T. W. Rave, *J. Amer. Chem. Soc.*, 87, 393 (1965); R. S. Atkinson and C. W. Rees, *Chem. Commun.*, 1230 (1967); D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *ibid.*, 146 (1969); *J. Chem. Soc. C*, 576 (1970); T. L. Gilchrist, C. W. Rees, and E. Stanton, *ibid.*, 988 (1971).

(14) K. Rosengren and G. C. Pimentel, *J. Chem. Phys.*, 43, 507 (1965).

(15) (a) E. J. Blau and B. F. Hochheimer, *ibid.*, 41, 1174 (1964); (b) A. Trombetti, *J. Chem. Soc. A*, 1086 (1971); *Can. J. Phys.*, 46, 1005 (1968).

(16) Reviewed by S. Hünig, H. R. Müller, and W. Thier, *Angew Chem., Int. Ed. Engl.*, 4, 271 (1965). Diazene reductions can be carried out with chloroacetylhydrazide; see ref 6a.

pursue the precise nature of the intermediate, but the following considerations apply. It should account for the yellow color and λ_{max} of 325 nm with ϵ_{max} 1500, and decompose to ketene and diazene *via* a first-order process which is independent of base at least at a hydroxide ion concentration above 10^{-3}.

A number of simple α-lactams are known,[17] and some of these, such as 1,3-di-*tert*-butylaziridinone, are quite stable; a still simpler one, *N*-*tert*-butylaziridinone, has been detected as a transient intermediate through its ir spectrum.[18] It has been reported that these compounds are colorless with a maximum at 250 nm.[19] The *N*-amino group may very well lower the energy of the open form.[17] It is difficult to believe that a zwitterionic form such as VI should survive in strongly basic media. We were completely unable to extract the colored compound into methylene chloride at 0° even when the aqueous phase was saturated with sodium chloride. This argues against neutral acetyldiazene (VII); only an anion of VII such as VIII, IX, or X remains as a possibility. Of these, we prefer IX; VIII is expected to have a λ_{max} much longer than 325 nm,[20a] and X would have an ϵ_{max} much below that observed.[20b] Several substituted diazetidones with skeleton XI are known, but these are colorless compounds.[21]

In summary, our conclusion is that the base induced fragmentation of chloroacetylhydrazide is not concerted as claimed earlier, that the first intermediate is the α anion rather than the β isomer, that the second intermediate is *N*-amino-α-lactam, and, tentatively, that structure IX represents the intermediate visually observable at high pH. This study marks a further example of the use of the activation volume as a criterion of concertedness in multiple bond fissions.

Experimental Section

Materials. Chloroacetylhydrazide hydrochloride (I) was prepared as described.[6b] Chloroacetyl-*N*,*N*-dimethylhydrazide hydrochloride (III·HCl) was prepared in the same way. It was purified by dissolution in methanol and addition of ether, yield 60–65%, mp 175° dec. *Anal.* Calcd for III·HCl: C, 27.76; H, 5.83; Cl, 40.98; N, 16.19. Found: C, 27.69; H, 5.60; Cl, 40.82; N, 16.20. *sym*-Dimethylhydrazine was prepared from 150 g of the solid dihydrochloride by slowly adding a saturated aqueous solution of an equivalent amount of sodium hydroxide and distilling to complete dryness. The distillate was treated with 200 g of solid potassium hydroxide; the organic phase was isolated, treated with 100 g of barium oxide and allowed to stand for 48 hr, decanted, and distilled, bp 80–82°, yield 95%.

Chloroacetyl-*N*,*N*′-dimethylhydrazide (IV) could not be purified as the hydrochloride, which appeared to be extremely hygroscopic. Solutions of IV were therefore prepared as follows. *p*-Nitrophenyl chloroacetate (21.5 g) in 200 ml of methylene chloride is stirred and a solution of 6 g of *sym*-dimethylhydrazine in 30 ml of methylene chloride is adding in a 10-min period at 0°; 200 ml of 1 *N* hydrochloric acid is added and after extraction, the aqueous phase is extracted six times with 200 ml of methylene chloride. This is followed by the addition of 100 ml of methylene chloride and 200 ml of 1 *N* potassium hydroxide; after extraction the organic phase is evaporated to about 20 ml; this solution is about 0.5 *M* in IV, and is indefinitely stable at freezer temperatures. Aqueous solutions of the nitrate of IV are readily obtained by extraction with dilute nitric acid. The nmr signals of I, III, and IV as hydrochlorides in D_2O and as the free hydrazides in CH_2Cl_2 are listed in Table I. The preparation of ketene has been described.[22]

Table I. Nmr Signals of the Hydrazides[a]

	CH_2	α-NMe	β-NMe
I·HCl in D_2O	5.71		
I in CH_2Cl_2	*b*		
III·HCl in D_2O	5.77		6.83
III in CH_2Cl_2	5.60		7.33[c]
IV·HCl in D_2O	5.43	6.47	6.88
IV in CH_2Cl_2	5.68	6.98	7.44[d]
NH_2–NMe_2·HCl in D_2O		7.06	
NH_2–NMe_2 in CH_2Cl_2		7.66	
NHMe–NHMe·HCl in D_2O		7.25	
NHMe–NHMe in CH_2Cl_2		7.51	

[a] Spectrum recorded in τ units. [b] The reaction with base is too rapid to permit extraction of the free hydrazide with methylene chloride. [c] The doublet (3-Hz separation) is unaffected in D_2O and hence is attributed to the restricted rotation often observed in N-substituted amides. [d] Unsharp doublet with J = 6 Hz due to coupling with NH; raising the temperature to 40° caused coalescence and conversion to a singlet; the addition of a little D_2O also converts it into a sharp singlet. The fact that only one "rotamer" is observed is attributed to the internal NH–O bond.

Rate Measurements. The rate of chloride formation of chloroacetylhydrazide in saturated aqueous sodium bicarbonate at 25.0° (pH 7.85) was followed by titrating samples acidified with nitric acid with silver nitrate. The reaction gave a linear first-order plot for at least two half-lives; k_1 is 3.48×10^{-5} sec^{-1}. The high-pressure procedures have been described elsewhere;[8] measurements were made at 0.5, 1, 2, 3, and 4 kbar. The reaction of III at 25° in a bicarbonate buffer is similarly first-order over three half-lives; $k_1 = 3.46 \times 10^{-6}$ sec^{-1}. Aqueous solutions of IV made 0.2 *N* in hydroxide ion released chloride only very slowly at 25°; a temperature in excess of 60° was required for several hours in order to reach the infinity titer.

Stopped-Flow Measurements. The apparatus has been described previously.[23] Measurements of the transmittance *vs.* time gave values of the rate constants of formation (k_1) and of decomposition (k_2) of the intermediate. These measurements were repeated at several concentrations of I and of hydroxide ion, over a temperature interval from 15 to 35° (for k_1 and k_2, $\Delta H^{\ddagger}$ is +8.7 and +14.9 kcal/mol and $\Delta S^{\ddagger}$ is −29.2 and −10.2 eu, respectively) and at wavelengths 2–10 nm apart over the range of 250–450 nm (neither I nor the final products absorb in this region). The latter experiment permitted a point by point calculation of the uv-visible spectrum of the intermediate. If a solution in which the intermediate had not yet fully decomposed was quenched in dilute acetic acid, I was not regenerated as shown by nmr and chloride ion analysis.

Acknowledgments. Mr. T. Hayakawa carried out some of the early exploratory work. We thank Profes-

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Metal–Ammonia Reduction. XII. Mechanism of Reduction and Reductive Alkylation of Aromatic Hydrocarbons[1]

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Abstract: The mechanism of reduction of biphenyl with alkali metals in liquid ammonia is shown to involve formation of a dianion rapidly protonated by the medium at 4 position (in accord with HMO theory) to afford a stable phenylcyclohexadienyl anion (**6**). Evidence for the intermediacy of **6** rather than the unprotonated dianion **5** or the related radical-anion **4** (or their ion pairs) includes demonstration of efficient *hydride transfer* from the product of interaction of lithium with 4,4′-dideuteriobiphenyl in ammonia to anthracene; *electron transfer* from **4** or **5** fails to compete to significant extent. Analogous reductive alkylation follows a similar mechanism, with dialkylated products arising *via* back reaction involving proton abstraction by amide ion on the initially formed 1-alkyl-1,4-dihydrobiphenyl rather than dialkylation of **6**. The extent of di- and trialkylation parallels the solubility of the corresponding amides (Na > Li > Ca). The radical-anion **4**, like **6**, is stable in ammonia, undergoing neither protonation nor alkylation efficiently. Related investigations with anthracene demonstrate considerable similarity between the two systems, and the following general mechanism is proposed: (1) formation of a dianion which protonates rapidly with lithium or calcium, but more slowly with sodium; (2) facile alkylation of the monoprotonated anion and the dianion (if present); and (3) further alkylation of these products through back reaction involving proton abstraction by amide ion.

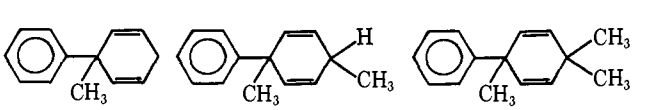
Reduction of polycyclic aromatic hydrocarbons by means of solutions of alkali metals in liquid ammonia has proven remarkably regiospecific[1-4] (*i.e.*, only a single dihydro isomer formed at each stage), in accord with predictions of molecular orbital theory.[5] However, greater complexity of mechanism than assumed in the theoretical treatment is indicated by the recent demonstration of important counterion and solvent effects in reductive methylation of naphthalene.[6] Also, little is known regarding the nature of the anionic intermediates, the existence and structure of which has largely been inferred from the structure of products of reduction and reductive alkylation.[6-8]

We report now investigations into the mechanisms of reduction and reductive alkylation of aromatic hydrocarbons. Evidence will be presented relating to the stability of the intermediate anionic species, the relative importance of ion-pair association and protonation by the medium, and the relative rates and significance of the various possible reaction pathways.

Initial studies were conducted with the biphenyl system. Although interaction of biphenyl with alkali metals was first described over 40 years ago,[9] product structure has been the subject of controversy until recently. Grisdale, *et al.*,[10] utilizing modern techniques of separation (glc) and analysis (nmr) established that the calculated dihydro derivative, 1,4-dihydrobiphenyl, is the initial product; rapid protonation is necessary to prevent its isomerization and further reduction. With sodium, some biphenyl is always recovered;[10] with lithium and rapid product isolation, transformation is virtually quantitative.[3]

Results

Reductive methylation of biphenyl with lithium in ammonia and methyl bromide proceeded virtually quantitatively to afford 1-methyl-1,4-dihydrobiphenyl (**1**). The integrated nmr spectrum was consistent with only the assigned structure (sharp methyl singlet at δ 1.42, benzylic protons absent); the vinylic protons appeared as an apparent singlet (δ 5.61) resembling those of 1,4-dihydrobiphenyl and differing from the more complex patterns of the isomeric phenylcyclohexadienes.[10] Analogous reaction with calcium also furnished **1** as the sole product. With sodium, however, the major products were **1** and *cis*- and *trans*-1,4-dimethyl-1,4-dihydrobiphenyl (**2**); these were accompanied by minor amounts of 1,4,4-trimethyl-1,4-dihydrobiphenyl (**3**).



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