The enhanced reactivity of cations generated in aprotic solvents is a reflection of the decreased solvating character of the media. Less polar solvents such as benzene, chloroform, etc., are unable effectively to stabilize the cation in the absence of a stabilizing anion such as hexafluoroantimonate, and thus kinetic control of products is observed. In more polar (and/or protic) media such as glyme,[9] glacial acetic acid, and ultimately water, cation stabilization is increased and more rearrangement is observed, a consequence of greater thermodynamic control and/or decreased counterion activity.

(9) Reactions in more polar aprotic solvents such as acetonitrile give extensive rearrangement as well as significant amounts of solvent-derived products (~20%): A. T. Jurewicz, unpublished data.

(10) NASA Fellow.

A. T. Jurewicz, J. H. Bayless,[10] L. Friedman

Department of Chemistry, Case Institute of Technology
Cleveland, Ohio 44106

Received October 29, 1965

Aprotic Diazotization of Aliphatic Amines. Intra- and Intermolecular Reactions of Poorly Solvated Cations[1]

Sir:

The fate of carbonium ions is assumed to be dependent upon their mode of formation and environment. For example, cationoid species formed by diazotization of amines in protic solvents are more "reactive" than those formed by solvolysis.[2] This has been ascribed mainly to differences in degree of solvation.[2] It is reported herein that diazotization in aprotic media[3] yields species that are markedly different from those formed in protic media in that hydrocarbon yields are greatly enhanced, skeletal rearrangements and double-bond migration are minimized, and cyclopropane formation is significantly increased.

The formation of cyclopropanes from cationoid precursors has been sporadically observed in terpene chemistry since the turn of the century.[4] More recently small amounts of cyclopropane products were reported in the protic diazotization of aliphatic amines[5] and the deoxidation of alcohols.[6] This is in contrast to the extensive amount of insertion observed in many of the corresponding carbenic systems.[7]

(1) (a) The results reported here for the isomeric C_4 amines are representative for a wide variety of aliphatic and alicyclic amines. (b) A premature account of part of this work was presented by L. Friedman and F. D. Mendicino, Abstracts of Papers, 145th National Meeting, American Chemical Society, New York, N. Y., Sept. 1963, p. 86Q.

(2) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); J. H. Ridd, *Quart. Rev.* (London), **15**, 418 (1961).

(3) Solvents that are not proton donors. Other examples of such diazotizations are summarized by D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Am. Chem. Soc.*, **87**, 863 (1965).

(4) For example: G. Wagner, S. Moycho, and F. Zienkowski, *Chem. Ber.*, **37**, 1035 (1904); G. M. Komppa and G. A. Nyman, *Ann.*, **535**, 252 (1938); W. Hückel and G. Meinhardt, *Chem. Ber.*, **90**, 2025 (1957); M. Bredt-Savelsberg, *ibid.*, **56**, 554 (1923). The intermediacy of cyclopropane intermediates was postulated, but not proven, by many investigators to explain extensively rearranged olefinic products.

(5) (a) M. Silver, *J. Org. Chem.*, **28**, 1686 (1963); (b) P. S. Skell and I. Starer, *J. Am. Chem. Soc.*, **82**, 2971 (1960); (c) O. E. Edwards and M. Lesage, *Can. J. Chem.*, **41**, 1592 (1963); (d) M. Hanach and H. Schneider, *Tetrahedron*, **20**, 1863 (1964).

(6) P. S. Skell and R. J. Maxwell, *J. Am. Chem. Soc.*, **84**, 3963 (1962).

(7) W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, pp. 52–64.

Diazotization of isobutylamine (Table I) in solvents such as chloroform, benzene, and cyclohexane with alkyl nitrites in the presence of 1 equiv. of acetic acid[8a] gives hydrocarbon products in approximately 30% yield. The hydrocarbons are mainly isobutylene (70–73%) and the insertion product methylcyclopropane (14–16%).[8b] Of the skeletal-rearranged products (the butenes), 1-butene predominates. The ratio of acetates to alcohols is 25; while the ester portion is mainly isobutyl acetate (~89%), much rearrangement (~66%) is observed in the alcohol products. As the medium becomes more protic, *e.g.*, 50% aqueous acetic acid, the ratio of acetates to alcohols drops to 5, hydrocarbon yields are decreased, and extensive rearrangement occurs.[9]

In aqueous systems the cationic species are stabilized by solvation and thus rearrangement to thermodynamically more stable intermediates occurs. However, under aprotic conditions products are derived from kinetic rather than thermodynamic factors.[10]

The effect of the reaction medium on product composition from the diazotization of *n*-butylamine (Table I) is similar; methylcyclopropane (~4%) and 1-butene (~90%) are formed with a minimum of products (6%) from 1,2-hydride shift in the more aprotic environments. As the medium becomes more highly protic methylcyclopropane is formed in only trace amounts and the amount of *cis*- and *trans*-2-butenes increases extensively at the expense of 1-butene.

Diazotization of *sec*-butylamine over a wide range of conditions yields only *sec*-butyl derivatives, whose nature (*i.e.*, ratio of alcohol to ester or halide) reflects the activity of the counterions[10] in the medium. However, the composition of the hydrocarbon products is more revealing. In aprotic media the *sec*-butyl cation or diazonium ion yields mainly 1-butene (X^- = Cl, 76%; AcO^-, 57%),[11] while in aqueous systems the 2-butenes predominate. The relatively large amounts of 1-butene formed are not far removed from an expected statistical result (60%) based on available protons if an E2-type mechanism or cyclic elimination sequence is considered wherein the transition state more closely re-reflects reactants (Hofmann rule). In more protic media E1-type eliminations predominate.[2] The formation of significant amounts of methylcyclopropane (~4%) is of interest since in this case none is formed in the corresponding carbenic system.[12] This is just one of several instances where intramolecular carbonium ion insertion occurs to a greater extent than carbene insertion.[13]

(8) (a) Nitrous oxide is quantitatively formed from free alkylamine and alkyl nitrite; (b) methylcyclopropane (0.5%) was also observed in the hydrocarbon products (~1% yield) from the solvolysis of isobutyl tosylate.

(9) This is even more striking in acetonitrile and acetonitrile–water mixtures. Concomitant changes occur in hydrocarbon product formation: A. T. Jurewicz, unpublished data.

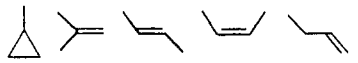
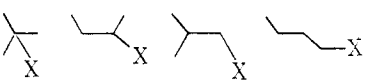
(10) D. H. Froemsdorf and M. E. McCain, *J. Am. Chem. Soc.*, **87**, 3983 (1965).

(11) The large amount of terminal olefin formed from the aprotic diazotization of both *sec*- and isobutylamine may reflect the amount of E2 type elimination (ref. 10) and the relative stability of the three conformers of the *sec*-butyl cation (*cf.* D. J. Cram and M. R. V. Sahyun, *ibid.*, **85**, 1257 (1963)). The difference observed with different counterions might be related to the solvating (*i.e.*, stabilizing) ability of the counterion in the ion pair.

(12) *Cf.* ref. 7, p. 55.

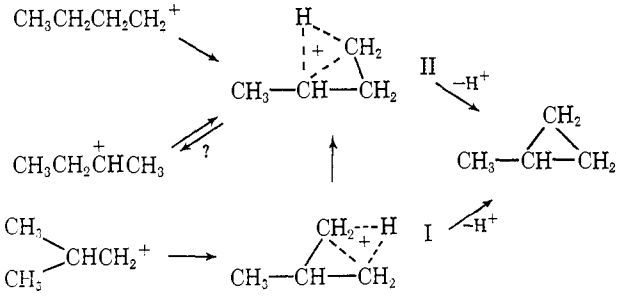
(13) For example, bicyclobutane formation: J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Shechter, *J. Am. Chem. Soc.*, **87**, 661 (1965).

Table I. Diazotization of Isobutyl- and *n*-Butylamine[a]

Acid	Solvent	Hydrocarbon products[b] % yield[c]	Composition					Butyl derivatives[b] % yield	Product composition[d]			
												
Isobutylamine												
HOAc	$CHCl_3$	33	14	73	4.2	2.1	6.9	54	5	9	86	
HCl	$CHCl_3$	8	15	57	5.0	3.7	19					
HOAc	Glyme[g]	35	10	76	4.1	2.2	7.7	44	4	11	85	
HCl	Glyme[g]	20	9.7	68	5.6	3.2	13	54[e,f]	5	9	86	
HOAc	HOAc	20	4.5	62	14	7.1	12	51	47	28	25	
HOAc	50% aq. HOAc	12	2.5	40	25	11	21	21	54	20	26	
n-Butylamine												
HOAc	$CHCl_3$	8	4.3		4.5	2	89			4		96
HCl	$CHCl_3$	9	3.1		3.1	2	92					
HOAc	Glyme[g]	18	2.9		6.6	3	88	75[e]		4		96
HCl	Glyme[g]	12	3.5		6.6	3	87	72[e]		2		98
HOAc	HOAc–$NaNO_2$[h]	5	0.7		25	11	63	30		30		70
HOAc	50% aq. HOAc–$NaNO_2$	11	0.3		29	14	56	48		32		68

[a] Amine (0.005 mole), acid (0.005 mole), and alkyl nitrite (0.0055 mole) in 10 ml. of solvent, at reflux (*t*-$C_4H_9NH_2$ data not included here, since only isobutene and *t*-butyl products are formed). [b] Hydrocarbons analyzed on Dowtherm-A (20%), Chromosorb P.; and $AgNO_3$–benzyl cyanide, Chromosorb P (room temperature). Acetates, alcohols, and halides analyzed on diisodecyl phthalate (5%), Bentone (5%), Chromosorb P (Hy-Fi), at 75°. [c] Yields determined *via* quantitative g.l.p.c. [d] Alcohols and acetates (or halides) combined. [e] Ether cleavage products not included here (see A. T. Jurewicz, J. H. Bayless, and L. Friedman, *J. Am. Chem. Soc.*, **87**, 5788 (1965)). [f] N.m.r. analysis of unresolved g.l.p.c. trapped sample. [g] Hydrocarbon compositions from thermal decomposition of nitrosoamides, nitroamides, and nitrourethans are essentially identical. Slightly more rearrangement is observed in butyl derivatives. [h] *Cf.* ref. 16c.

In addition to other routes,[2] poorly solvated cations may yield by "neighboring group participation" (*internal solvation*) the more stable protonated cyclopropane intermediate.[14] Cyclopropanes could then result by simple loss of proton.[15] Some of the rearranged solvent- and counterion-derived products could result from nucleophilic attack at the quaternary carbon with concomitant ring cleavage.



Since *n*- and *sec*-butyl cations do not give any iso- and *t*-butyl derivatives it may be concluded that II best describes the intermediate. It is significant that *t*-butyl derivatives cannot be derived from either I or II.

The results obtained are essentially independent of the cation precursor[11] (amine diazotization, rearrangement of nitroso- and nitrourethans and ureas)[16] and reflect mainly the environment of the cation, thus suggesting that all of these precursors generate the same *primary reactive intermediate(s)* in a given solvent system. Product fallout can then occur as described or *via* the other accepted pathways.[2]

(17) (a) NASA Fellow; (b) Case Undergraduate Research Participant.

J. H. Bayless,[17a] F. D. Mendicino,[17b] L. Friedman
Department of Chemistry, Case Institute of Technology
Cleveland, Ohio 44106
Received October 29, 1965

(14) G. J. Karabatsos, C. E. Orzech, Jr., and S. Meyerson, *J. Am. Chem. Soc.*, 87, 4394 (1965), and references contained therein.

(15) (a) C. C. Lee and J. E. Kruger, *ibid.*, 87, 3986 (1965). (b) Dimethylcyclopropane (1%) was formed by aprotic diazotization of neopentyl amine. *Cf.* ref. 5b. (c) Protic diazotization of *trans*-8-hydrindanylcarbinylamine (a neopentyl system) gave tricyclo[4.3.1.0^{1,6}]-decane in 74% yield: W. G. Dauben and P. Laug, *Tetrahedron*, **20**, 1259 (1964).

(16) (a) Table I; (b) E. H. White and D. W. Grisley, Jr., *J. Am. Chem. Soc.*, **83**, 1191 (1961), and references contained therein; (c) A. Streitwieser and W. D. Schaffer, *ibid.*, **79**, 2888 (1957).

Isolation and Characterization of Anthramycin, a New Antitumor Antibiotic

Sir:

It has been observed by Tendler and Korman[1] that a thermophilic actinomycete (*Streptomyces refuineus* var. *thermotolerans*, NRRL 3143) produces a fermentation broth possessing antibiotic properties and exhibiting *in vivo* antitumor activity. We wish to report the isolation of a pure, crystalline antibiotic which is responsible for the observed antitumor activity.

The isolation of this antibiotic, which we have named anthramycin,[2] was followed by the use of a quantitative cup-plate assay method employing *Sarcina lutea* (PCI-1001) and *Bacillus sp. TA* (NRRL B-3167) as test organisms. Anthramycin was removed from the fermentation broth filtrate[3] by countercurrent column extraction with 1-butanol, and the resulting extract was subjected to a fractional liquid extraction employing 1-butanol

(1) M. D. Tendler and S. Korman, *Nature*, **199**, 501 (1963).

(2) The name "refuin" has been used by Tendler and Korman for the initial designation of the antitumor active principle, which they assumed to be a protein; *cf.* S. Korman and M. D. Tendler, Abstracts, Meeting of the American Association for Cancer Research, Toronto, Canada, May 1963. Their crude preparation contained approximately 0.5% of anthramycin. We have subsequently designated the anticancer active principle as Roche 5-9000. The generic name, anthramycin, has been derived from the structure of this antibiotic, an integral part of which is an anthranilic acid moiety.

(3) The fermentation procedure will be published elsewhere.