[Contribution from The Wellcome Research Laboratories]

The Rate of Quaternization of a Piperazine by Some Propargylic and Allylic Bromides[1]

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The rate of quaternization of a tertiary amine, 1-carbethoxy-4-methylpiperazine, with allyl bromide ($10k$ = 2.25 l./mole-min.), methyl iodide ($10k$ = 1.22), propargyl bromide ($10k$ = 0.892) and 1-bromo-2-heptyne ($10k$ = 3.50) was measured in acetone–water solution. The order of these rate constants is somewhat different from that reported for other S_N2 reactions with these and related halides.

Many studies have been reported on relative reactivities of halides with nucleophilic reagents. In particular, the rate of reaction of halides with metallic iodides in dry acetone has been studied with a wide variety of halides, because this reaction is normally relatively free of side reactions and is almost invariably bimolecular (S_N2). However, although the rates of exchange of several propargylic chlorides and bromides with iodide have been reported, it has been said that "The primary products of the reaction of propargyl. . . chlorides and bromides with sodium iodide were difficult or impossible to determine."[2] Similarly, attempts to determine the S_N2 reactivity of propargyl halides with ethoxide ion in ethanol gave unsatisfactory results due to the occurrence of side reactions.[3,4] Of the determinations of S_N2 reactivities of propargyl halides listed in Table I, the "symmetrical exchange" of propargyl chloride with radioactive chloride in acetone seems most likely to be free of side reactions.

Table I

Rates of Some Bimolecular Reactions of Allyl and Propargyl Halides

Halide	k, l./mole-min.
A. With inorganic iodide in acetone at 25°[a]	
$CH_2{=}CHCH_2Cl$	0.0111[2]
$CH_2{=}CHCH_2Br$	7.30[b]
$CH{\equiv}CCH_2Cl$	0.0181[2,3,a,d]
$CH{\equiv}CCH_2Br$	10.2[2]
$CH_3C{\equiv}CCH_2Cl$	0.0273[3,d,a]
$C_4H_9C{\equiv}CCH_2Br$	4.150[b]
$(CH_3)_3CC{\equiv}CCH_2Br$	5.270[b]
$C_6H_5C{\equiv}CCH_2Cl$	0.111[c,d]
B. With lithium chloride in acetone at 44.6°[4]	
$CH_2{=}CHCH_2Cl$	0.00352
$CH{\equiv}CCH_2Cl$	0.00394

[a] Recalculated to 25° where indicated, using the formula: $\log \frac{k_2}{k_1} = 4000\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$ [J. B. Conant, W. R. Kirner and R. E. Hussey, This Journal, **47**, 488 (1925)]. [b] P. D. Bartlett and L. J. Rosen, *ibid.*, **64**, 543 (1942). [c] M. J. Murray, *ibid.*, **60**, 2662 (1938). [d] Multiplied by 2.303 since $\log_{10}$ appears to have been used.

The author had occasion to quaternize 1-carbethoxy-4-methylpiperazine with a variety of halides.[5] In the course of these syntheses it was observed that the rates of the reactions with the propargylic halides appeared to be in a somewhat different order from those anticipated from the previous work. Since substantially quantitative yields of pure quaternary salts were readily obtained from these reactions, it was felt that a more precise determination of the rate constants of some representative quaternizations would be of value. Rates were therefore determined for the reaction of 1-carbethoxy-4-methylpiperazine with propargyl bromide, allyl bromide, 1-bromo-2-heptyne and with methyl iodide. The last might serve as a reference halide to allow the data reported here to be used to anticipate results with other amines for which methyl iodide quaternization rates are known. The solvent used was a mixture of equal volumes of acetone and water ("50% acetone") which was found to dissolve the reactants and the products.

Experimental

Materials.—Allyl bromide (Matheson–Coleman and Bell), propargyl bromide (General Aniline and Film Corp.), and methyl iodide (R.S.A. Corp.) were distilled within one week of each use, retaining an arbitary center cut, and were stored in the dark.[6] The 1-bromo-2-heptyne[7a,b] made from hept-2-yne-1-ol (Farchan Research Laboratories) was redistilled *in vacuo* within two days of each use, since it darkened quite rapidly. This bromoheptyne gave 101% of the theoretical amount of halide after hydrolysis with excess of hot alcoholic sodium hydroxide. The 1-carbethoxy-4-methylpiperazine was an arbitrary center cut of material[8] with acceptable values for the boiling point, made from hydrochloride of proper m.p.

Method.—Rates were measured by adding an equimolar amount of the halide to a solution of the amine in "50% acetone"[9] contained in a glass-stoppered 250-ml. volumetric flask thermostated at 25 ± 0.15°. Approximately 12 millimoles of each reagent was normally taken, although only

Table II

Reaction of 1-Bromo-2-heptyne with 1-Carbethoxy-4-methylpiperazine in "50% Acetone"

Initial wt. amine = 974.5 mg. (5.662 millimoles); initial wt. of halide = 990.8 mg. (5.659 millimoles); volume = 250.0 ml.; T = 25.0°; slope found: 7.98×10^{-3}; $k = 3.52 \times 10^{-1}$ l. moles^{-1} min.$^{-1}$

Time, min.	10	60	114	174	244
Ml. Ag^+ (0.1000 N)	0.400	0.800	1.200	1.500	1.800
Ml. SCN^- (0.0110 N)	2.010	.585	1.070	1.720	2.950
Millimoles Br^-/l.	1.79	7.366	10.82	13.11	14.75
$A - X$ (millimoles/l.)	20.85	15.27	11.82	9.53	7.49
$X/A - X$	0.086	0.483	0.916	1.376	1.970

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(1) This is paper No. 12 on unsymmetrical piperazines from these laboratories. For the previous paper see M. Harfenist and E. Magnien, This Journal, **79**, 2215 (1957).

(2) T. L. Jacobs and W. F. Brill, *ibid.*, **75**, 1314 (1953).

(3) L. F. Hatch and V. Chiola, *ibid.*, **73**, 360 (1951).

(4) C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).

(5) M. Harfenist, This Journal, **79**, 2211 (1957).

(6) (a) A single run with slightly discolored propargyl bromide which had been stored for 6 months and not distilled just before use gave a normal rate of quaternization; (b) propargyl bromide: b.p. 82–83°, $n^{24.5}D$ 1.4910; allyl bromide: b.p. 68–69°, $n^{26.8}D$ 1.4640.

(7) (a) M. S. Newman and J. H. Wotiz, This Journal, **71**, 1292 (1949); (b) b.p. 83.3–85° (22 mm.), $n^{23.5}D$ 1.4884.

(8) L. P. Albro, R. Baltzly and A. P. Phillips, *J. Org. Chem.*, **14**, 771 (1949).

(9) The "50% acetone" was made of equal volumes of acetone and of water, and was therefore 44.1% acetone by weight.

5.66 millimoles of each component could be used in the reactions of 1-bromo-2-heptyne in "50% acetone," because of the low solubility of this halide. At measured intervals 10.0-ml. aliquots were pipetted from the reaction flasks into 20 ml. of 0.5 *N* aqueous nitric acid, treated with a slight excess of standard 0.1 *N* silver nitrate, 2 ml. of nitrobenzene was added, and the excess of Ag^+ was back-titrated with thiocyanate. Preliminary experiments proved that no detectable change in titer was found in aliquots titrated after 0.5 hour as compared with aliquots titrated immediately.[10]

The results of the titrations were converted to rate constants by plotting $X/A - X$ *vs. t*, where X was the amount of halide ion produced in t minutes, and A was the initial amount of alkyl halide and amine in moles/l. The slopes of the resulting straight lines were equal to Ak. The reactions were followed to 50–70% of completion. Five points were taken for each of the duplicate runs with the bromoheptyne in "50% acetone," and 8–11 points for each of the other runs. All constants reported were determined at least in duplicate.

The results of typical runs with the two acetylenic halides are given in Tables II and III.

TABLE III

REACTION OF PROPARGYL BROMIDE WITH 1-CARBETHOXY-4-METHYLPIPERAZINE IN "50% ACETONE"

Initial wt. amine = 2.1062 mg. (12.23 millimoles); initial wt. of halide = 1.4552 mg. (12.24 millimoles); volume = 250.0 ml.; T = 24.90°; slope found: 4.43×10^{-3}; $k = 9.07 \times 10^{-2}$ l moles^{-1} min.$^{-1}$

Time, min.	2	14	60	90	122	162	200	261	325	394
Ml. Ag^+ (0.1000 *N*)	0.300	0.400	2.350	3.000	3.000	3.000	3.000	3.500	4.000	4.000
Ml. SCN^- (0.1100 *N*)	0.227	0.100	1.158	1.440	1.178	0.897	0.650	0.784	0.987	0.805
Millimoles Br^-/l.	.50	2.90	10.76	14.06	17.04	20.13	22.85	26.38	29.14	31.14
$A - X$, millimoles/l.	48.44	46.04	38.18	34.88	31.90	28.81	26.09	22.56	19.80	17.80
$X/A - X$	0.013	0.0630	0.2820	0.4067	0.5341	0.6995	0.8763	1.161	1.472	1.749

Results and Discussion

The rate constants found in this work are given in Table IV.

TABLE IV

RATE CONSTANTS FOR QUATERNIZATION OF HALIDES WITH 1-CARBETHOXY-4-METHYLPIPERAZINE AT 25°

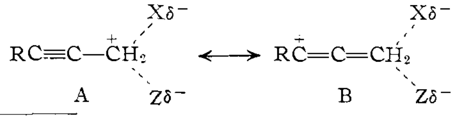
Halide	Solvent	10*k*, l./mole-min.	No. of determ.	Relative *k* CH_3I = 1
CH_3I	"50% acetone"[9]	1.22 ± 0.02	2	1
$CH_2{=}CHCH_3Br$	"50% acetone"[9]	2.25 ± .03	2	1.84
$CH{\equiv}CCH_2Br$	"50% acetone"[9]	0.892 ± 0.007	4[11]	0.73
$C_4H_9C{\equiv}CCH_2Br$	"50% acetone"[9]	3.50 ± .02	2	2.86
$C_4H_9C{\equiv}CCH_2Br$	"75% acetone"[12]	1.59 ± .02	2	

The rate of quaternization is seen to be 2.5 times as fast for allyl bromide as for propargyl bromide. Comparison of this result with those summarized in Table I shows that our results are in opposite order to those found with the halide interchange reactions of either iodide or of radiochloride. However, the same order of reactivity appears to occur in the initial rate constants for the SN2 reactions of hydroxyl ion with allyl and propargyl chlorides in aqueous ethanol,[4] although the variation of the rate constant for the allyl chloride with concentration of base in Vernon's work makes precise comparison impossible. It was separately shown in preliminary experiments that the sum of the halide ion produced by solvolysis and by the SN2 reaction with hydroxyl ion was too small to account for the results reported here.[13]

The increase in rate of quaternization in going from propargyl bromide to 1-bromo-2-heptyne (Table IV, lines 3 and 4) is in the same direction as the results reported (Table I, lines 3 and 5) for propargyl chloride *vs.* 1-chloro-2-butyne with iodide. The opposite order, however, would be anticipated from the propargyl bromide results (Table I, lines 4, 6 and 7). The increase in rate constant obtained for the iodide reaction on going from the 3-*n*-butyl- to the 3-*t*-butyl-substituted propargyl bromide (Table I, lines 6 and 7) shows an activating influence of additional alkyl groups, as would be expected from our results and from those based on the chlorides with iodide in acetone.

The high SN2 reactivity of propargyl halides is not readily understood. It is commonly explained in terms of a contribution toward lowered energy of the transition state by a resonance form (illustrated for attack by nucleophile Z^-), by analogy with similar explanations for allylic systems (*cf.* ref. 4). Contribution of a resonance form resembling B to the structure of the propargyl halides has been used to explain the C–halogen distances determined by electron diffraction for those compounds.[14] An increased stabilization of B by electron feed-in when R = alkyl as compared to B when R = H might lead to the increase in rate found going from the propargyl bromide to the heptynyl bromide quaternization.

The structure B seems to have an unlikely electronic distribution. However, attempts were made



$$\underset{\text{A}}{RC{\equiv}C{-}\overset{+}{C}H_2} \longleftrightarrow \underset{\text{B}}{R\overset{+}{C}{=}C{=}CH_2}$$

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(10) Two adsorption indicators were tried unsuccessfully in an attempt to use direct titration with silver nitrate solution. Phenosafranin gave a poor end-point, as it frequently does with bromides, and eosin could not be used because the halide production was not "frozen" adequately by acetic acid solutions. Conductimetric measurement [*cf.* R. W. D. Preston and H. O. Jones, *J. Chem. Soc.*, **101**, 1930 (1912); R. P. Larsen and C. A. Kraus, *Proc. Nat. Acad. Sci.*, **40**, 70 (1954)] gave rate constants higher than were obtained titrimetrically, which increased with time. It is presumed that this was due to an increase in the relative contribution of the unimolecular solvolysis with lowered concentration of amine and halide. A disproportionately large effect of the hydrogen ion produced by the solvolysis on the conductivity of the solution would be expected.

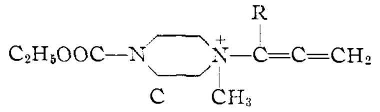
(11) One of these, run in the presence of an equivalent of potassium nitrate to test for interference due to salt effect of the quaternary salt formed by the reaction under study, gave $k = 0.891 \times 10^{-2}$, in excellent agreement with the others.

(12) Three volumes of acetone to one of water; therefore, 70.3% by wt. of acetone.

(13) Neither propargyl bromide, 1-bromo-2-heptyne nor methyl iodide gave appreciable amounts of halide after 200 minutes in "50% acetone" containing an equimolar amount of disodium phosphate [pK_a for the conjugate acid, $H_2PO_4^-$ = 7.12; pK_a for the conjugate acid of 1-carbethoxy-4-methylpiperazine = 7.31—*cf.* M. Harfenist, THIS JOURNAL, **76**, 4991 (1954)]. Only 7% of the amount of bromide produced by the SN2 reaction in that time (70% completion) was produced in 200 minutes under those conditions by allyl bromide.

(14) L. Pauling, W. Gordy and J. H. Saylor, THIS JOURNAL, **64**, 1753 (1942). However, see L. F. Hatch and D. J. Mangold, *ibid.*, **77**, 176 (1955), and reference 2.

to detect any allene C which might have been produced by attack of the nucleophilic amine at the positive carbon of resonance form "B." The quaternary salt from propargyl bromide gave the



theoretical titer of acetylenic hydrogen by silver ion titration, and so appears free of detectable allene C, R = H. The hept-2-ynyl quaternary salt which might contain C, R = C_4H_9, showed no infrared absorption in the 5 μ region characteristic of allenic absorption (0.1 mm. thickness, 5% in $CHCl_3$). Surprisingly, for a compound with a "buried" acetylenic group,[15] this latter quaternary salt showed moderately intense acetylenic absorption at 4.41 μ.

It is, of course, possible to reconcile non-detection of allenes with existence of the allenic resonance form B. It would seem wiser, however, to tentatively explain the high S_N2 reactivity of propargylic halides as due to the great polarizability of the triple bond,[16] and the increase in rate when R = alkyl by an increase in electron availability leading to a further increase in polarizability. This of course does not explain the electron-withdrawing properties of the propargyl group which are shown, for example, by the low basicity of propargylamines,[17] and the high acidity of α,β-acetylenic acids.[18]

The rate of quaternization with methyl iodide as compared with allyl bromide reported here seems reasonable. The most nearly comparable experiments[18] are the quaternizations of dimethylaniline by allyl *iodide* (k = 1.08) and methyl iodide (k = 0.143) in ethanol solution. If it is assumed that the rate of reaction of allyl bromide is slower than that of the iodide by a factor of about 6–7,[19] these constants would be in reasonable agreement with the ratio of rates reported here. Although the ratio of the results of Preston and Jones for triisoamylamine and the same halides differs from what would be expected from the work reported here, their methyl iodide results with this amine are also out of line with the rest of their own data.[20]

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(15) J. H. Wotiz and F. A. Miller, THIS JOURNAL, **71**, 3441 (1949).

(16) *Cf.* J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3452 (1953).

(17) K. N. Campbell, F. C. Fatora, Jr., and B. K. Campbell, *J. Org. Chem.*, **17**, 1141 (1952). A possible explanation of the electronegativity of the acetylenic bond has been advanced by A. D. Walsh, *Disc. Faraday Soc.*, **2**, 18 (1947).

(18) R. M. Hixon and I. B. Johns, THIS JOURNAL, **49**, 1786 (1927).

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(20) N. Menschutkin, *Z. physik. Chem.*, **5**, 589 (1890).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE TOKYO INSTITUTE OF TECHNOLOGY]

On the Thermal Dissociation of Organic Compounds. XIII. The Effect of Ring Size on the Rate of the Thermal Dissociation of Cyclopolymethyleneureas

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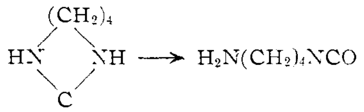
On heating, cyclic ureas dissociate into ω-aminoalkyl isocyanates with opening of the ring. The rate constants of the thermal dissociation of eight cyclic ureas in fatty acid were determined. The rates increase in the order 5-, 6- < 15- < 17- < 13- < 11- < 7- < 8-membered ring ureas. The relation between ring size and reactivity in this dissociation is discussed.

Introduction

It already has been shown that, on heating, ureas dissociate into isocyanates and amines.

$$RHN—CO—NHR \rightleftharpoons R—NCO + H_2N—R \quad (1)$$

The kinetics of the thermal dissociation of urea and some substituted ureas in fatty acids[2–6] have been studied. Similarly, in the case of cyclotetramethyleneurea, for example, the mechanism shown by equations 2–4 is considered.



(2)

$$H_2N(CH_2)_4NCO + 2ClCH_2COOH \longrightarrow ClCH_2CONH(CH_2)_4NHCOOCOCH_2Cl \quad (3)$$

$$ClCH_2CONH(CH_2)_4NHCOOCOCH_2Cl \longrightarrow ClCH_2CONH(CH_2)_4NHCOCH_2Cl + CO_2 \quad (4)$$

The reaction in chloroacetic acid can be followed by measuring the rate of evolution of carbon dioxide[5] (eq. 4), as reaction 2 is rate-determining.

In the present work, the kinetics of the thermal dissociation of eight cyclopolymethyleneureas in chloroacetic acid were studied, and the relation between ring size and the reactivity of the cyclic ureas was obtained.

Ring ureas were synthesized from polymethylene diisocyanate and water *via* equations 6 and 7.

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