466. *Kinetics and Mechanisms of Reaction of 2-Benzamidoethyl Bromide.*

By Y. Pocker.

The initial rate of formation of 2-phenyloxazolinium ion from 2-benzamidoethyl bromide in absolute ethanol is not depressed by added tetraethylammonium chloride, bromide, iodide, thiocyanate, or azide; a small positive salt effect is observed which is practically identical with the one caused by the corresponding perchlorate, borofluoride, or nitrate. Also, the initial rates for bromide-ion production equal the corresponding rates of cyclisation.

In nitromethane, in the presence of weakly nucleophilic reagents, the initial rates of cyclisation and of bromide-ion production are again equal. However, in the presence of the strongly nucleophilic azide ions the rate of bromide-ion production is larger than the initial rate of cyclisation, the excess being directly proportional to the azide-ion concentration. The mechanism is discussed in terms of two simultaneous reactions: an internal S_N2 cyclisation, as in ethanol, and an external S_N2 attack by N_3^-.

The rates of cyclisation of 2-benzamidoethyl bromide in various solvents are strikingly parallel with the data for bimolecular Menschutkin reactions; this accords with the proposed mechanism.

Neighbouring-group participation occurs with acylamino-groups in both substitution and addition reactions.[1-3] This paper deals with the mechanism of cyclisation of 2-benzamidoethyl bromide as revealed by competitive experiments with added nucleophiles which are relatively weak bases, and by the dependence of the cyclisation rate on solvent composition.

Experimental

Materials.—Nitromethane was purified, chromatographed, and fractionated as previously described.[4] Commercial ethyl alcohol was dried by Lund and Bjerrum's method [5] and fractionated with exclusion of moisture under oxygen-free nitrogen. Commercial methyl alcohol, purified by Bjerrum and Zechmeister's method,[6] had n_D^{25} 1·3271. Isopropyl alcohol was freed from peroxides with solid stannous chloride and dried with magnesium (activated with iodine). Benzyl alcohol, dried ($CaSO_4$) and fractionated with exclusion of moisture under oxygen-free nitrogen, had b. p. 205—206°; n_D^{25} 1·5371. Nitrobenzene was crystallised five times from itself,[7] dried (P_2O_5), and distilled at reduced pressure.

Acetone was boiled with potassium permanganate. After being distilled, the product was dried and fractionally distilled from $Mg(ClO_4)_2$. Chloroform was dried according to Walden, Ulich, and Werner's method.[8]

Acetonitrile and benzonitrile were dried, distilled from phosphoric oxide, and chromatographed through freshly dried alumina. Pyridine was purified by Burgess and Kraus's method.[9]

2-Benzamidoethyl bromide, prepared by condensation of benzoyl chloride with 2-bromoethylamine hydrobromide in the presence of alkali,[10] and recrystallised from benzene, had m. p. 105—106°. 2-Bromoethylamine hydrobromide, prepared from fractionated 2-hydroxyethylamine (b. p. 167—169°) and hydrobromic acid,[11] and recrystallised from water, had m. p. 172—173°. 2-Benzamidoethyl azide was prepared from benzoyl chloride and 2-azidoethylamine in

[1] McCasland, Clark, and Caster, *J. Amer. Chem. Soc.*, 1949, **71**, 637.
[2] Winstein and his co-workers, series of papers in *J. Amer. Chem. Soc.*, 1950 onwards; *Chem. and Ind.*, 1956, 56; *Experientia*, 1957, **13**, 183.
[3] Heine and his co-workers, *J. Amer. Chem. Soc.*, 1956, **77**, 310.
[4] Pocker, *J.*, 1958, 240.
[5] Lund and Bjerrum, *Ber.*, 1931, **64**, 211.
[6] Bjerrum and Zechmeister, *Ber.*, 1932, **65**, 894.
[7] McAlpine and Smyth, *J. Chem. Phys.*, 1935, **3**, 55.
[8] Walden, Ulich, and Werner, *Z. phys. Chem.*, 1925, **116**, 261.
[9] Burgess and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 706.
[10] Gabriel, *Ber.*, 1889, **22**, 2222; Gabriel and Heyman, *ibid.*, 1890, **23**, 2495.
[11] *Organic Syntheses*, Coll. Vol. 2, p. 91.

the presence of alkali.[12] Tetraethylammonium iodide was recrystallised from acetone–methanol and dried under vacuum (Found: I, 49·3. Calc. for $C_8H_{20}NI$: I, 49·35%). The bromide was recrystallised and dried as above (Found: Br^-, 38·1. Calc. for $C_8H_{20}NBr$: Br^-, 38·0%). The chloride, perchlorate, and borofluoride were prepared by the exact neutralisation of the hydroxide, recrystallised, and dried as above. The nitrate was prepared by the potentiometric titration of the iodide with silver nitrate in acetonitrile.

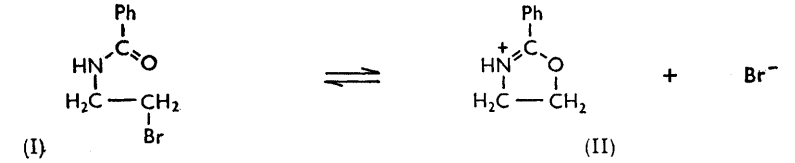
The azide and thiocyanate were prepared by extracting into ether an acidified solution of the corresponding sodium salt and shaking the ethereal solution with aqueous tetraethylammonium hydroxide [Found: N_3^-, 24·5. Calc. for $C_8H_{20}N^+N_3^-$: N_3^-, 24·4. Found: CNS^-, 30·6. Calc. for $C_8H_{20}N(CNS)^-$: CNS^-, 30·8%].

Kinetic Measurements.—Reaction mixtures were prepared by addition of the necessary amount of a standard solution of the tetraethylammonium salts and solvent, both at 25·0°, to a dry weighed sample of 2-benzamidoethyl bromide kept in a glass stoppered flask (50 c.c.) at 25·0°. The sample for kinetic zero could therefore be pipetted as soon as the addition of solvent and dissolution were complete. Aliquot portions (5 c.c.) were delivered into 40 c.c. of acetone (−80°) and titrated with standard sodium methoxide (lacmoid). Tetraethylammonium azide in acetone behaves as a base towards lacmoid and the overall rate of its disappearance (either in the form of HN_3 or $Ph{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2N_3$) was followed by titration with standard acid.

Bromide ions were determined potentiometrically by titration with standard silver nitrate either at low temperatures (−80°) in acetonitrile or after preparing samples for titration by extraction. In the latter method, samples from kinetic runs were delivered into carbon tetrachloride (60 c.c.) at −10° and this solution was shaken three times with 20 c.c. of ice-cold water. 2-Phenyloxazoline was identified as the picrate, $C_9H_9ON,C_6H_3O_7N_3$, yellow needles, m. p. 177°.

Results

2-Benzamidoethyl bromide (I) cyclises to 2-phenyloxazolinium bromide (II) to an extent of *ca.* 30% in absolute ethanol and *ca.* 35% in nitromethane at 25°. In absolute ethanol the initial rate of cyclisation is $k_\Delta = 2{\cdot}42 \times 10^{-5}$ sec.$^{-1}$. Added pyridine (0·25M) has no effect on the initial rate of cyclisation; $k_\Delta = 2{\cdot}42 \times 10^{-5}$ sec.$^{-1}$. As expected, however, the equilibrium position moves towards the product because pyridine transforms the latter into the less reactive 2-phenyl-



(I) (II)

oxazoline. Added water has a small accelerative effect (Table 1). Charges are being created in the cyclisation, and the transition state is more polar than the initial state. Accordingly, added NEt_4ClO_4 (0·10M) also causes a small increase in rate ($k_\Delta = 2{\cdot}56$) but has almost no effect on the equilibrium position. The initial rate of cyclisation is similarly increased by other tetraethylammonium salts (see Table 1).

TABLE 1. *Initial first-order rate coefficients of cyclisation, k_Δ (sec.$^{-1}$), and of bromide-ion production of 2-benzamidoethyl bromide* (RBr) *in ethanol and aqueous ethanol at 25·0°.*

(*a*) In absolute ethanol in the presence of 0·10M-tetraethylammonium salts; [RBr] = 0·050M.

[Salt]	10^5k_Δ	$10^5k_1^{Br}$	[Salt]	10^5k_Δ	[Salt]	10^5k_Δ	$10^5k_1^{Br}$
NEt_4ClO_4	2·56	2·60	NEt_4Cl	2·54	NEt_4NO_2	—	2·58
NEt_4BF_4	2·60	2·54	NEt_4Br	2·60	NEt_4CNS	2·51	—
NEt_4NO_3	2·51	2·62	NEt_4I	2·57	NEt_4N_3	2·50	2·55

(*b*) In ethanol–water. (By "*x*% EtOH" we mean a mixture of *x* volumes of ethanol and 100 − *x* volumes of water.) [RBr] = 0·050M.

%EtOH	100	90	80	70	60	50	40	30
10^5k_Δ	2·42	3·6	4·7	5·5	6·85	7·95	9·3	11·3

In nitromethane the initial first-order rate coefficient of cyclisation is 2·5 times its value in absolute ethanol ($k_\Delta = 6{\cdot}65 \times 10^{-5}$ sec.$^{-1}$). Both bromide and perchlorate ions produce a

similar increase in the *initial* rate of cyclisation (see Table 2). In the presence of azide ions, however, the overall rate of disappearance of 2-benzamidoethyl bromide is higher than the corresponding rate of cyclisation. The initial first-order rate coefficients of disappearance of azide ions increase linearly with azide concentration, *i.e.*, $k_1^{Br} = k_1^{N_3} = k_0 + k_2[NEt_4N_3]$. Azide ions disappear (*a*) by combining with ("neutralising") the oxazolinium ion to form oxazoline and HN_3 ($k_0 = k_\Delta = 6{\cdot}65 \times 10^{-5}$ sec.$^{-1}$) and (*b*) by direct displacement of bromine from 2-benzamidoethyl bromide to produce 2-benzamidoethyl azide ($k_2 = 6{\cdot}0 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$). The bimolecular rate of substitution of bromine from the parent ethyl bromide by azide ions was similarly investigated. The rate in ethanol at 25·0° was extremely small ($k_2^{EtBr} \sim 1{\cdot}3 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$) so that in the presence of 0·1M-NEt_4N_3 the rate is still much slower than the cyclisation of 2-benzamidoethyl bromide in this solvent. On the other hand, in nitromethane at 25·0°, $k_2^{EtBr} = 6{\cdot}2 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. A comparison of this value with that obtained for 2-benzamidoethyl bromide indicates that the effect on k_2 of substituting a benzamido-group in the 2-position is relatively small.

The initial rate of cyclisation was also determined in various solvents (Table 3). In some of these, the cyclisation reaches an early equilibrium and the initial rate had to be confirmed by

TABLE 2. *Initial first-order rate coefficients of cyclisation, k_Δ (sec.$^{-1}$), of 2-benzamidoethyl bromide in the presence of various tetraethylammonium salts, and of disappearance of tetraethylammonium azide, $k_1^{N_3}$ (sec.$^{-1}$), in nitromethane at 25·0°.*

$d\Delta/dt = k_\Delta[RBr]$, $-d[NEt_4N_3^-]/dt = k_1^{N_3}[RBr]$, $dBr^-/dt = k_1^{Br}[RBr]$.

	[RBr] = 0·020M				[RBr] = 0·0163M			
Salt	Concn. (M)	10^5k_Δ	$10^5k_1^{Br}$	Salt	Concn. (M)	10^5k_Δ ‡	$10^5k_1^{Br}$	$10^5k_1^{N_3}$
NEt_4ClO_4...	0·05	6·92	7·02	NEt_4N_3 †	0·00175	—	—	7·7
NEt_4BF_4 ...	0·05	7·00	6·95	NEt_4N_3 ...	0·0035	6·7	8·9	8·8
NEt_4NO_3...	0·05	6·98	7·07	NEt_4N_3	0·0070	—	10·5	10·8
NEt_4Br ...	0·05	6·96	7·1	NEt_4N_3 ...	0·0105	6·6	13·5	13·2
NEt_4I	0·05	6·94	—	NEt_4N_3 ...	0·0140	—	—	15·0

* By acidity measurements.
† In the absence of RBr in nitromethane at 25·0°: $-d[NEt_4N_3]/dt \sim 0$.
‡ By direct estimation of the cyclisation product.

TABLE 3. *Initial first-order rate coefficients of cyclisation, k_Δ (sec.$^{-1}$), of 2-benzamidoethyl bromide in various solvents at 25·0°.*

Solvent.....	Ph·CH_2OH	Me·NO_2	Me·CN	Ph·NO_2	Ph·CN	Me·COMe	MeOH
10^5k_Δ	8·06	6·65	5·36	5·32	4·91	3·84	3·22
Solvent.....	EtOH	PriOH	$CHCl_3$	EtOH–MeCN (1 : 1, v/v)			
10^5k_Δ	2·42	1·86	1·74	6·44			

measurements in the presence of pyridine. This amine is not sufficiently basic to induce the basic mechanism of cyclisation,[2,3] or nucleophilic to compete with the internal cyclisation, so that with sufficiently low concentrations of pyridine the rate of cyclisation is almost independent of its concentration and confirms the values obtained from very early points in the pure solvent.

DISCUSSION

The ring formation cannot be an S_N1 ionisation followed by cyclisation, since the reaction proceeds thousands of times more rapidly than the ethanolysis of ethyl bromide, which is anyway largely bimolecular, and there is no reason to expect a 2-benzamido-group to stabilise a carbonium ion this much. In agreement with this conclusion, the initial rate of cyclisation is not depressed by nucleophilic competitors. In both ethanol and nitromethane the cyclisation of 2-benzamidoethyl bromide is best described as an internal displacement resembling a bimolecular nucleophilic substitution in which the bond-forming and bond-breaking processes are kinetically synchronous.[13] In accord with

[12] Forster and Newman, *J.*, 1911, **99**, 1277.
[13] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953.

this view, a Walden inversion occurs in the cyclisation of the toluene-*p*-sulphonate of *N*-benzoylallothreonine methyl ester in ethyl alcohol containing potassium acetate.[14]

The various anions used vary widely in reactivity, but none can attack the primary carbon atom of 2-benzamidoethyl bromide in *ethanol* as rapidly as the oxygen atom which is already present in the molecule. This causes most displacement reactions of 2-benzamidoethyl bromide in ethanol to go through the cyclic intermediate. But in nitromethane azide ions are sufficiently nucleophilic (probably because they are not hydrogen-bonded as in ethanol) to attack this at a rate comparable with that of the cyclisation. Direct substitution can therefore proceed simultaneously with cyclisation and the overall reaction is a mixture of both internal and external S_N2 reactions:

$$\text{2-Phenyloxazoline} + HN_3 + Br^- \xleftarrow[\text{(Zeroth order in } N_3^-)]{\text{Internal } S_N2} \text{(I)} \xrightarrow[\text{(First order in } N_3^-)]{S_N2 \text{ with } N_3^-} Ph{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2N_3$$

The initial rates of cyclisation of 2-benzamidoethyl bromide in a series of ethanol–water mixtures indicate that water has only a small accelerative effect, which if expressed by the Winstein–Grunwald equation [15] $\log k = \log k_0 - mY$ leads to $m = 0{\cdot}15$. This is because a considerable amount of assistance towards bond fission in the transition state does not come from the solvent but from the bond being formed, *i.e.*, from the participation of the neighbouring benzamido-group *via* an internal S_N2 process.

The order of solvent effectiveness is the order usually found in bimolecular Menschutkin-type reactions: [16–20]

Reaction	$Ph{\cdot}CH_2{\cdot}OH$	Me·COMe	MeOH	EtOH
1. $NEt_3 + EtI \longrightarrow NEt_4I$ (at 100°) [16–19]	(100)	45·7	38	27·9
2. Cyclisation of $Ph{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Br$ (at 25·0°) ...	(100)	47·6	40	30

	$MeNO_2$	MeCN	Me·COMe	MeOH	EtOH	$CHCl_3$
3. Quaternisation rates [20]	(100)	72·4	65·4	55·5	39·4	19·4
4. Cyclisation rates (Table 3) ...	(100)	82·5	57·7	48·4	36·4	26·2

The rate of cyclisation by either S_N1 or internal S_N2 mechanism should increase with the ion-solvating power of the medium, since the reaction by either mechanism involves charge formation in the transition state. However, in S_N1 reactions with initially neutral molecules, methyl and ethyl alcohols facilitate the bond fission more than acetone, acetonitrile, or nitrobenzene, confirming the conclusion that the reaction is best described as an internal S_N2 process.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1. [*Received, November 25th*, 1958.]

[14] Attenburrow, Elliot, and Penny, *J.*, 1948, 310.
[15] Grunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846 and subsequent papers in that Journal.
[16] Menschutkin, *Z. phys. Chem.*, 1890, **6**, 41.
[17] Grimm, Ruf, and Wolff, *ibid.*, 1931, *B*, **13**, 301.
[18] Pickles and Hinshelwood, *J.*, 1936, 1353.
[19] Moelwyn-Hughes, " The Kinetics of Reactions in Solution," 2nd edn., Oxford University Press, 1947, p. 207.
[20] Newmann, " Steric Effects in Organic Chemistry," Chapter 2 by Eliel, p. 70, John Wiley and Sons Inc., New York, 1956.