[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, NAVAL POWDER FACTORY, AND CHEMISTRY DEPARTMENT, THE GEORGE WASHINGTON UNIVERSITY]

Kinetics and Mechanism of the Cyclization of Substituted Alkylnitroguanidines[1]

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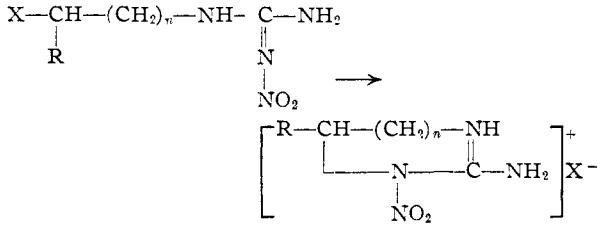
The kinetics of the cyclization of 1-β-nitroxy(or halo-)alkyl-2-nitroguanidines and 1-γ-nitroxyalkyl-2-nitroguanidines to give 1-nitro-2-amino-1,3-diazacyclo-2-pentene and -diazacyclo-2-hexene salts, respectively, in aqueous solution have been studied by a conductimetric technique. In later stages of the reactions, conductance–concentration relationships are complicated by hydrolysis of the products. The relative rates of cyclization have been found to be 1-β-bromoethyl->1-β-chloroethyl->1-β-nitroxyethyl->1-γ-nitroxypropyl->1-β-nitroxypropyl-2-nitroguanidine. The reaction rates obeyed a first-order law. The relative rates of the β-bromoethyl, β-chloroethyl and β-nitroxyethyl compounds are in the order expected from the bond energies of the C–Br, C–Cl and C–O covalent links. The more rapid cyclization of the 1-β-nitroxyethyl-, as compared to the 1-β-nitroxypropyl-2-nitroguanidine, favors an internal SN2 mechanism rather than SN1. From the rate–temperature relationships, energies and entropies of activation have been computed. These quantities have been interpreted in terms of the SN2 mechanism. The data are supported by data from analogous reactions reported in the literature.

Introduction

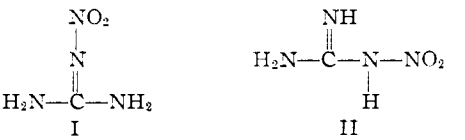
The isomerization of 1-β-nitroxy(or halo-)alkyl-2-nitroguanidines and 1-γ-nitroxyalkyl-2-nitroguanidines to 1-nitro-2-amino-1,3-diazacyclo-2-pentene (imidazolinium) and -diazacyclo-2-hexene (tetrahydropyrimidinium) salts, respectively, was first reported by McKay and co-workers.[2,3] Other cases of this cyclization have been reported by Fishbein and Gallaghan.[4] The general equation for the reaction may be represented as



where X = Cl, Br, or ONO_2, R = H or CH_3, n = 1 or 2

A study of the kinetics of these reactions was of interest for evaluating the effect of molecular structure on reaction rate in homologous series of compounds and for the information that would thereby be obtained about the reaction mechanism. This paper reports the results of such an investigation.

The structure of nitroguanidine has been only recently established[5–10] as the symmetrical nitramine form I rather than the asymmetrical nitramine form II.



Although conventional single and double bonds are shown in I, actually considerable resonance exists and all the C–N bonds and the N–N bond are found to be the same length (1.34–1.36 Å.) within experimental precision, these bond lengths differing substantially from those usually observed. Presumably the nitrimine structure is also characteristic of alkylnitroguanidines.

Kinetics

The kinetics of this reaction in aqueous solution have been studied by a conductimetric technique, since the reactants are non-ionic and the cyclic products are ionic. The limited solubility of the reactants in water restricts the investigation to very dilute solutions, in which linear relationships of conductance to concentration of cyclic products hold. The validity of the conductimetric technique was established by an independent gravimetric determination. In the later stages of the reaction, hydrolysis of the cyclic product vitiates the linear relationship between conductance and extent of reaction.

The relative rates of cyclization have been found to be 1-β-bromoethyl- > 1-β-chloroethyl- > 1-β-nitroxyethyl- > 1-γ-nitroxypropyl- > 1-β- nitroxypropyl-2-nitroguanidine. Rate constants were determined for all except the bromo compound which cyclizes so readily that it was practically completely cyclized during purification by recrystallization. The reaction rates obeyed a first-order law. The rate constants found are given in Table I, below, along with average deviations noted in duplicate determinations.

Plots of log k against $1/T$(°K.) for those compounds whose rates were measured at three temperatures show a very good fit to the straight line required by the Arrhenius equation, $k = Ae^{-E_a/RT}$. The energy of activation, E_a, and the frequency factor, A, together with the entropy of activation, ΔS^*, which has been obtained by the application

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(3) A. F. McKay and H. P. Thomas, *Can. J. Chem.*, **29**, 391 (1951).

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(6) M. W. Kirkwood and G. F Wright, *J. Org. Chem.*, **18**, 629 (1953).

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(8) W. D. Kumler, *ibid.*, **18**, 676 (1953).

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TABLE I

RATE CONSTANTS FOR THE CYCLIZATION OF SUBSTITUTED-1-ALKYL-2-NITROGUANIDINES

Compound	T (°C.)	k (sec.$^{-1}$)
1-β-Chloroethyl-	49.87	$61.6 \pm 0.3 \times 10^{-6}$
	39.85	$17.7 \pm .4 \times 10^{-6}$
	30.00	$4.75 \pm .02 \times 10^{-6}$
1-β-Nitroxypropyl-	49.83	$49.9 \pm .65 \times 10^{-7}$
	39.87	12.19×10^{-7}
	30.00	$2.68 \pm .09 \times 10^{-7}$
1-β-Nitroxyethyl-	49.84	$19.41 \pm .06 \times 10^{-6}$
	39.85	$5.41 \pm .02 \times 10^{-6}$
	30.00	$1.366 \pm .0115 \times 10^{-6}$
1-γ-Nitroxypropyl-	50.00	$11.10 \pm .03 \times 10^{-6}$
	40.00	$3.14 \pm .03 \times 10^{-6}$

of Eyring's transition state theory, are given in Table II below. The deviation measures given are those computed from deviations of rate constant values at the two extreme temperatures by applying the equations of Purlee, Taft and DeFazio.[11]

TABLE II

ARRHENIUS CONSTANTS AND ENTROPIES OF ACTIVATION FOR THE CYCLIZATION OF SUBSTITUTED-1-ALKYL-2-NITROGUANIDINES

Compound	E_a (kcal.)	A (sec.$^{-1}$)	ΔS^* (e.u.)
1-β-Chloroethyl-	25.09 ± 0.06	5.90×10^{12}	-2.2 ± 0.2
1-β-Nitroxypropyl-	$28.69 \pm .36$	1.30×10^{14}	$+4.0 \pm 1.1$
1-β-Nitroxyethyl-	$26.03 \pm .08$	8.02×10^{12}	-1.6 ± 0.3
1-γ-Nitroxypropyl-	$25.39 \pm .21$	1.65×10^{12}	-4.7 ± 0.7

Experimental

Synthesis.—1-β-Chloroethyl-2-nitroguanidine, m.p. 115.7–116.0°, resolidified at 116.5° and remelted at 187.5–187.8° with decomposition, was synthesized according to the method of McKay and Milks,[2,12] recrystallized from 95% ethanol, washed with ethanol, ice-water (from distilled water) to remove ionic impurities and finally with ethanol. A portion of the product was cyclized by heating dry at 74° for 23 days. The purity of the linear and cyclic compounds was checked by microgravimetric chloride ion determinations.[13] Since the linear compound would be expected to cyclize during the usual heating of the solution on the steam-bath[14] in the precipitation step of the analysis, separate determinations were made using or omitting the heating step after solution of the compound in water. The results were: linear compound, 0.4% (cold precipitation); 21.0% (hot precipitation); cyclized compound, 21.8% (cold precipitation); 22.0% (hot precipitation); theoretical chloride ion in cyclic compound, 21.3%. The small amount of chloride ion shown in the cold precipitation of the linear compound is doubtless due to cyclization during the solution and precipitation processes; turbidity developed slowly in this solution as it stood at room temperature after addition of the silver nitrate solution prior to filtration.

1-β-Bromoethyl-2-nitroguanidine was also synthesized according to the method of McKay and Milks.[2] In dissolving the crude product in hot 95% ethanol for the recrystallization process, the hot solution remained cloudy and became more cloudy on cooling. The crystals obtained on standing stuck together as though obtained from an oil rather than through the normal recrystallization process. The crystals were filtered, washed with 95% ethanol, ice-water (in which they appeared to be quite soluble) and finally 95% ethanol again. During the melting point determination, the solid became translucent at 94°, but did not melt then, becoming opaque again at 107° and finally melting with decomposition at 178–179°.

The above evidence indicated that considerable cyclization to the ionic compound had taken place during the recrystallization, and an aqueous solution of the crystals gave a positive qualitative test for halide ion. Microgravimetric analysis for bromide ion, performed as for the chloride ion above, showed 38.3% by hot precipitation and 38.1% by cold precipitation, compared to a theoretical value of 37.9%. It was evident that 1-β-bromoethyl-2-nitroguanidine cyclizes much more rapidly than 1-β-chloroethyl-2-nitroguanidine. Since the rapid cyclization interfered with purification of the bromo compound, no quantitative rate measurements were made.

1-β-Nitroxypropyl-2-nitroguanidine was also synthesized by the method of McKay and Milks.[2] The crude product was recrystallized from 95% ethanol, washed with distilled water and finally with ethanol.

A separate sample of 1-β-nitroxypropyl-2-nitroguanidine[15] which had been synthesized *via* the Rathke procedure[16] was obtained for checking the purity and identity of the compound prepared above. A portion of this material was purified by recrystallization from 95% ethanol as above. Melting points of the material prepared *via* the Rathke procedure and the McKay method and a mixed melting point were determined to be 130.5–131°, 130° and 130–130.5°, respectively.

Attempts to cyclize the recrystallized 1-β-nitroxypropyl-2-nitroguanidine by refluxing in *n*-butanol gave no insoluble crystals.[17] The compound was cyclized by heating dry at 74° for 23 days. The cyclic product was readily soluble in water in contrast to the limited solubility and slow rate of solution of the linear compound; this is also true of all the other pairs of linear and cyclic isomers examined.

Samples of 1-β-nitroxyethyl-2-nitroguanidine which had been synthesized *via* the Rathke procedure[16] were obtained.[18] This compound, after two to three years at room temperature, contained an appreciable quantity of cyclic isomer, as indicated by the conductance of freshly prepared aqueous solution. This material was purified by repeatedly slurrying with distilled water, filtering and air drying, then recrystallizing from 95% ethanol, followed by washings with distilled water and 95% ethanol. The conductance of an aqueous solution of the material so purified did not differ appreciably from that of conductance water itself. The melting point was found to be 109–110° which is the same as that reported by McKay and Milks[2] for their crude product.[19]

A sample of 1-nitro-2-amino-2-imidazolinium nitrate, m.p. 160–162° with decomposition, which had been prepared from 1-β-nitroxyethyl-2-nitroguanidine by the method of McKay and Milks[2] was obtained[20] for use as a reference standard in rate measurements.

Samples of 1-γ-nitroxypropyl-2-nitroguanidine and its cyclic isomer, 1-nitro-2-amino-1,3-diazacyclo-2-hexene nitrate[21] had been synthesized *via* the Rathke procedure.[4,16] The linear compound was purified by the same technique of slurrying with distilled water and recrystallizing from 95%

(11) E. L. Purlee, R. W. Taft, Jr., and C. A. DeFazio, THIS JOURNAL, **77**, 837 (1955).

(12) The 1-methylnitroso-2-nitroguanidine and β-chloroethylamine hydrochloride were generously supplied by Dr. A. F. McKay.

(13) All microanalyses were performed by Mrs. P. P. Wheeler, microanalyst of the Research and Development Department, Naval Powder Factory.

(14) J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 44, 157–158.

(15) Synthesized by Dr. J. A. Gallaghan.

(16) L. Fishbein and J. A. Gallaghan, THIS JOURNAL, **76**, 1877 (1954).

(17) This is not surprising. McKay and Milks[2] report the cyclization of β-nitroxypropylnitroguanidine with water only. In a subsequent review article (*Chem. Revs.*, **51**, 301 (1952)) McKay indicates (p. 334) that cyclization was performed by refluxing with 2-pentanol, giving as the original reference McKay and Milks, ref. 2. This is a matter of some importance because the melting of nitramines is usually accompanied by decomposition, and the boiling point of 2-pentanol is above the reported melting point of the cyclic isomer, 1-nitro-2-amino-5-methyl-2-imidazolinium nitrate.

(18) Synthesized by R. Evans, Dr. J. A. Gallaghan and R. Scharf.

(19) These authors report that recrystallization twice from 95% ethanol yielded crystals melting at 92–93.5°. In our determination of the melting point, special care was exercised in observing the crystals on a hot stage through a microscope and no evidence of melting was detected at 90–95°. It appears that McKay and Milks' recrystallization was done without precautions (short heating period of solution and washing of crystals with water) necessary to exclude cyclic impurity from the recrystallized product.

(20) Synthesized by R. Evans.

(21) Synthesized by Lawrence Fishbein.

ethanol as was used for 1-β-nitroxyethyl-2-nitroguanidine above. Its melting point was found to be 121–122°.

Apparatus for Rate Measurements.—An Industrial Instruments, Inc., Conductivity Bridge, Model RC-1B, was used throughout. This instrument supplies a 1000-cycle bridge source voltage, and bridge balance is observed by a cathode ray null indicator. The scale was calibrated against precision resistors (accuracy ±0.1%). Resistance readings were always made with the dial moving from high to low to eliminate worm corrections. Initial experiments were made with a dip-type platinum electrode conductivity cell, Industrial Instruments Model CEL 2A, with cell constant approximately 0.1 $cm.^{-1}$. Later measurements were made using ground glass stoppered cells (constant approximately 0.17 $cm.^{-1}$) into which the solution could be placed (Fisher Scientific Co. Catalog No. 9-366) and which could be immersed in constant temperature baths. Constant temperature baths at 30, 40 and 50° were used and temperature controlled to ±0.02° during each run in which final rate measurements were made.

Exploratory Measurements.—The linearity of conductance of aqueous solutions with concentration of cyclic isomer was established with a thermostat at 30° and a dip-type cell. Solutions of 1-nitro-2-amino-2-imidazolinium nitrate in conductivity water, of this cyclic compound together with its linear isomer, 1-β-nitroxyethyl-2-nitroguanidine, and of 1-nitro-2-amino-5-methyl-2-imidazolinium nitrate were tested and showed the expected linear relationship for concentrations of 200 mg./l. and less.

In exploratory rate measurements with 1-β-nitroxyethyl-2-nitroguanidine in conductivity water, the reaction appeared to follow a first-order law initially but seemed to deviate from this in the later stages, the conductance reading eventually exceeding that for 100% conversion to the cyclic form. The data for one such series of measurements are shown in Table III.

TABLE III

EXPLORATORY RATE MEASUREMENTS OF THE CYCLIZATION OF 1-β-NITROXYETHYL-2-NITROGUANIDINE (100.0 MG./L.) IN AQUEOUS SOLUTION AT 50°

Time (hr.)	Conductance × 10^5 (mhos)	Apparent concn. linear compd. (mg./l.)
0	5.0	97.2
1	8.6	91.0
2	10.8	87.2
4	18.5	74.3
6	25.4	62.6
12	38.3	40.3
22	52.5	15.9
26	55.4	11.0
46	66.9	<0
70	74.3	<0

The deviation from first-order linearity occurring in the later stages of the reaction suggests that we have a case of successive reactions, in which the initial cyclic product undergoes a reaction which leads to solutions of further increased conductance. It would seem that hydrolysis of the cyclic product is likely, considering the evidence for hydrolysis of imidazoline rings previously reported. Such evidence includes the hydrolysis of 1,3-dinitro-2-imino-1,3-diazacyclopentane reported by McKay and Milks,[2] the better yields of cyclic products that they obtained by refluxing substituted alkylnitroguanidines with 2-pentanol rather than water, Miescher and co-workers' data[22] showing that imidazoline rings were readily opened when the free bases were boiled with water and McKay and Viron's work[23] on the hydrolysis of 1-nitro-2-nitramino-2-imidazoline.

In support of the proposition of successive reactions and as justification for the use of conductance measurements, at least prior to the point at which hydrolysis of the cyclic product noticeably affects conductance, the following facts may be cited: Heating a substituted alkylnitroguanidine by itself for increasing periods of time yields products whose conductance reaches as an upper limit that of the cyclic isomer. Conductance of aqueous solutions of a cyclic isomer at constant temperature increases with time, and this increase accounts quantitatively for the non-linearity of cyclization rate data. An independent method of analysis for extent of cyclization yields the same results as the conductance measurements in the absence of hydrolysis effects.

(1) **Dry Heating.**—Samples of approximately 5 mg. each of 1-β-nitroxyethyl-2-nitroguanidine were accurately weighed into ground-glass stoppered erlenmeyer flasks. The samples were heated in an oven at 96° and individual samples removed hourly. Conductivity water was then added from a buret to given solutions of 100 mg./l. concentration, and the conductance of the solutions at 30.0° was determined using the dip-type cell. The five samples withdrawn at 3, 4, 5, 6 and 7 hr. gave solutions whose conductance was 63.0 ± 0.2 (average deviation) × 10^{-5} mho. Another sample of 1-β-nitroxyethyl-2-nitroguanidine had been heated for 372 days at 65.5°. Two samples of this material, approximately 5 mg. each, were weighed out and made up, as above, to solutions of 100 mg./l. The conductance of the solutions was 62.7 ± 0.2 × 10^{-5} mho.

(2) **Conductivity of Hydrolysis Products.**—A solution of 100.0 mg./l. of 1-nitro-2-amino-2-imidazolinium nitrate in conductivity water was made up and placed in a constant temperature bath at 50.0°. The variation of conductance of the solution with time was determined with the dip cell at 30.0° in exactly the same manner as was done in the measurement of the cyclization rate of the linear isomer at 50.0°, above. The data in Table IV show the slow rate, but considerable magnitude of increase in conductance which accompanies hydrolysis of the cyclic isomer.

TABLE IV

INCREASE OF CONDUCTANCE OF AQUEOUS SOLUTION OF 1-NITRO-2-AMINO-2-IMIDAZOLINIUM NITRATE (100.0 MG./L.) AT 50°

Time (hr.) Conductivity water	Conductance (mho) 1.49×10^{-5}
0	62.3 × 10^{-5}
23	66.9 × 10^{-5}
48	73.3 × 10^{-5}
71	78.2 × 10^{-5}
121	88.7 × 10^{-5}
216	104.9 × 10^{-5}
312	117.6 × 10^{-5}
479	133.5 × 10^{-5}
811	151.5 × 10^{-5}
909	155.0 × 10^{-5}

The data on the rate of change of conductance of an aqueous solution of the cylic isomer (Table IV) can be used to correct conductance values obtained during investigations of the rate of cyclization of the corresponding linear compound at the same temperature. A virial equation, −corr. = $(Kt - Lt^2) \times 10^{-5}$ mho (t in hours) where $K = 0.235$ and $L = 1.82 \times 10^{-4}$, can be fitted to the data of Table IV up to 479 hr. In the course of cyclization in aqueous solution, an increment of cyclic isomer formed in any time interval, dt, will alter the conductance according to the above equation for the time that it is in solution if it is assumed that the linear compound does not affect the rate at which the cyclic isomer hydrolyzes. To get the correction at any time, t', the incremental corrections from time zero to t' are summed.

$$-\text{corr.} = \int_0^{t'} dc'(K[t' - t] - L[t' - t]^2) \times 10^{-5}$$

$$dc' = kc_0 e^{-kt}\, dt$$

(c' here represents concentration of cyclic isomer, and c_0 is the initial concentration of linear isomer).

$$-\text{corr.} = 10^{-5} kc_0 \int_0^{t'} e^{-kt} (K[t' - t] - L[t' - t]^2)\, dt$$

This last equation is equally integrable, yielding

$$-\text{corr.} = 10^{-5} c_0 \left[K(A - B) - L(t'[A - B]) - \frac{e^{-kt'}[k^2t'^2 + 2kt' + 2] - 2)}{k^2} \right]$$

(22) K. Miescher, A. Marxer and E. Urech, *Helv. Chim. Acta*, **34**, 1 (1951).

(23) A. F. McKay and S. J. Viron, THIS JOURNAL, **72**, 3905 (1950).

where

$$A = -t'(e^{-kt'} - 1)$$

and

$$B = \frac{e^{-kt'}(-kt' - 1) + 1}{k}$$

The above procedure is a general one for the case of successive first-order reactions. It can be applied to the data of Table III. A rate constant of 0.0656 hr.$^{-1}$ is estimated from the slope of the straight line drawn to fit, approximately, the early points in the cyclization of 1-β-nitroxyethyl-2-nitroguanidine. Using this rate constant, corrections to conductance readings at the last three points, 70, 46 and 26 hours, were computed. The value of 0.97 for c_0 was used, and small additional correction terms were computed to correct for conductance due to hydrolysis of the 0.03 portion of the linear isomer which had cyclized by the time the initial reading was taken. The total conductance corrections for hydrolysis of cyclic isomer at 70, 46 and 26 hours are 12.3, −7.2 and −3.1 × 10^{-5} mhos, respectively. The corrected conductance values, 62.0, 59.7 and 52.1 × 10^{-5} mhos correspond to 0, 3.8 and 16.6%, respectively, of linear isomer remaining. Without this correction the corresponding amounts of linear isomer are −21, −10 and 11%. The concentration expected at any time on the basis of the estimated rate constant and the concentration of linear isomer at zero time can be predicted from the first-order rate relationship, $\log(c_0/c) = kt/2.303$. From this relationship (using the rate constant estimated above) we get values of 1.0, 4.7 and 17.6% at 70, 46 and 26 hours, respectively. These values differ by only 1% from those obtained using conductance readings corrected for hydrolysis of the cyclic isomer. Considering the exploratory nature of the rate measurements, this agreement is quite good.

(3) Reaction Rate by Chloride Determination.—Microgravimetric determination of chloride ion[14] was selected as the independent method of analysis for extent of cyclization of 1-β-chloroethyl-2-nitroguanidine. A solution of 190.56 mg. of the linear compound in 1000 ml. of conductivity water was prepared and made up to volume at 25 ± 1°. Closed conductivity cells were used for the conductance measurements. The cells were first kept filled for many days with hot distilled water in order to extract soluble ionic matter from the glass inner wall. They were then calibrated with solutions of approximately 200 mg./l. of the cyclic isomer, 1-nitro-2-amino-2-imidazolinium chloride, at 30.0°. In the calibration the filled cells were placed in the thermostat and resistance readings taken after allowing 0.5 hr. for temperature equilibration.

Part of the solution of the linear compound prepared above was put into the rinsed calibrated conductivity cells after which the remainder of the solution and the filled cells were placed in the bath at the same time. After allowing 0.5 hr. for temperature equilibration, resistance of the solutions in the cells was measured and a 50-ml. portion from the flask was pipetted into a clean beaker, silver nitrate solution added and the resulting suspension of silver chloride filtered immediately. The same procedure was repeated at measured time intervals. From the weight of silver chloride found at each determination was deducted the weight of silver chloride obtained in a blank determination using conductivity water. Table V below shows the good agreement between the two independent methods of estimating per cent. cyclization. The agreement fails only when most of the linear material has been converted to the cyclic isomer and the effect of hydrolysis of the cyclic isomer on conductance of the solution becomes important.

Precise Rate Measurements and Computation of Specific Rate Constants.—For final rate measurements, time of reaction was measured to the nearest second or five seconds, as required, at each reading of solution resistance. All conductivity cells were calibrated with aqueous solutions of each of the cyclic isomers at the temperatures at which rates were to be measured. The rate of change of conductance of the conductivity water alone in each cell in the appropriate constant temperature bath was determined in order to make corrections as necessary. When measurements are made over a long period of time, the conductance of the water increases gradually, presumably because of the slow solution of ions from the glass walls. Initially, this effect is counteracted by a decrease in conductance which is probably due to loss of dissolved carbon dioxide as equilibrium is established at the bath temperatures.

Cyclization rate measurements were made on aqueous solutions of 1-β-chloroethyl-2-nitroguanidine (217.1 mg./l.), 1-β-nitroxypropyl-2-nitroguanidine (189.9 mg./l. and 94.9 mg./l., the latter prepared by dilution of a portion of the former), 1-β-nitroxyethyl-2-nitroguanidine (208.9 mg./l.), and 1-γ-nitroxypropyl-2-nitroguanidine (186.8 mg./l.).

TABLE V

MICROGRAVIMETRIC AND CONDUCTIMETRIC DETERMINATION OF CYCLIZATION OF 1-β-CHLOROETHYL-2-NITROGUANIDINE AT 30.0°

Time (hr.)	% Cyclized Conductimetric Cell 1	% Cyclized Conductimetric Cell 2	% Cyclized Conductimetric Av.	% Cyclized gravimetric
0	1.5	1.6	1.6	1.4
2.5	5.5	5.6	5.6	6.0
4.5	8.7	8.9	8.8	8.2
22.0	32.4	31.8	32.1	30.4
23.0	33.3	33.1	33.2	32.1
24.0	34.4	33.9	34.2	
24.5	34.9	34.3	34.6	34.8
26.5	37.1	36.7	36.9	
26.75	37.4	36.9	37.2	36.7
28.5	39.2	38.6	38.9	38.1
46.0	55.2	54.6	54.9	54.5
48.0	56.8	55.8	56.3	55.1
52.5	60.2	59.2	59.7	58.4
70.0	71.1	70.1	70.6	67.5
76.5	74.4	73.2	73.8	74.1
99.0	83.4	82.2	82.8	
143.0	94.3	92.3	93.3	90.5
190.0	98.9	97.3	98.1	95.7

The cyclization rates were determined as described above and the rate constants obtained by the standard least squares treatment.[24] For 1-β-chloroethyl-2-nitroguanidine at 39.85 and 49.87°, a modification of the treatment of Dills[25] was also used to obtain the rate constant. This method involves a least squares treatment applied to the exponential form of the first-order rate equation after the introduction of a Taylor expansion. It requires only that a first-order rate expression hold and that a proportionality relationship exist between extent of reaction and the physical property measured; neither the proportionality constant nor any information about concentrations need be known. The rate constants obtained by this method are thus independent of calibrations with the cyclic isomer. The constants obtained agreed quite closely with those resulting from the conventional treatment.

Plots of the rate data for the four compounds show the first-order linearity of the reaction and also show the apparent deviation due to the effect of hydrolysis of the product on conductance of the solution. This hydrolysis effect appears earliest (with respect to extent of reaction) for the slowest cyclization reaction. This is to be expected since the structural factors governing rate of cyclization should have little effect on the rate of hydrolysis of the cyclic product. In the computation of rate constants, data from regions where non-linearity was shown were discarded.

Reaction Mechanism and Structure–Reactivity Relationships

The relative rates of cyclization of the three substituted ethylnitroguanidines are in the order expected from the relative ease of breaking the covalent bond to give ions. The bond energies for the covalent links have been reported as 60 kcal. for C–Br, 73 kcal. for C–Cl and 77 kcal. for C–O.[26] Hughes and co-workers[27–29] found, in investigations of the

(24) A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons Inc., New York, N. Y., 1943, p. 240.

(25) C. E. Dills, M.S. Thesis, The George Washington University, 1951.

(26) T. L. Cottrell, "The Strengths of Chemical Bonds," Butterworths, London, 1954.

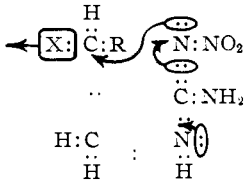
(27) E. D. Hughes, C. K. Ingold and U. G. Shapiro, *J. Chem. Soc.*, 1277 (1937).

(28) K. A. Cooper, E. D. Hughes and C. K. Ingold, *ibid.*, 1280 (1937).

(29) E. D. Hughes and B. J. McNulty, *ibid.*, 1283 (1937).

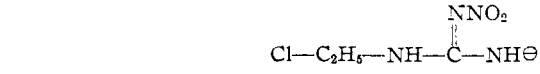
rates of hydrolysis of *t*-butyl halides, *t*-amyl halides and *sec*-octyl halides, that the bromo compounds hydrolyzed considerably more rapidly than the corresponding chloro compounds. This is in agreement with our findings on the relative reactivity of the bromo and chloro compounds.

There are, *a priori*, at least two possible mechanisms for the cyclization of substituted alkylnitroguanidines, the SN1 and SN2 mechanisms.[30] In the former the rate-controlling step involves the splitting of the carbon–halogen or carbon–nitrate bond to form carbonium and negative ions, followed by a rapid ring closure step. The SN2 type mechanism would require "backside attack" by the nitrimine nitrogen on the carbon bearing the halogen atom or nitrate group along with simultaneous displacement of the halogen or nitrate. The transition state would be one in which there was partial formation of the C–N bond and partial separation of the C–X or C–O bond. The electronic shifts required for the over-all reaction are pictured below. (This representation of the bonds does not indicate the resonance system in the cation.)



Substitution of alkyl groups for hydrogen on a carbon atom bearing a negative group increases the tendency of the negative group to ionize. Therefore, an increase in the rate of cyclization of substituted alkylnitroguanidines with additional alkyl substitution of that carbon atom would be expected if the reaction proceeded *via* SN1. On the other hand, additional alkyl substitution of the carbon bearing the negative group would reduce the rate of an SN2 reaction by hindering attack of the approaching nucleophilic group. The relative rates of cyclization of 1-β-nitroxyethyl and 1-β-nitroxypropyl-2-nitroguanidines therefore favor the internal SN2 mechanism. McKay[31–33] has previously proposed a carbonium ion mechanism for this cyclization but admitted that this was premature in the absence of kinetic studies.

An anionic mechanism is not expected for this reaction. McKay[31–33] has reported the cyclization of 1-β-chloroethyl-2-nitroguanidine in the presence of alkali to yield 2-nitramino-2-imidazoline and has offered a mechanism involving an extremely unlikely carbonium ion. An anionic mechanism is likely in alkali, presumably one involving



as intermediate. Since the product obtained in cyclization under neutral conditions is different from that obtained in alkaline solution, the mechanism must be different.

Interpretations of the Arrhenius constants and the entropies of activation in terms of reaction mechanism can also be made. Although the deviation measures determined on the basis of deviation between duplicate determinations of rate constant may indicate in most cases a precision somewhat greater than the accuracy of the data because of the possibility of systematic errors, significant differences in energy and entropy of activation for the cyclization of different compounds have been found here. It should also be pointed out that, where three points fit the linear relationship between log k and $1/T$ so well, greater confidence can be placed in the values of slope and intercept than is reflected in Taft's two point equations.[11]

The 0.9 kcal. difference in energy of activation (see Table II) between 1-β-chloroethyl- and 1-β-nitroxyethyl-2-nitroguanidine reflects the differences in bond energy between the chloro and nitroxy links to carbon. The 2.7 kcal. difference in energy of activation between 1-β-nitroxyethyl- and 1-β-nitroxypropyl-2-nitroguanidine is a reflection of the additional energy needed to overcome the steric hindrance of the methyl group to attack on the central carbon atom by the nitrimine nitrogen. This is evidence for the unimolecular SN2 mechanism. The fact that entropy of activation is 6 e.u. higher for 1-β-nitroxypropyl- than for 1-β-nitroxyethyl-2-nitroguanidine can be attributed to a greater separation of the C–O nuclei in the transition state of the *sec*-compound as compared to the primary.

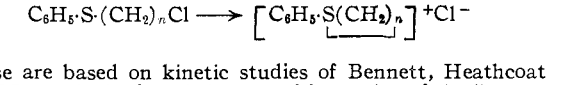
The increased entropy of activation corresponds to a larger q/T term where q is the thermal energy necessary for stretching the C–O bond from the ground state to the activated state. Increase of both energy and entropy of activation in SN2 reactions when a secondary halide is compared to a primary halide appears to be quite common. Thon[34] tabulates kinetic data on isotopic exchange of halogen in alkyl halides. In each case for which values of energy of activation and frequency factor are given, the secondary halides show higher energies of activation and frequency factors than the isomeric or homologous primary halides. A higher frequency factor corresponds to a more positive (or less negative) entropy of activation.

The 3 e.u. difference in entropy of activation for formation of the 5- and 6-membered rings (cyclization of 1-β-nitroxyethyl- and 1-γ-nitroxypropyl-2-nitroguanidine, respectively) may be regarded as an illustration of the Price–Hammett rule that, in a polar reaction, the more complex (entropy containing) molecule loses more in entropy in attaining the activated state.[35]

The effect of product ring size on reaction rate for a somewhat analogous reaction, the cyclization of haloalkylamines to give cyclic imines has been investigated by Freundlich and Salomon.[36] They found that formation of the 5-membered ring proceeded most rapidly. Our data also show the 5-membered ring to be formed more readily than the 6-membered ring, although the difference in rates of formation is not as great as that reported by Freundlich and Salomon. The conditions in their study were somewhat different from ours, *e.g.*, their cyclization was carried out in the presence of sodium hydroxide (to liberate the haloalkylamine originally present as the hydrohalide), however, the reaction velocity was found to be independent of alkali concentration and to follow a first-order rate law.

Salomon[37] reported Arrhenius constants for this cyclization. For the 5- and 6-membered rings obtained by the cyclization of 4-chlorobutylamine and 5-chloroamylamine, respectively, activation energies of 19.4 ± 1 and 20.9 ± 0.7 kcal. and log frequency factor values corresponding to entropies of activation at 40° of −5 and −8 e.u., respectively, are given. This 3 e.u. difference is exactly what we have found in this investigation.

In the same paper, Salomon also computes Arrhenius constants for the cyclization of ω-chloroalkyl phenyl sulfides to give cyclic sulfonium halides.



These are based on kinetic studies of Bennett, Heathcoat and Mosses[38] who found the rate of formation of the 5-membered ring to be 76 times as fast as the 6-membered ring. For formation of the 5- and 6-membered rings, the activation energies are 23.4 ± 1 kcal. and 23.9 kcal., and entropies of activation at 40° are −8 and −15 e.u., respectively. Again, the entropy of activation for formation of the 6-membered ring is more negative than for the 5-membered ring.

Salomon[37] also gives data showing the effect of steric hindrance on the cyclization of haloalkylamines. For formation of the 5-membered ring from 4-chloro-*n*-butylamine, the activation energy is 19.4 ± 1 kcal. For formation of the same ring from 4-chloro-1-methyl-*n*-amylamine, in which methyl groups at two positions serve to hinder formation of the cyclic compound, the activation energy is 23.0 ± 1 kcal. Here there is a significant increase in activation

(30) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 79 ff.

(31) A. F. McKay, *J. Org. Chem.*, **16**, 1395 (1951).

(32) A. F. McKay and R. O. Braun, *ibid.*, **16**, 1829 (1951).

(33) A. F. McKay, *Chem. Revs.*, **51**, 301 (1952).

(34) N. Thon, Editor, "Tables of Chemical Kinetics—Homogeneous Reactions," National Bureau of Standards Circular 510, Washington, 1951, pp. 279–281.

(35) F. P. Price, Jr., and L. P. Hammett, THIS JOURNAL, **63**, 2387 (1941).

(36) H. Freundlich and G. Salomon, *Ber.*, **66B**, 355 (1933).

(37) G. Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933).

(38) G. M. Bennett, F. Heathcoat and A. N. Mosses, *J. Chem. Soc.*, 2567 (1929).

energy due to steric hindrance, just as we have found. The entropy of activation values at 40° are −5 e.u. for the unhindered ring formation and +2 e.u. for the cyclization involving steric hindrance and the displacement of a substituent from a secondary carbon atom. Thus displacement of the substituent from the secondary carbon gives a slightly positive entropy of activation, as we have found, and the difference in entropy of activation involved in cyclization by attack at a secondary carbon compared to a primary is +7 e.u., which is in excellent agreement with our +6 e.u. difference for the cyclization of substituted alkylnitroguanidines.

The analogies between the thermodynamic quantities of activation for the cyclization of substituted alkylnitroguanidines and the cyclizations of both chloroalkyl phenyl sulfides and haloalkylamines, especially the latter, are evidence that the unimolecular SN2 mechanism is common to all these reactions.

In general, it may be pointed out that the entropies of activation of the cyclizations of substituted alkylnitroguanidines do not differ much from zero, as is expected of a unimolecular reaction.

Acknowledgments.—Thanks are due to Dr. Arthur F. McKay, who graciously consented to this kinetic investigation and to many colleagues in research for aid, advice and discussions.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Rates of Reaction of Some Halogen-containing Esters with Potassium Iodide in Dry Acetone[1,2]

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RECEIVED MARCH 9, 1956

The rates of reaction of ethyl bromoacetate, ethyl bromochloroacetate, ethyl bromofluoroacetate, ethyl α-bromopropanoate, ethyl chloroacetate and ethyl dibromoacetate at 20 and 0°, and of ethyl chlorofluoroacetate, ethyl dibromofluoroacetate and ethyl dichloroacetate at 40 and 20° with potassium iodide in dry acetone have been measured. The results show that inductive and steric effects are significant.

Alexander[3] and Royals[4] state that in SN2 reactions, the effect of a second halogen atom on the reactivity of a halogen atom attached to the same carbon atom is twofold. First, due to the higher partial positive charge on the carbon atom, the approach of a negative ion is facilitated. Secondly, the size of the halogen atom itself would tend to shield the carbon atom from rearward attack. The higher partial positive charge on the carbon atom would tend to make a stronger carbon to halogen bond thus making it more difficult for this bond to be broken.[5] Since the van der Waals radii of fluorine and hydrogen are similar (1.35 Å. compared to 1.29 Å.[6]), it would be expected that polar effects become of greater relative importance when the second halogen is fluorine. There are, however, no data available in the literature for this type of reaction.[7]

In the present investigation, rates have been measured for the reaction of potassium iodide with a series of dihalo esters in which the second halogen was varied successively from fluorine to chlorine to bromine. The results (Table I) show that both inductive and steric effects are significant in the reaction. The great drop in reactivity from the bromo- to the bromofluoro ester and also of the dichloro- to the chlorofluoro ester must be explained almost entirely on the basis of an inductive effect. This observation shows that Reeve, McCaffery and Kaiser[8] probably understated inductive effects for this type of reaction when they claimed that polar effects are unimportant. The decreasing reactivity of ethyl bromochloro- and dibromoacetate indicate that steric effects are also important, since one would expect the reverse order of reactivities based on the inductive effect. It is also clearly shown that the steric effect of the methyl group in ethyl α-bromopropanoate greatly overshadows the inductive effect. If based on the inductive effect entirely, its rate would be faster than that of ethyl bromoacetate. To show that the measured rate of the reaction between ethyl bromofluoroacetate and

(1) This paper represents part of a thesis submitted by D. L. Christman to the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Ethyl Corporation Fellow, 1953–54.

(2) From a thesis submitted by R. W. Johnson, Jr., to the Graduate School, Purdue University in partial fulfillment of the requirements for the degree of Master of Science.

(3) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 88–89.

(4) E. E. Royals, "Advanced Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1954, p. 291.

(5) Available data indicate that the steric effect is predominant. Thus, E. D. Hughes, *Trans. Faraday Soc.*, **37**, 625 (1941), found that methylene chloride reacts more slowly than methyl chloride with basic reagents, and H. A. C. McKay, THIS JOURNAL, **65**, 702 (1943), observed the same effect in a comparison of relative reactivities of methyl iodide and methylene iodide toward exchange with radioactive iodide ion. H. A. Smith and W. H. King, *ibid.*, **72**, 95 (1950), found from ethanolysis reactions that a chlorine atom on a double-bonded carbon in allyl chloride had little effect on the rate of reaction or energy of activation but that the rate decreased 100-fold, while the activation energy increased by nearly 6 kcal. per mole, when there was a second chlorine atom in the allylic position. P. Petrenko-Kritschenko and V. Okatzky, *Ber.*, **59B**, 2131 (1926), made similar observations regarding reactivities of a number of polyhalo methanes and ethanes compared with the monohalo compounds.

(6) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 189.

(7) The hydrolysis of benzodifluorochloride in 50% aqueous acetone studied by J. Hine and D. E. Lee, THIS JOURNAL, **74**, 3182 (1952), is an SN1 reaction. J. Banus, H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, 60 (1951), have shown that the exchange of radioactive iodide ion with the iodine atom of trifluoroiodomethane is first order with respect to organic iodide and zero order with respect to inorganic iodide and have explained this finding by an initial ionization of the trifluoromethyl iodide. J. E. Boggs, *Dissertation Abst.*, **14**, 591 (1954), recently determined the kinetics of exchange of isotopic chlorine between hydrogen chloride and methyl chloride, chlorofluoromethane, chlorodifluoromethane and chlorotrifluoromethane. However, these reactions are either first order or complex order in reactants.

(8) W. Reeve, R. L. McCaffery and T. E. Kaiser, THIS JOURNAL, **76**, 1858 (1954).