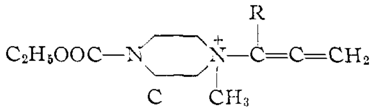
to detect any allene C which might have been produced by attack of the nucleophilic amine at the positive carbon of resonance form "B." The quaternary salt from propargyl bromide gave the



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$_N$2 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]

Acknowledgment.—The author acknowledges helpful discussions with Dr. R. Baltzly. The infrared absorption curve was run by Mr. J. E. Murphy of The Analytical Research Laboratory, Burroughs Wellcome & Co.

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[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

BY SHOICHIRO OZAKI, TERUAKI MUKAIYAMA[1] AND KEIKICHI UNO

RECEIVED DECEMBER 7, 1956

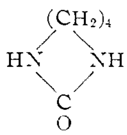
On heating, cyclic ureas dissociate into ω-aminoalkyl isocyanates with opening of the ring. The rate constants of the thermal dissociation of eight cyclic ureas in fatty acid were determined. The rates increase in the order 5-, 6- < 15- < 17- < 13- < 11- < 7- < 8-membered ring ureas. The relation between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

Introduction

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

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

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.



$$\longrightarrow H_2N(CH_2)_4NCO \quad (2)$$

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

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

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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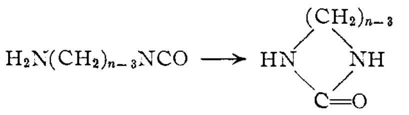
$$OCN(CH_2)_{n-3}NCO + H_2O \longrightarrow H_2N(CH_2)_{n-3}NCO + CO_2 \quad (6)$$



$$H_2N(CH_2)_{n-3}NCO \longrightarrow \underset{C=O}{\overset{(CH_2)_{n-3}}{HN\qquad NH}} \quad (7)$$

Experimental

Procedure.—The procedures for measuring the rates of dissociation of ureas in fatty acid[2,3,5] have been described previously. On plotting the logarithm of volume of carbon dioxide, ΔY, evolved at regular intervals of time, a straight line was obtained. This indicates a first-order reaction rate. The rate constant is given by the gradient of such a plot.[7]

Preparation of Materials.—Cylic ureas were synthesized[8] from the corresponding diisocyanates and water by methods a and b.

(a) **Without Using a High Dilution Technique. Cyclotetramethyleneurea (I).**—To a solution of 120 ml. of acetone and 120 ml. of water was added dropwise the mixture of 5.4 g. of tetramethylene diisocyanate and 40 ml. of acetone in a period of 3 hr. under refluxing. After another 30 minutes the reaction mixture was cooled and polytetramethyleneurea precipitated was filtered off. The filtrate was evaporated to about 20 ml., then the precipitate which deposited was separated. Recrystallization from acetone yielded 2.8 g. (64%) of I, as colorless crystals, melting at 172–173°.

(b) **Using a High Dilution Technique. Cyclooctamethyleneurea (II).**—To a solution of 900 ml. of acetone and 900 ml. of water was added, in the rate of a drop in 10 seconds, the mixture of 3.2 g. of octamethylene diisocyanate and 70 ml. of acetone in a period of 17 hr. using a Hunsdiecker apparatus.[9] After another 30 minutes, the solution was evaporated to about 900 ml., the poly-octamethyleneurea precipitated was filtered off and again evaporated to about 10 ml. and the precipitate was collected. Recrystallization from acetone yielded 0.5 g. (18.1%) of II as colorless crystals melting at 159–160°. The melting point, synthetic method, yield of cyclic ureas and boiling point for the corresponding diisocyanate are listed in Table I.

TABLE I

Methylene-ureas	Ring number	M.p., °C.	Synthetic method	Yield, (%)	B.p. °C. (corresponding diisocyanate)	B.p. Mm. (corresponding diisocyanate)
Cyclo-di-	5	129	a	35	85–86	76
Cyclo-tri-	6	258	b	60	98	26
Cyclo-tetra-	7	172–173	a	64	93	7
Cyclo-penta-	8	238	b	22	128–130	19
Cyclo-hexa-	9		b	0	139	18
Cyclo-hepta-	10		b	0	103–104	6
Cyclo-octa-	11	159	b	18	150	10
Cyclo-deca-	13	190–191	b	49	132	0.45
Cyclo-dodeca-	15	201–202	b	41	168–169	3
Cyclo-tetradeca-	17	195–196	b	36	171	0.45

Solvent.—Chloroacetic acid was distilled thrice, b.p. 185–186°.

Identification of Reaction Product.—N,N′-Diphenylacetyltetramethylenediamine was produced by heating cyclotetramethyleneurea in phenylacetic acid for 6 hr. at 170°. It was obtained as an ether-insoluble product, m.p. 176–177°, recrystallized from acetone.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.44; H, 7.43; N, 8.63. Found: C, 74.01; H, 7.44; N, 8.44.

The rate constants of the thermal dissociation of cyclic ureas were determined under the following condition: the ratio of ureas to solvents was 1 mole:100 moles. The kinetic results are summarized in Table II and Fig. 1.

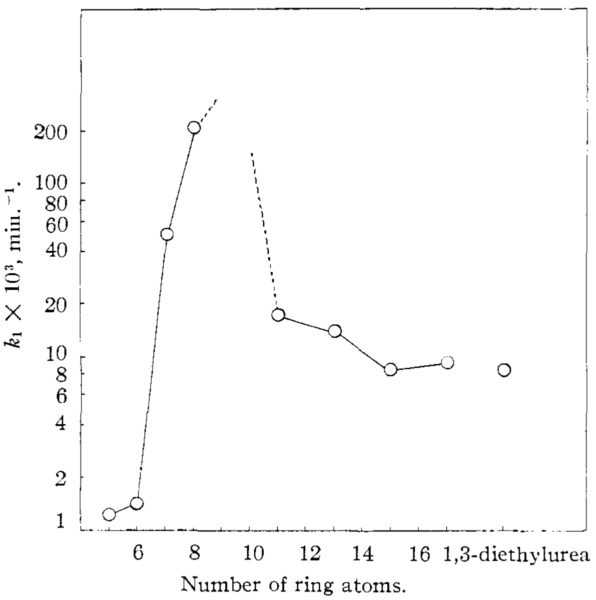


Fig. 1.—Relation between ring size and reactivity on the thermal dissociation of cyclopolymethyleneurea in chloroacetic acid: the plot of k_1 (at 139.5°) against ring number.

TABLE II

SUMMARY OF THE RATE DATA FOR THE THERMAL DISSOCIATION OF CYCLOPOLYMETHYLENEUREA IN CHLOROACETIC ACID AT 139.5°

Ring number	Rate constant $k_1 \times 10^3$, min.$^{-1}$	Relative rate
5	1.21	1
6	1.47	1.2
7	50.3	41.5
8	210	174
11	17	14
13	14.1	12
15	8.36	6.9
17	9.55	7.9
1,3-Diethylurea	8.51	7.0

Result and Discussion

It is commonly known that the reactivity of cyclic compounds depends on their ring sizes. On this matter, many[10] available kinetic results have been reported for common ring and several[11–14] for medium and large ring compounds. The SN1, SN2 and free radical type reactions proceed rapidly in 5- and 7-membered ring compounds and slowly in 6-membered compounds. 5- and 7-membered ring compounds react slower than 6- in the carbonyl-type reaction. In all reaction types mentioned above, the large ring compounds have medium reactivity between these two extremes and have almost the same reactivity as that of open chain compounds.

In the dissociation of ureas, the reaction mech-

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anism[5,6] is different from the above-mentioned reactions. The dissociation reaction of cyclic ureas proceeds through the double transfer of protons with opening of the ring. In this mechanism, two nitrogen atoms in the ring change their coördination numbers; that is, the coördination numbers of nitrogen atoms change from three to two and three to four, respectively. These points are different from those of the S_N1, S_N2, free radical and carbonyl-type reactions. Accordingly, different reactivity is expected.

In chloroacetic acid of all ring ureas studied, the 8-membered ring urea dissociates most rapidly (k_1 210 × 10^{-3} min.$^{-1}$ at 139.5°) and the 5- dissociates most slowly (k_1 1.21 × 10^{-3}). Eleven- and large ring compounds dissociate moderately. Comparing the results with those of other ring compounds reported, they generally resemble the reactivity of S_N1, S_N2 and radical-type reactions.[14] Accordingly, the reactivity of ring ureas is in inverse relation with that of carbonyl-type reactions.[11] A characteristic result obtained in the present experiment is that 5- and 6- ring ureas have similar reactivity, which has not been observed in other reaction types.

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[CONTRIBUTION NO. 1383 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Electron Exchange Polymers. IX. Synthesis of Polymers of 2,5-Dihydroxyphenylalanine and of 3,4-Dihydroxyphenylalanine (DOPA)[1]

BY H. JAMES HARWOOD[2] AND HAROLD G. CASSIDY

RECEIVED JANUARY 23, 1957

Methods are given for the preparation by the N-carboxyl anhydride technique of high molecular weight polypeptides of 2,5-dihydroxyphenylalanine and 3,4-dihydroxyphenylalanine and of copolymers of each with L-glutamic acid. The methods include those for the preparation of the appropriate monomers in which the phenolic hydroxyls of the dihydroxyphenylalanines are protected by acetyl groups. These syntheses now make available new electron exchange polymers that are also polypeptides.

In the first paper of this series,[3] the possible usefulness of electron exchange polymers of suitable composition and structure as models for certain biological systems was suggested. It seemed desirable to investigate this possibility. The postulate on which this work was based is that a reactive group when incorporated in a polymeric structure will show one or more properties different in kind or different in quantity from those of the "same" group in the molecularly dispersed monomeric state. A number of investigations have been carried out effectively from this point of view. For example, the investigations of Haskell and Hammett[4] and the further investigations of Hammett and co-workers[5] fall in this category. These investigators compared the catalytic behavior of hydrochloric acid and the acid forms of cation exchangers toward the hydrolysis of esters. They found differences in rate and specificity effects. As another example from a growing literature, Morawetz and Zimmering[6] found that solvolysis of the ester group in acrylic acid–*p*-nitrophenyl methacrylate copolymers seemed to proceed by a mechanism different from that of the solvolysis of the ester group in the monomeric model *p*-nitrophenyl trimethylacetate. As a third example, Lautsch and his co-workers[7] have carried out extensive investigations of the changes in spectra, in catalytic properties and in oxidation–reduction potential that occur when a porphyrin group is incorporated into a large molecule. We have set out to examine the properties of hydroquinone and catechol groups when present as side-chains to a polypeptide structure, thus supplementing our earlier work.[8]

This paper reports the first steps in this investigation: the synthesis of polymers of 2,5-dihydroxyphenylalanine and 3,4-dihydroxyphenylalanine and copolymers of these two amino acids with L-glutamic acid by the N-carboxyl anhydride technique. Our synthesis is patterned after the polytyrosine synthesis reported by Schlögl, Wessely and Wawersich[9] and the polyserine synthesis reported by Frankel, Cordova and Breuer.[10]

2,5-Dihydroxyphenylalanine, (I), was treated

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(1) Abstracted from the Dissertation submitted by H. James Harwood to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Union Carbide and Carbon Corp. Fellow in Organic Chemistry, 1954–1955; Procter and Gamble Co., Summer Fellow, 1955. This work was supported for several months by a research grant G 3207 (C2) from the National Institutes of Health, Public Health Service, and by a grant from the Research Corporation.

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