Cyclization and Polymerization of ω-(Bromoalkyl)dimethylamines[1]

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Received June 30, 1978

We have examined the kinetics of S_N2 ring closure of 3-bromopropyldimethylamine (**1**) (C-3) to a four-membered ring and of 6-bromohexyldimethylamine (**5**) (C-6) to a seven-membered ring as part of a study of steric factors in substitution reactions. We have made a few measurements on the cyclization of the C-5 homologue **4** and the polymerization of the C-8 homologue **6**. At 25 °C in methanol the rates for cyclization (k_1) and for polymerization (k_2) are as follows (10^5 s^{-1} and 10^5 M^{-1} s^{-1}): C-3, 5.3, 2.9; C-5, 1130, —; C-6, 1.7, 1.5; and at 80 °C $k_2 = 85 \times 10^{-5}$ M^{-1} s^{-1} for C-8. Both four-membered ring formation and seven-membered ring formation dominate over polymerization in solutions more dilute than 0.1 M. Thermodynamic data for ring-closure reactions have been summarized and it is shown that the classical explanation of ring-closure effects gives the wrong ratio for five-membered vs. six-membered ring closure by a factor of about 10^4 and the wrong ratio for four-membered vs. seven-membered ring closure by about 10^{12}.

Current interest in substitution reactions of the S_N2 type embraces a number of different aspects ranging from detailed theoretical studies[2,3] and mechanistic considerations of possible ion pair intermediates[4,5] to the energetics of solvent effects[6-8] and the computation of steric effects.[9-12] We are particularly interested in steric effects and are obtaining experimental data on ring closure reactions since these may provide valuable examples for testing the computations.

The general features of ring-closure reactions are well known; in the competition between cyclization and polymerization, cyclization wins out for formation of five-membered or six-membered rings.[13] Ring-closure reactions have been reviewed by Capon,[15] Page,[14] and Stirling,[16] and recently Baldwin[17] has proposed some general correlations.

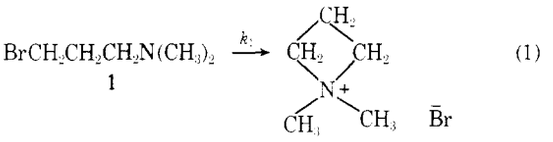
The classical explanation of the relative rates of closure of rings is based on a competition between hindrance of ring strain, which is large for three-membered and four-membered rings, smaller for five, and negligible for six, and the monotonically decreasing probability of the ends reaching each other.[18] There is also transannular hydrogen crowding in intermediate rings (8–12 atoms).

The energy factors are intriguing. For the prototype ring closures pentane to cyclopentane and hexane to cyclohexane, the six-membered ring is favored by about 3 kcal/mol based on $\Delta G°_f$.[14] In some S_N2 reactions the rate constants for closure of the five-membered ring are faster than closure to the six-membered ring by factors of about 100 to 1000. This amounts to about 3 to 4 kcal/mol. There is accordingly a discrepancy of some 6 to 7 kcal/mol that needs an adequate theoretical explanation. In other words, the product rings are not good models for the transition states.[14] We return to this question in the Discussion.

Other steric factors are also important. Alkyl substitution on the backbone accelerates the rate of ring closure.[18,19] This is often called the gem-dialkyl effect, and several examples are known.[20-22] The magnitude of the gem-dimethyl effect is sometimes predictable from consideration of enthalpies of conversion of substituted alkanes to substituted cycloalkanes.[19]

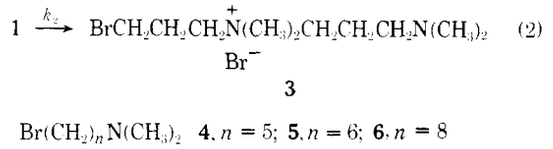
Results

In this study we have examined the rate of the thermal S_N2 reactions of 3-bromopropyldimethylamine **1**, and of related homologues in methanol. We are mainly interested in relatively large rate differences among a series of compounds, and the purpose of the present study was to explore the general characteristics of the reactions. There have been several studies of cyclizations of primary amines,[23-26] but numerous possibilities for side reactions have raised some questions of interpretation.[26] The tertiary bromoamines such as **1** (and **4**, **5**, and **6**) can still undergo a variety of reactions, but cyclization (eq 1) and polymerization (eq 2) predominate. The principal



$$\mathrm{BrCH_2CH_2CH_2N(CH_3)_2} \xrightarrow{k_1} \mathrm{CH_2(CH_2)_2N^+(CH_3)_2\ Br^-} \quad (1)$$

1



$$1 + 1 \xrightarrow{k_2} \mathrm{BrCH_2CH_2CH_2\overset{+}{N}(CH_3)_2CH_2CH_2CH_2N(CH_3)_2\ Br^-} \quad (2)$$

3

$\mathrm{Br(CH_2)_nN(CH_3)_2}$ **4**, $n = 5$; **5**, $n = 6$; **6**, $n = 8$

disadvantage is that cyclic products such as **2** and polymer such as **3** are not in general easy to separate nor to analyze, although **2** itself can be determined by NMR.

It is well known that reactions between amines and alkyl halides, often called Menshutkin reactions,[27] are particularly sensitive to solvent effects.[6-8] The reactions in alcohols show an intermediate rate, and the rates are only moderately sensitive to small amounts of water. In most of our studies we used the hydrobromide salts of **1** and its homologues. The salt was dissolved in methanol and prepared for reaction by adding a known amount of a solution of sodium hydroxide in methanol. This in effect introduces a small amount of water (2% maximum, usually much less).

The reactions of **1**, **4**, and **5** are more or less first order. The detailed kinetics are in principle complex: there is a competition between first-order cyclization (eq 1) and second-order polymerization (eq 2). With a large excess of alkali (mostly $NaOCH_3$) there is a direct second-order reaction which we designate k_{base}. Reactions 1 and 2 also are subject to a salt effect, eq 3 (acceleration).

$$k_1 = k_1°(1 + b'[\mathrm{salt}])$$
$$k_2 = k_2°(1 + b'[\mathrm{salt}]) \quad (3)$$

There is one other complicating feature in that dimer **3** (eq 2) does not cyclize appreciably under the present conditions, and hence the reaction is not strictly of the first plus second order type. It is nevertheless possible to effect a reasonable dissection based on an analysis of the apparent first-order constants obtained over an extended fraction of the reaction using eq 4.

$$k_1(\mathrm{apparent}) = k_1 + k_2[\mathrm{bromoamine, initial}]/2 \quad (4)$$

We have, however, computed k_1, k_2, and b' of eq 3 by a least-squares procedure based on numerical integration of eq 5. In

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Table I. Rate Constants for Cyclization (k_1) and Polymerization (k_2)[a]

	C-3 (1),[g] 25 °C	C-5 (4),[h] 25 °C	C-6 (5),[i] 25 °C	C-8 (6),[j] 80 °C
$10^5 k_1$[b]	5.3	1130[c]	1.7	...
$10^5 k_2$[d]	2.9	...	1.5	85[e,f]
b' (eq 3)	0.4	...	0.4	...

[a] Solvent is methanol; rate constants have std dev of about 15%. [b] In s^{-1}. [c] Extrapolated. [d] $M^{-1} s^{-1}$. [e] 0.5×10^{-5} at 25 °C. [f] $k_{base} = 3 \times 10^{-3} M^{-1} s^{-1}$ at 80 °C. [g] Registry no.: 53929-74-1. [h] Registry no.: 65102-10-5. [i] Registry no.: 65102-11-6. [j] Registry no.: 63411-31-4.

Table II. Yields of Dimethylazetidinium Bromide (2)

Concn of 1, M	% yield of 2, obsd	% yield of 2, calcd[a]
0.02	100	99
0.1	89	94
0.2	90	...
0.5	75	77
1.0	63	63

[a] From eq 5 and rate constants in Table I by numerical integration.

these equations A stands for bromoamine 1 or **5**, and Z is dimer or polymer having reactive end groups.

$$\mathrm{A(1)} \xrightarrow{k_1} \text{cyclic product(2)} + \mathrm{Br^-}$$

$$\mathrm{A + A} \xrightarrow{k_2} \mathrm{Z(3) + Br^-}$$

$$\mathrm{A + Z} \xrightarrow{2k_2} \mathrm{Z + Br^-} \qquad (5)$$

$$\mathrm{Z + Z} \xrightarrow{k_2} \mathrm{Z + Br^-}$$

$$\mathrm{A + base} \xrightarrow{k_{base}} \mathrm{AOCH_3}$$

$$\mathrm{Z + base} \xrightarrow{k_{base}} \mathrm{ZOCH_3}$$

The relevant rate constants are summarized in Table I, product data for 1 are presented in Table II, and Arrhenius equation parameters are in Table III. The approximate k_{base} for 1 and for **5** is about $1 \times 10^{-5} M^{-1} s^{-1}$. The reported rate constant for reaction for *n*-butyl bromide and sodium methoxide in methanol at 25 °C is $0.9 \times 10^{-5} M^{-1} s^{-1}$.[28]

Discussion

Since the purpose of our studies has been to explore overall effects of structure on reactivity, we have not sought to carry out the range of experiments necessary to evaluate in detail the effects of temperature on the cyclization or the polymerization, nor have we sought to explore salt effects in detail. Our studies do establish the fact that closure to four-membered rings and to seven-membered rings will usually dominate in solutions more dilute than 0.1 M, and they provide the necessary guidelines to show when serious departures may be anticipated.

Our data also show that competition from direct reaction with methoxide ion is not important in the presence of 0.1 M sodium methoxide, nor are other intermolecular substitution reactions important at such concentrations. These conclusions are significant in that they serve to validate the various previous studies of cyclization of primary bromoalkylamines, whose behavior had been in some doubt.[26] With the primary amines it is, of course, necessary to use an excess of base to avoid complexities of acid–base competition between reactants and products.

Table III. Arrhenius Parameters for Overall Reaction

	$A \times 10^{-10}$/ s^{-1} [a]	E/kcal mol^{-1} [a]	Temp range, °C
C-3 (1)	34.151	21.510 ± 0.1	25, 35, 40, 45
C-5 (4)	2.270	16.781 ± 0.5	−2, −11, −22
C-6 (5)	2.537	20.695 ± 0.12	25, 35, 45, 55
C-8 (6)	0.1443	19.761 ± 1.3	60, 70, 80

[a] Units for C-8 are $s^{-1} M^{-1}$. Error limits on A are 10% for 1, 20% for **5**, and a factor of 2 for **4** and **6**. A and E are correlated; they are given to enough places to reproduce the rate constants without round-off error. The solvent was methanol, concentrations were 0.2 M or less, and the principal reaction is cyclization for 1, **4**, and **5** and polymerization for **6** (C-8).

Table IV. Rates of Cyclization of $H_2N(CH_2)_nBr$ in Water at 25 °C[24,25]

$(H_2NCH_2CH_2Br)$	0.036
$H_2N(CH_2)_3Br$	0.0005
$H_2N(CH_2)_4Br$	30.0[a]
$H_2N(CH_2)_5Br$	0.5
$H_2N(CH_2)_6Br$	0.001
$H_2N(CH_2)_4Cl$	0.0075
$H_2N(CH_2)_5Cl$	0.00011

[a] Rough estimate; not measured.

We shall not attempt to review the literature, but our studies now indicate that most of the previous work based on primary amines can be accepted as valid measures of cyclization rates. The Freundlich data is an example (Table IV). In these studies the relative rate for cyclization to six-membered vs. seven-membered rings is about 500 while we find about 650; the relative rate of seven- vs. four-membered rings is 2 while we find $\frac{1}{3}$ for the dimethylamino series.

Table V summarizes the enthalpies, entropies, and free energies of representative cyclization reactions. In making such comparisons it is advisable to be sure that the reactions are isostructural, that, for example, hydrogen removal consistently comes from methyl as in the first nine entries. The entries show the modern assignment of strain ($\Delta\Delta H$), of entropy ($\Delta\Delta S$), and of overall strain plus entropy effects ($\Delta\Delta G$). For a given sized ring the data do correlate the gem-dimethyl effect, cyclization to 1,1-dimethylcyclohexane being favored over cyclization to cyclohexane.

Table VI summarizes the ring closure data of Table V. If cycloalkanes are taken as models for the cyclization process, then the $\Delta\Delta G$ values of Table VI summarize the classical predictions. Because of the large values of the strain energy terms ($\Delta\Delta H$), the formation of four-membered rings is predicted to be slower than formation of seven-membered rings by $\Delta G \sim 17$ kcal/mol or about 10^{12}. Experimentally the rates are about equal. The relative rates for five-membered rings and six-membered rings are also in the wrong order. The prediction is a ratio of $\frac{1}{300}$ and the observed ratio is perhaps 1000. It is clear that rate predictions based on the classical explanation are of limited value.

Experimental Section

3-Bromopropyldimethylamine (1). 3-Dimethylaminopropanol (21 g) was added to 50 mL of 48% hydrobromic acid and the flask was swept with nitrogen. The mixture was heated rapidly to 110–120 °C and held there for about 4 h. Solvent was removed at water pump pressure and the residue was further dried by azeotropic distillation

Table V. Enthalpy, Entropy, and Free Energy of Cyclization, Based on Formal Reactions

Product	Registry no.	ΔS^b	ΔH	ΔG^b	$\Delta\Delta S^{b,c}$	$\Delta\Delta H^c$	$\Delta\Delta G^{b,c}$
		$2RCH_3 \rightarrow RCH_2CH_2R + H_2$					
Alkane[d]		−5.1	10.2	11.7	0	0	0
Cyclopropane	75-19-4	17.1	37.6	32.5	22.2	27.4	20.8
Cyclobutane	287-23-0	14.2	36.5	32.3	19.3	26.4	20.6
Cyclopentane	287-92-3	11.5	16.5	13.1	16.7	6.4	1.4
Cyclohexane	110-82-7	3.3	10.5	9.5	8.4	0.4	−2.2
Cycloheptane	291-64-5	4.4	16.4	15.0	9.5	6.2	3.4
Cyclooctane	292-64-8	1.0	19.8	19.5	6.1	9.6	7.8
1,1-Dimethylcyclopentane[e]	1638-26-2	15.0	15.7	10.9	20.1	5.5	−0.8
1,1-Dimethylcyclohexane[e]	590-66-9	8.2	9.9	7.5	13.3	−0.3	−4.2
		$RCH{=}CH_2 + R'CH_3 \rightarrow R(CH_2)_3R'$					
Alkane[d]		−29.0	−19.9	−11.4	0	0	0
Cyclopropane		−7.0	7.9	10.0	21.9	27.7	21.4
Cyclobutane		−9.6	6.4	9.3	19.4	26.3	20.7
Cyclopentane		−12.7	−13.5	−9.7	16.3	6.4	1.7
Cyclohexane		−20.7	−19.5	−13.3	8.3	0.4	−1.9
Cycloheptane		−19.4	−13.6	−7.8	9.5	6.2	3.6
Cyclooctane		−22.9	−10.2	−3.4	6.1	9.6	8.0
		$RCH(CH_3)_2 + R'CH_3 \rightarrow RC(CH_3)_2CH_2R'$					
Alkane[d]		−10.2	9.2	12.2	0	0	0
1,1-Dimethylcyclopentane		10.4	13.5	10.4	20.6	4.3	−1.8
1,1-Dimethylcyclohexane		3.3	8.2	7.3	13.5	−1.0	−4.9
		$RC{\equiv}CH + R'CH_3 \rightarrow$ *cis*-$RCH{=}CHCH_2R'$					
cis-Alkene		−25.3	−31.1	−23.6	0	0	0
Cyclobutene	822-35-5	−6.5	−8.5	−6.5	18.8	22.6	17.6
Cyclopentene	142-29-0	−9.6	−26.6	−23.8	15.7	4.5	−0.2
Cyclohexene	110-83-8	−13.9	−30.8	−26.7	11.4	0.3	−3.1
		cis-$R{-}CH{=}CHR' \rightarrow$ cycloalkene + H_2					
Alkane (from 1st line above)		−5.1	10.2	11.7	0	0	0
Cyclobutene		14.6[f]	32.7	26.4[f]	19.7	22.5	14.7
Cyclopentene		11.3	14.6	9.3	16.5	4.4	−2.4
Cyclohexene (from 2-hexene)		6.8	11.2	9.2	11.9	1.1	−2.5
Cyclohexene (from 3-hexene)		7.0[f]	10.1	8.0[f]	12.2	−0.1	−3.7

[a] Primary data (kcal/mol) are for gaseous hydrocarbons at 25 °C from ref 29. [b] Entropy and free energy corrected to molar concentration basis (correction is 6.35 gibbs). [c] $\Delta\Delta Q$ values are ΔQ(cyclic) − ΔQ(alkane). [d] Average of four typical examples. [e] Averages of values for 2,2-dimethylalkane and 3,3-dimethylalkane. [f] Corrected for symmetry of *cis*-alkene (R ln 2).

Table VI. Average $\Delta\Delta Q$ Values for Ring Closure[a]

Product	Symmetry number (σ)[b]	$\Delta\Delta S$(avg)	$\Delta\Delta H$(avg)	$\Delta\Delta G$(avg)	$\Delta\Delta S_{int}$ (avg)[c]
Cyclopropane	6	22.1	27.6	21.7	25.9
Cyclobutane	8	19.4	26.4	20.6	23.5
Cyclopentane[d]	10	16.3	5.6	0.4	20.8
Cyclohexane[d]	6	9.2	−0.2	−2.8	12.9
Cycloheptane	1	9.5	6.2	3.4	9.5
Cyclooctane	8	6.1	9.6	7.8	10.2

[a] Based on $\Delta\Delta Q$ values in Table V (omitting cycloalkenes); units kcal/mol. [b] As recommended in ref 30. [c] $\Delta\Delta S$(avg) + R ln σ. [d] $\Delta\Delta S$ for dimethyl examples was reduced by R ln σ before averaging so as to convert to common basis. The std dev of $\Delta\Delta S$ is 0.6 based on cyclopentane and cyclohexane (6 df); std dev of averages is about 0.3, 95% confidence limits of averages is about 0.8; bias is uncertain.

and then stored over phosphorus pentoxide and sodium hydroxide pellets. The salt was recrystallized from methanol followed by addition of ether. Various preparations had titratable and total bromide of 100 ± 3% (range). At slightly higher temperatures reduction occurs as a side reaction and *n*-propyldimethylamine is formed.

Other members of the series were prepared analogously: 6-bromohexyldimethylamine was prepared from 6-dimethylamino-1-methoxyhexane by the above hydrobromic acid procedure. The sequence employed was 1,6-dibromohexane to 6-bromo-1-methoxyhexane to 6-dimethylamino-1-methoxyhexane.

Marvel and others have prepared these compounds previously by treatment of bromophenoxyalkanes with hydrobromic acid.[31,32]

Kinetic Measurements. A weighed sample of the salt was dissolved in methanol and to this was added an exact equivalent or a known excess of a solution of sodium hydroxide in methanol. For studies above 50 °C the samples were sealed in ampules. Reactions were quenched with dilute nitric acid and the bromide ion was titrated with silver nitrate solutions using a potentiometric end point. Representative data are reported in Table VII.

Computations. The kinetics data were treated either as first order or second order using LSKIN1[33] or LSKIN2.[34] Sets of kinetic data were then processed using the general least-squares program GENLSS[34] which was provided with a subroutine for numerical integration of eq 5 including all salt effects. The results were further checked by performing representative computations using REMECH.[35,36]

Product Studies. Representative runs for **1** were examined by GLC for the presence of $(CH_3)_2NCH_2CH_2CH_2OCH_3$ or $(CH_3)_2NCH_2CH{=}CH_2$, which were synthesized independently. Amounts present were very small.

The *N,N*-dimethylazetidinium ion (**2**) shows a triplet for $CH_2N(+)$

Table VII. Representative Rate Data for 3-Bromopropyldimethylamine (1)[a]

Initial concn, M		$k_{obsd} \times 10^5$/
1	$LiNO_3$	s^{-1} [b]
0.02	...	5.0
0.02	0.40	6.0
0.10	...	5.7
0.50	...	7.2
1.01	...	11.1

[a] Solvent methanol, 25 °C. [b] Apparent first-order rate constant.

at about 0.8 ppm lower field than the triplet for the polymer, and the separation permits an analysis for the amount of cyclic products. The difference is smaller for the C-6 compound.

Registry No.—3-Dimethylaminopropanol, 3179-63-3.

References and Notes

(1) This work was supported in part by the National Science Foundation.
(2) J. J. Dannenberg, *J. Am. Chem. Soc.*, **98**, 6261 (1976).
(3) F. Keil and R. Ahlrichs, *J. Am. Chem. Soc.*, **98**, 4787 (1976).
(4) D. J. McLennan, *Acc. Chem. Res.*, **9**, 281 (1976).
(5) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46 (1973).
(6) A. J. Parker, *Adv. Phys. Org. Chem.*, **5**, 173 (1967); D. Cook and A. J. Parker, *J. Chem. Soc. B*, 142 (1968).
(7) M. H. Abraham, *J. Chem. Soc. B*, 299 (1971); *Progr. Phys. Org. Chem.*, **11**, 1 (1974).
(8) R. Fuchs and L. L. Cole, *J. Am. Chem. Soc.*, **95**, 3194 (1973).
(9) P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955).
(10) N. L. Allinger and J. C. Graham, *J. Org. Chem.*, **36**, 1688 (1971).
(11) M. H. Abraham, P. L. Grellier, and M. J. Hogarth, *J. Chem. Soc., Perkin Trans. 2*, 1365 (1975).
(12) D. F. DeTar, D. F. McMullen, and N. P. Luthra, *J. Am. Chem. Soc.*, **100**, (1978).
(13) W. H. Carothers, *J. Am. Chem. Soc.*, **51**, 2548 (1929).
(14) M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).
(15) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).
(16) C. J. M. Stirling, *J. Chem. Educ.*, **50**, 844 (1973).
(17) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
(18) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 198.
(19) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).
(20) T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, **87**, 4846, 4851 (1965).
(21) R. F. Brown and N. M. van Gulick, *J. Org. Chem.*, **21**, 1046 (1956).
(22) C. A. Grob and F. A. Jenny, *Tetrahedron Lett.*, **23**, 25 (1960).
(23) R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1215, 1221 (1973).
(24) H. Freundlich and A. Kroepelin, *Z. Phys. Chem.*, **122**, 39 (1926).
(25) H. Freundlich and A. Krestovnikoff, *Z. Phys. Chem.*, **76**, 29 (1911).
(26) G. Salomon, *Helv. Chim. Acta*, **19**, 743 (1936).
(27) N. Menshutkin, *Z. Phys. Chem.*, **5**, 589 (1890).
(28) H. Hunsdiecker, *Ber.*, **75**, 1190 (1942).
(29) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds", Wiley, New York, N.Y., 1969.
(30) S. W. Benson, "Thermochemical Kinetics", 2nd ed, Wiley, New York, N.Y., 1976.
(31) E. R. Littmann and C. S. Marvel, *J. Am. Chem. Soc.*, **52**, 287 (1930).
(32) C. F. Gibbs, E. R. Littmann, and C. S. Marvel, *J. Am. Chem. Soc.*, **55**, 753 (1933).
(33) D. F. DeTar and C. E. DeTar in "Computer Programs for Chemistry", D. F. DeTar, Ed., W. A. Benjamin, Menlo Park, Calif., 1968, Vol. I, p 126.
(34) D. F. DeTar in "Computer Programs for Chemistry", D. P. DeTar, Ed., Academic Press, New York, N.Y., Vol. 4, 1972.
(35) D. F. DeTar and C. E. DeTar in "Computer Programs for Chemistry", Vol. II.
(36) D. F. DeTar, *J. Chem. Educ.*, **44**, 193 (1967).

Effect of Hexadecyltrimethylammonium Bromide on the Thiolysis of *p*-Nitrophenyl Acetate

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Received October 19, 1977

Micelles of hexadecyltrimethylammonium bromide produce a rate increase of ca. 50-fold in the thiolysis of *p*-nitrophenyl acetate by thiophenoxide anions. The distribution constants between the water and the micellar phase, determined spectrophotometrically, of *p*-Cl, *p*-CH_3, *p*-CH_3O, and thiophenoxide anions were 20×10^3, 8.2×10^3, 2.7×10^3, and 4.8×10^3 M^{-1}, respectively. The calculated distribution constants of all four undissociated thiophenols were of the order of 1×10^3 M^{-1}. The apparent pKs of the thiophenols were lowered upon incorporation into the micellar phase. The entire rate increase produced by hexadecyltrimethylammonium bromide in the thiolysis of *p*-nitrophenyl acetate by thiophenoxides can be explained on the basis of concentration of the reagents on the micellar phase.

Only a limited number of nucleophiles have been unequivocally demonstrated to participate in covalent catalysis by enzymes.[1] Among these, the SH group of cysteine residues shows an unusually high reactivity when situated in the active site of "SH enzymes" such as papain,[2] ficin,[3] bromelin,[4] or glyceraldehyde-3-phosphate dehydrogenase.[5] The nucleophilic reactivity of SH groups in proteins can range from those which are extremely reactive to those which are nonreactive or "masked".[6,7] Although the details are far from clear, there is general agreement that this wide range of reactivities can be attributed to differing microenvironments of the potentially reactive SH group. Unusually high SH reactivities are also found with low molecular weight compounds such as coenzyme A (CoASH) and glutathion (GSH), which participate covalently as coenzymes in a number of enzyme-catalyzed reactions.[6,7] Since the reactivities of the SH groups of GSH or CoASH are entirely within the expected range[8] (on the basis of comparison with other mercaptans), the SH group of both GSH and CoASH must be "activated" by the apoenzyme, much in the same manner as active site SH groups.

Since micelles serve as models of the (possible) role of charged and/or neutral interphases on nucleophilic reactivity (for recent reviews on micelles see 9–12) the study of micellar effects on SH reactivity has relevance to the question of the reactivity differences found in biological systems. There is indeed evidence that micelles affect, markedly in some cases, the rates of different SH reactions:[8,13–16] (1) The rate of reaction of *N*-dodecanoyl-*dl*-cysteine (DCS) with chloroacetamide, iodoacetamide, and *p*-nitrophenyl acetate (NPA) is increased by 5–7-, 60–100-, and 100–200-fold, respectively, upon addition of hexadecyltrimethylammonium bromide (CTAB).[13] On the other hand, incorporation of DCS into negative micelles leads to a decrease of the apparent reactivity of the SH group.[13] (2) The rate of reaction of alkyl mercaptans

0022-3263/78/1943-2248$01.00/0