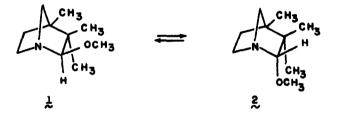
A NOVEL METHOD FOR THE EPIMERIZATION OF A-AMINOETHERS

Paul G. Gassman, Angelo J. Battisti, and Koichi Shudo Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (Received in USA 15 June 1972; received in UK for publication 2 August 1972)

The reaction of polyhalogenated hydrocarbons with amines has been known for over a half century.¹ In particular, reactions of a variety of amines with carbon tetrachloride have been described.^{2,3} We now wish to report a new reaction of polyhalogenated hydrocarbons with bicyclic α -aminoethers, which involves the epimerization of the ether function.

When 1^4 was heated in methanol-carbon tetrachloride or with methanol-chloroform, an equilibrium was established between 1 and 2.⁵ Approaching this equilibrium from both sides established that the endo isomer, 2, was favored, with $K_{eq} = 1.47 \pm 0.03$ at 120° .



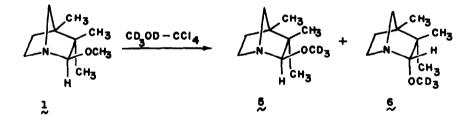
In view of the rather intriguing aspects of this equilibration, and with knowledge of the suggested ionic³⁸ and free radical^{3b} mechanisms for the reactions of amines with carbon tetrachloride, we attempted to gain an insight into the nature of this isomerization. Table 1 lists some of the more critical experiments which were run. The product ratios were determined by vapor phase chromatography. As can be seen from an examination of Table 1, pure methanol gave no epimerization, while acid (HC1) gave epimerization, but at a much slower rate than methanol-carbon tetrachloride. The difference in the rates of epimerization in methanol-carbon tetrachloride, methanol-carbon tetrachloride-hydrogen chloride, and methanol-carbon tetrachloride. Thus, it would appear that the epimerization

Solvent System	Time (hr)	\$2 \$1
Снзон	72	0.00
CH3OH-0.001M HC1	72	0.01
CH3OH-0.010M HEL	72	0.22
CH3OH-0.100M HCl	72	0.32
CH30H-0.100M HCL	144	0.75
CH3OH-CCl4 (1:1)	72	1.50
CH3OH-CCl4-NaOCH3	72	1.44
CH3OH-CHC13	72	1.08

Table 1. Epimerization of 1 (0.01M) at 130°

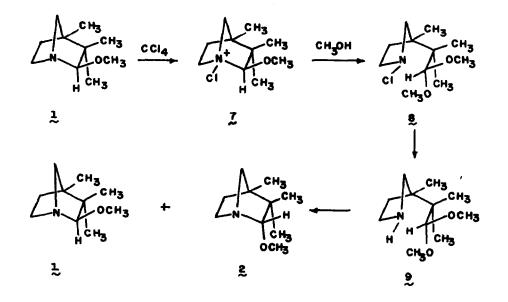
was not a simple acid-catalyzed process.

The effectiveness of carbon tetrachloride and chloroform initially suggested that a



free radical process might be involved. However, addition of benzoylperoxide or azobisisobutyronitrile (up to 10 equivalents) failed to accelerate the epimerization at 130° or to promote any epimerization at 80° in methanol-carbon tetrachloride. Additional evidence against a free radical process was obtained when the reaction was carried out in methanol-d₄. In the presence of the labelled methanol, only the methoxyl group was exchanged. No exchange of the proton at the 2-position could be detected. After <u>ca</u>. 5% epimerization, approximately 15% of the methoxyl groups had been exchanged. When the exc/endo ratio became 46/54, only 20% of the non-labelled methoxyl groups remained.

Mechanistically, we prefer a process in which the first step involves nucleophilic attack on carbon tetrachloride to displace a trichloromethyl anion, in a manner similar to that discussed by Heublein⁹⁸ for the reaction of aliphatic amines with carbon tetrachloride. The trichloromethyl anion would be expected to be protonated by the methanol to yield chloroform⁸ which can be isolated from the reactions. Cleavage of the N-chlorinated ammonium salt, 7, and addition of methanol would then yield 8. N-Chloropyrrolidine was instantaneously converted to pyrrolidine under the reaction conditions.⁷ Thus, 8 would be expected to yield 9. When an independently synthesized sample of 9⁹ was exposed



to the reaction conditions, it was immediately converted to a mixture of 1 and 2. Thus, the tentative mechanistic scheme shown above is consistent with all of the known facts connected with this epimerization.

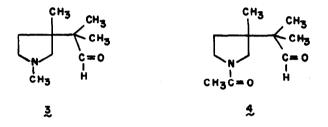
Acknowledgement. We are indebted to the National Cancer Institute of the Public Health Service for a grant which supported this investigation.

Bibliography

- 1. W.M. Dehn and A.H. Dewey, <u>J. Amer. Chem. Soc.</u>, <u>33</u>, 1588 (1911).
- 2. For leading references see J.R. Lindsay Smith and Z.A. Malik, J. Chem. Soc. (B), 920

(1970); R.F. Collins, Chem. Ind. (London) 704 (1957); H.J. Bittrich and H. Schirge, <u>Wissenschaftl. Zeitschr.</u>, 8, 306 (1966).

- 3. a) G. Heublein, <u>J. prakt. Chem.</u>, 31, 76 (1966); b) T. Latowski and E. Sikorska, <u>Rocz.</u> <u>Chem.</u>, 42, 1063 (1968); E.T. Chukovskaya, A.A. Kamyshova and R.K. Freidlina, <u>Zh</u>. <u>Org. Khim</u>., 3, 1358 (1967).
- P.G. Gassman and R.L. Cryberg, <u>J. Amer. Chem. Soc.</u>, 91, 2047 (1969); P.G. Gassman, R.L. Cryberg, K. Shudo, and A.J. Battisti, <u>Tetrahedron Lett.</u>, 875 (1972).
- In addition to the formation of 2 from 1, small amounts of 3 were slowly produced. The structure of 2 was established on the basis of extensive spectroscopic evidence,



via its conversion back to 1, and through the conversion of both 1 and 2 into 4 on reaction with acetic anhydrIde.

- 6. In the methanol-chloroform epimerization, methylene chloride was isolated as a by-product.
- 7. This transformation could involve either a homolytic cleavage of the N-Cl bond, followed by hydrogen abstraction from methanol, or a heterolytic cleavage of the N-Cl bond to yield a singlet nitrenium ion, which would be expected to spin invert to a triplet nitrenium ion.⁸ This triplet nitrenium would also be expected to abstract hydrogen from methanol. In either instance, formaldehyde should be formed. This formaldehyde was isolated in the form of its dimethyl acetal, dimethoxymethane.
- 8. P.G. Gassman and R.L. Cryberg, J. Amer. Chem. Soc., 91, 5176 (1969).
- 9. The details of this synthesis will be presented in a full paper on this subject.