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THE VON BRAUN CYANOGEN BROMIDE REACTION - STRUCTURE OF THE INTERMEDIATE

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We reported recently (a) on the preparation and spectral characterization of N-cyanoammonium hexachloroantimonates[1] derived from a variety of tertiary amines and $CNCl \cdot SbCl_5$; (b) on the first successful trapping,[2] elemental[3] and spectral analysis and cleavage of N-cyanoammonium bromides as intermediates in the reaction of triethylamine, N-methyl, N-ethyl, and N-methyl-4-hydroxy piperidines, N-methyl morpholine, 3-tropanone and 3α-tropanol, with cyanogen bromide; (c) on the conversion of these intermediates into the mesylates and tosylates, which are more stable due to the much lower nucleophilicity of these anions; (d) cyanoammonium salts are stronger alkylating agents than quaternary ammonium salts in consequence of the enhanced tendency of C-N bond-breaking which, in addition, gives a favorable leaving group, a dialkyl cyanamide. Therefore, their potential use in synthesis has been outlined.[2]

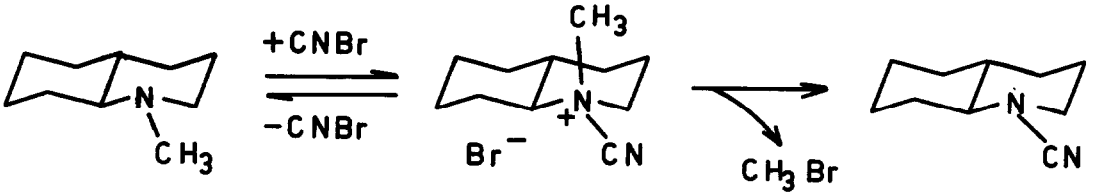
The preparation of similar, stabilized cyanoammonium salts, i.e., tetrafluoroborates, was reported soon thereafter by J. V. Paukstelis and Moon-gen Kim[4] along with decomposition of the same salts by different nucleophiles, essentially confirming our statements under (a), (c), and (d).

In our more recent work attention was focused on a direct study of the genuine intermediate bromide rather than on the stabilized product of interconversion.

Therefore, a low-temperature nmr-kinetic investigation of the amine-cyanogen bromide adduct in the von Braun cyanogen bromide reaction was undertaken on N-methyl-trans-decahydroquinoline (1). This model is conformationally more rigid than piperidines, therefore, in addition to mechanistic information it allows conclusions to be drawn as to the steric course of the first step which may be called 'cyanonation' as contrasted with 'cyanylation.'[5]

The reaction of amine 1 with cyanogen bromide in either chloroform-d or acetonitrile-d_3 has been monitored[6] by NMR at -30°, -22°, -20°, -17° and -15°. No N-methyl signal of the tertiary amine at δ 2.2 could be detected not even at -20° in acetonitrile-d_3 immediately after

the reaction has started while a $\overset{+}{N}Me$ signal appeared at δ 3.67 together with $\overset{+}{N}CH_2$ and $\overset{+}{N}$-CH resonance at δ 4.48 ppm. This indicates that the formation of the adduct is extremely fast,



1 2 3

therefore its rate of decomposition into cyanamide 3 and methyl bromide should be the rate determining step. The rate of the latter was followed by measuring the decrease in intensity[7] of the signal at δ 3.67 (4.0 in $CDCl_3$; 3.86 in CD_3NO_2), and it clearly exhibits the first-order rate characteristics. Fig. 1 shows log c plotted against time for 5 temperatures in chloroform-d; Fig. 2 describes a similar plot for the same temperatures in acetonitrile-d_3. These data proved to be completely reproducible. Table of the first-order rate constants shows the effect upon reaction rates by 3 different solvents. The decrease in rate tends to follow the order of increase in basicity (chloroform-d < nitromethane-d_3 < acetonitrile-d_3) rather than an increase in the dipole moment (chloroform-d < acetonitrile-d_3 < nitromethane-d_3)[8] of the

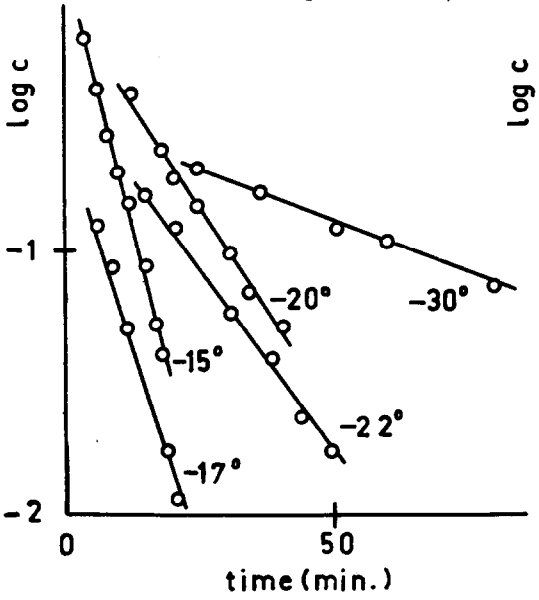


Fig. 1. First-order plots for the decomposition of 2 in $CDCl_3$ at various temperatures.

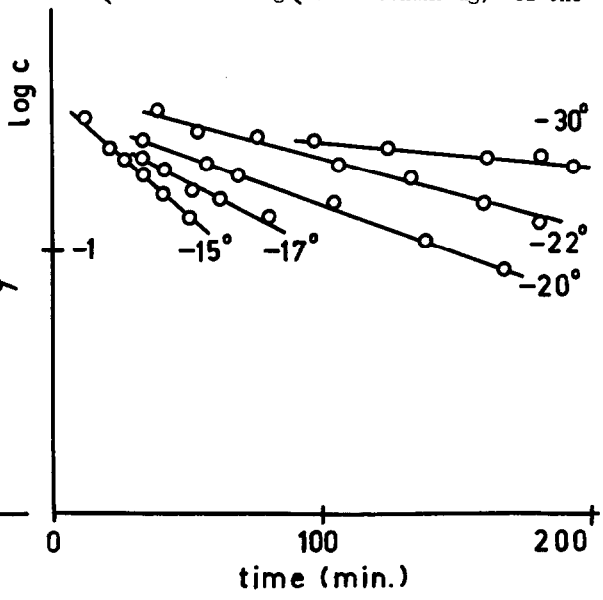


Fig. 2. First-order plots for the decomposition of 2 in CD_3CN at various temperatures.

solvent. The decomposition reaction is apparently ten times faster in chloroform-d than in acetonitrile-d_3 and two and one half times faster than in nitromethane-d_3 due to increasing

TABLE

First-Order Rate Constants (sec^{-1}) of the Decomposition of 2 into 3 and Methyl Bromide, at Different Temperatures (C°).

Solvent	-30°	-22°	-20°	-17°	-15°
Chloroform-d	3.0×10^{-4}	1.1×10^{-3}	1.2×10^{-3}	2.0×10^{-3}	3.0×10^{-3}
Acetonitrile-d_3	3.0×10^{-5}	1.0×10^{-4}	1.4×10^{-4}	2.0×10^{-4}	3.3×10^{-4}
Nitromethane-d_3	--	--	6.5×10^{-4}	--	1.2×10^{-3}

degree of solvation of 2. Energy of activation, calculated from our data amounts to 19 kcal/-mole for the decomposition in chloroform-d and 22 kcal/mole for the same in acetonitrile-d_3. Increase in the over-all concentration of the adduct did not affect reaction rates, this was also the case for an increase in concentration of cyanogen bromide alone. Added common ion, e.g., lithium bromide to acetonitrile solution resulted in 'salting out' of the crystalline cyanoammonium bromide 2. Adding 0.3 mole of lithium perchlorate per mole 2 brought about a five times deceleration, indicative of a negative salt effect. No difference was observed in kinetic behavior whether cyanonation was carried out in one of the solvents used or whether 2 was precipitated at -20° from ether solution and redissolved in the same (pre-cooled) solvent.

All these kinetic data reflecting the unimolecular step of the cyanogen bromide reactions are only compatible with a cyanoammonium bromide ion-pair structure of the intermediate. Although there was no spectral evidence for any appreciable dissociation of 2 into 1 and cyanogen bromide, upon addition of sodium iodide in acetonitrile or tetrahydrofuran oxidation of iodide to iodine took place. This reaction, also measured with cyanogen bromide alone, points to the reversibility of the cyanonation step. 'Consuming' cyanogen bromide by iodide ion shifts the equilibrium towards dissociation.

A remarkable steric selectivity in the electrophilic attack by cyanogen bromide upon this tertiary amine was indicated by a sharp singlet for the $\overset{+}{N}CH_3$ signal in the adduct. 'Cyanonation' having not been studied so far, its steric course was similarly unknown. Using the $CNCl \cdot SbCl_6$ complex as a cyanonating agent[1] in nitromethane the N-cyano-N-methyl decahydroquinolinium hexachloroantimonate shows for the $\overset{+}{N}CH_3$ a doublet separated by 10 cps at 20° consistent with a non-stereospecific cyanonation step. Reasons for this may be sought in similar conformational factors of the transition state as with tropanes.[10] Assignment to the N-methyl configuration

will be made based on measuring of NOE that should operate between axial N-Me and axial H-9, but not in the equatorial N-Me epimer. Furthermore, collection of X-ray data on 'stabilized' cyanonium salt of the same base is already in progress.

Details of this work shall be reported in a full paper. Differences in the behavior of 5-membered and 6-membered ring amines in the cyanogen bromide reaction will be discussed on conformational terms.

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3. Microanalyses were made on R&M Model 185 C H N Analyzer, 5 min after precipitating and drying of the intermediates by Mr. R. Dulude.

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