Amine Oxidation. Part VII.[1] The Effect of Structure on the Reactivity of Alkyl Tertiary Amines towards Alkaline Potassium Hexacyanoferrate-(III)

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Kinetic studies on the oxidation of *N*-methyl- and *N*-deuteriomethyl-di-n-butylamine confirm that the rate-determining step is an electron-transfer from the nitrogen to the potassium hexacyanoferrate(III); the relative rate of reaction k_H/k_D is 1·04. The influence of deuteriation on the product distribution (isotope effect 3·6) indicates that the second step is a product-determining proton loss.

Further information about the electron-abstraction and the nature of the first transition state has been obtained from the rates of oxidation of a selection of cyclic tertiary amines. The results are in accord with the transition state occurring late on the reaction co-ordinate. Thus, in the transition state electron-transfer from the amine to the hexacyanoferrate(III) is almost complete and the configuration of the nitrogen resembles that of the intermediate aminium radical cation rather than that of the substrate.

The order of increasing ease of oxidation of bridgehead bicyclic amines, triethylenediamine monomethiodide, quinuclidine, and triethylenediamine is discussed in the light of these conclusions.

TRIALKYLAMINES are oxidatively dealkylated with aqueous alkaline potassium hexacyanoferrate(III) *via* two successive one electron-abstractions.[2] In strongly alkaline solution the initial rate-determining electron-abstraction which is essentially irreversible is followed by a rapid product-determining proton loss. Four intermediate species arise during the course of the oxidation; in order of appearance these are an aminium radical cation, an α-amino-radical, an iminium ion, and a carbinolamine. Evidence for these species has been obtained from product and kinetic studies and by the use of linear free-energy correlations,[2,3] and iminium ions have been trapped intramolecularly in the oxidation of selected trialkylamino-alcohols and -amines.[4]

The work we report here is predominantly a kinetic study of the influence of structural changes on the ease of oxidation of aliphatic amines with alkaline potassium hexacyanoferrate(III). The results give further insight into and confirmation for the first two steps of the proposed mechanism.[2]

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[2] C. A. Audeh and J. R. Lindsay Smith, *J. Chem. Soc.* (*B*), 1970, 1280.
[3] C. A. Audeh and J. R. Lindsay Smith, *J. Chem. Soc.* (*B*), 1971, 1741.
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RESULTS

Product Studies.—Table 1 summarises the products obtained from the oxidation of *N*-methyl- and *N*-deuteriomethyl-di-n-butylamine with aqueous potassium hexacyanoferrate(III). Both oxidations were carried out at room temperature in an atmosphere of nitrogen using a two-fold molar excess of the amine. The products were analysed after the complete reduction of the potassium hexacyanoferrate(III); under these conditions there was no evidence for amide formation or further oxidation of secondary amines. The maximum expected yield of products based on the substrate is 25%. Although the unchanged substrate could be recovered quantitatively the complete recovery of the secondary amines from the oxidation mixture was not possible. Using synthetic aqueous solutions of these amines the extraction and analysis were standardised; the recovery of *N*-methyl-n-butylamine and di-n-butylamine was 67·5 and 76·2%, respectively. The values recorded in Table 1 are corrected for the efficiency of the extraction and analysis.

TABLE 1

Yields (%; based on substrate) of products from the oxidation of *N*-methyl- and *N*-deuteriomethyl-di-n-butylamine by potassium hexacyanoferrate(III) in 2M-potassium hydroxide

Substrate	Demethylation	Dealkylation	Unchanged amine	Ratio of demethylation to dealkylation
N-Methyldi-n-butylamine	9·7	3·1	82·3	3·1
N-Deuteriomethyldi-n-butylamine	3·1	3·6	83·5	0·86

TABLE 2

Second-order rate constants for the oxidation of some aliphatic tertiary amines by potassium hexacyanoferrate(III); $1{\cdot}84 \times 10^{-3}$M-$K_3Fe(CN)_6$, *ca.* 2×10^{-2}M-amine, 0·5M-KOH in 30% aqueous methyl alcohol

Substrate	$10^4k_2'$/l mol^{-1} s^{-1}	Rate relative to *N*-methylpiperidine (k'_{rel})
(A) Temp. 25·5 °C		
N-*n*-Butylaziridine	2·63 ± 0·15	$5{\cdot}75 \times 10^{-2}$
N-Methylpyrrolidine	2430 ± 50	53·2
N-Methylpiperidine	45·7 ± 0·4	1·0
N-Methylhexamethyleneimine	19,200 ± 800	420
N-Methylheptamethyleneimine	49,000 ± 600	1070
cis-1,2,6-Trimethylpiperidine	116 ± 1·0	2·54
trans-1,2,6-Trimethylpiperidine	228 ± 2·0	5·0
1,2,2,6,6-Pentamethylpiperidine	1810 ± 80	39·6
Quinuclidine	0·624 ± 0·003	$1{\cdot}37 \times 10^{-2}$
Triethylenediamine	3·53 ± 0·07 *	$7{\cdot}7 \times 10^{-2}$ *
Triethylenediamine monomethiodide	0·36 ± 0·002	$7{\cdot}9 \times 10^{-3}$
(B) Temp. 27 °C		
N-Methyldi-n-butylamine	382 ± 8·0	
N-Deuteriomethyldi-n-butylamine	366 ± 9·0	

* This value is corrected to allow for the two sites of oxidation.

Kinetic Studies.—The spectrophotometric method used in the kinetic studies has been described previously.[3] The reactions follow the kinetic relationship $-d[Fe(CN)_6^{3-}]/dt = k_2'[Amine][Fe(CN)_6^{3-}]$: with a large excess of amine, pseudo-first-order rate constants were obtained with a computer by use of a least-mean-square treatment of the kinetic data. The correlation coefficients were always >0·98. Each reaction was followed for at least three half-lives with the exception of the four slowest oxidations which were studied for the following number of half lives, triethylenediamine 1·0, *N*-n-butylaziridine 0·5, and triethylenediamine monomethiodide and quinuclidine 0·2. *N*-Methylaziridine which was too volatile to use in this study was replaced by *N*-n-butylaziridine.

Table 2(A) records the second-order rate constants for the oxidation of a series of cyclic and bicyclic amines derived from the pseudo-first-order values and the rate of each oxidation relative to that of *N*-methylpiperidine, k'_{rel}. The second-order rate constants for two acyclic amines, namely, *N*-methyl- and *N*-deuteriomethyl-di-n-butylamine, are also reported [Table 2(B)].

DISCUSSION

A steady-state approximation of reactions (1)—(7) [2] predicts that the rate of oxidation of *N*-methyldi-n-butylamine is given by $-d[Fe(CN)_6^{3-}]/dt = 2k_1[Fe(CN)_6^{3-}][Amine]$, and consequently the measured second-order rate constant $k_2' = 2k_1$.

$$MeNBu_2 + Fe(CN)_6^{3-} \xrightarrow[\text{slow}]{k_1} MeN\overset{+\bullet}{}Bu_2 + Fe(CN)_6^{4-} \quad (1)$$
(I)

$$(I) \xrightarrow{k_2} CH_2\overset{\bullet}{N}Bu_2 + H^+ \quad (2)$$
(II)

$$(I) \xrightarrow{k_3} MeN(Bu)\dot{C}HCH_2CH_2CH_3 + H^+ \quad (3)$$
(III)

$$(II) + Fe(CN)_6^{3-} \xrightarrow{k_4} CH_2=\overset{+}{N}Bu_2 + Fe(CN)_6^{4-} \quad (4)$$
(IV)

$$(III) + Fe(CN)_6^{3-} \xrightarrow{k_5} MeN(Bu)^{+}=CHCH_2CH_2CH_3 + Fe(CN)_6^{4-} \quad (5)$$
(V)

$$(IV) \xrightarrow[OH^-/H_2O]{k_6} Bu_2NH + HCHO \quad (6)$$

$$(V) \xrightarrow[OH^-/H_2O]{k_7} BuNHMe + CH_3CH_2CH_2CHO \quad (7)$$

Isotopic substitution of the methyl α-hydrogens with deuteriums results in a kinetic isotope effect ($k_2'H/k_2'D$) of 1·04, a value in agreement with the view that the rate-determining step involves an electron abstraction and not the cleavage of an α-C–H bond. Similar conclusions were reported by Rosenblatt and his co-workers who obtained a secondary isotope effect of between 1·3

and 1·8 for oxidation of trimethylamine and perdeuteriomethylamine with chlorine dioxide [5] and permanganate.[6] On the other hand Wei and Stewart [7] report a primary isotope effect of 7·0 for the oxidation of benzylamine and αα-dideuteriobenzylamine by permanganate; this latter reaction proceeds by a rate-determining α-C–H bond cleavage.

In contrast, the effect of deuteriation on the product distribution is marked and readily interpreted by the competitive deprotonation of the radical cation (I) illustrated in equations (2) and (3). With *N*-methyldi-n-butylamine the ratio of demethylation to debutylation is 3·1 while this ratio with the deuteriomethyl analogue is reduced to 0·86. Assuming that the rate constants k_3—k_7 are unaffected by deuteriation of the methyl group, the difference in these ratios must arise in step (2) from the difference in the methyl C–H and C–D bond energies. The isotope effect k_2^H/k_2^D obtained from the product distribution is **3·6**, a value which compares well with an isotope effect of 3·78 reported by Smith and Loeppky [8] for the nitrosative debenzylation of αα-dideuteriotribenzylamine.

In conclusion, a comparison of the results obtained from *N*-methyl- and *N*-deuteriomethyl-di-n-butylamine allows a clear discrimination between the rate- and product-determining steps in the oxidative dealkylation of trialkylamines with alkaline potassium hexacyanoferrate(III).

Aminium radical cations are planar unless constrained by the geometry of the molecule to be otherwise.[9] Consequently the ease of conversion of the tetrahedral nitrogen of a cyclic amine into an aminium radical cation will be controlled by the changes of ring and conformational strain, the magnitudes of which will depend on the ring size. A comparison of our results [Table 2(A)] with those obtained from the solvolysis of 1-methylcycloalkyl chlorides in 80% ethanol [10] and from the pyrolysis of cycloalkylazonitriles [11] and cycloalkyl peroxy-esters [12] is illustrated in the Figure. Clearly the effect of ring size on the rates of oxidation of the cyclic amines resembles the first two processes but is quite different from the third. This conclusion is reinforced from a plot of the logarithm of the second-order rate constants for oxidation of the cyclic amines against the logarithms of the rate constants for the corresponding cycloalkyl derivatives from the three reactions above. The correlation coefficients from the linear graphs obtained are >0·95 for the solvolysis of the chlorides and pyrolysis of the azonitriles, but is only 0·82 for the decomposition of the peroxy-esters.

Following the arguments of Rüchardt,[13] it is clear that in the hexacyanoferrate(III) oxidation of cyclic tertiary amines, like the solvolysis of the 1-methylcycloalkyl chlorides and the thermolysis of the cycloalkylazonitriles, the transition state of the rate-determining step occurs late on the reaction co-ordinate. Thus, the geometry of the nitrogen in the transition state for electron-abstraction resembles the planar configuration of the radical cation rather than the tetrahedral arrangement in the substrate. In agreement with this conclusion the

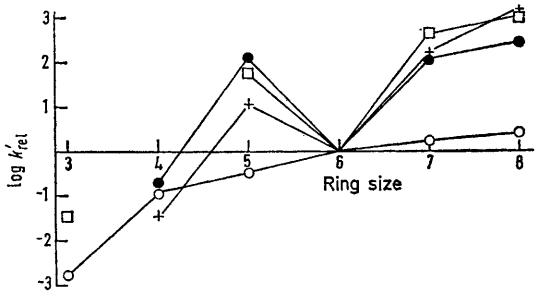

FIGURE Comparison of the dependence of log k'_{rel} on ring size for the oxidation of some cyclic tertiary amines with related results from the reactions of cycloalkyl derivatives: ○ pyrolysis of t-butyl-1-methylcycloalkylperoxycarboxylates of 80°; ● solvolysis of 1-methylcycloalkyl chlorides in 80% ethyl alcohol at 25°; + pyrolysis of 1,1′-azobis-1-cycloalkyl nitriles at 80°; □ oxidation of cyclic tertiary amines by potassium hexacyanoferrate(III) at 25·5°.

Brønsted free-energy correlation of the hexacyanoferrate(III) oxidation of some *para*-substituted *NN*-dimethylbenzylamines indicates that the nitrogen in the transition state for the initial electron transfer bears a high degree of positive charge.[3]

The inductive effect of the methyl groups in the 2 and 6 positions of *N*-methylpiperidine should aid the formation of the aminium radical cation [2] and in agreement with this conclusion the rate of oxidation increases with the degree of methylation. However, on closer examination it is seen that this increase is not as large as that found for the acyclic analogues.[2] The difference between the two series arises from an increase in conformational strain that develops with the formation of the radical cation from the *N*-methylpiperidines which is not present in the oxidation of the acyclic amines. Thus, forming the *N*-methylpiperidinium radical cation increases non-bonded interactions between the N–Me group and the α-C–H bonds [(VI) ⟶ (VII); $R^1 = R^2 = R^3 = R^4 = H$] and this conformational strain is increased further by replacing the α-hydrogens with methyl groups. Using a similar argument Brown and Ichikawa [14] conclude that changing the hybridisation of one of the ring carbon atoms in a cycloalkyl derivative

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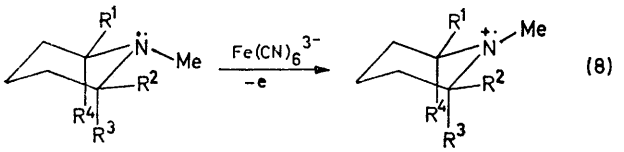
from sp^3 to sp^2 should be favoured in a five-membered but resisted in a six-membered ring; the major factor contributing to this difference being the change in bond opposition between the reaction centre and the α-C–H



(VI) (VII) (8)

bonds which accompanies the change in hybridisation. Again, the readier chromium trioxide oxidation of *cis*- than *trans*-2-alkylcyclohexanols [15] and the decreasing rate of reaction of cyclopentanone, 2-n-propylcyclopentanone, and *cis*-2,5-di-n-propylcyclopentanone with hydroxylamine [16] must, in part, be due to analogous non-bonded interactions. An examination of models shows that the conformational strain associated with the formation of *cis*-1,2,6-trimethylpiperidinium radical cation [(VI) ⟶ (VII); $R^1 = R^2 = Me$, $R^3 = R^4 = H$] is greater than that for the *trans* isomer [(VI) ⟶ (VII); $R^1 = R^3 = Me$, $R^2 = R^4 = H$] in agreement with the relative ease of oxidation of *cis*- and *trans*-1,2,6-trimethylpiperidine. Again these results illustrate that the transition state for the electron-abstraction resembles the intermediate radical cation.

From the discussion above it is not surprising that the second-order rate constant for the oxidation of the bridgehead bicyclic amine quinuclidine is over 70 times smaller than that for *N*-methylpiperidine. The cage structure constrains the radical cation, distorting the nitrogen atom from the preferred planar configuration and thereby increasing the enthalpy of activation for electron-abstraction. A similar observation has been reported for the rate of formation of bridgehead carbon radicals from the thermolysis of azobicyclicalkanes.[17] Interestingly, triethylenediamine, despite the constraints of the ring,[18] the unfavourable inductive effect of the second nitrogen atom on the formation of a radical cation, and allowing for a statistical correction for the two possible sites of oxidation, is oxidised almost six times more readily than quinuclidine. This readier oxidation of triethylenediamine must arise from a through-bond or possibly a through-space coupling [19] between the two nitrogens which stabilises the intermediate-like transition state relative to the ground state. The importance of this type of stabilisation in the intermediate triethylenediaminium radical cation has been discussed.[20] Quaternisation of one of the nitrogens not only removes this interaction but introduces a positively charged nitrogen which enhances the destabilising influence of the inductive effect on radical cation formation. Accordingly, the rate constant for the oxidation of triethylenediamine monomethiodide is almost a twentieth of that for the parent compound. The influence of through-bond and through-space interactions on the formation of radical cations is presently under investigation and will be the subject of a later paper.

EXPERIMENTAL

The spectroscopic methods were the same as those reported previously.[2]

Gas Chromatography.—Glass columns (1·6 m × 0·4 mm) and (1·6 m × 0·8 mm) were used in Pye Series 104 and 105 chromatographs for analytical and preparative chromatography, respectively. Both instruments were equipped with a flame-ionisation detector coupled to a Goerz Servoscribe recorder. The packing materials were prepared from Celite 80—120 mesh (B.D.H. Ltd.) treated with 5% KOH and coated with Carbowax 20M (20% w/w, J.J.'s Chromatography Ltd.).

Materials.—Potassium hydroxide and hexacyanoferrate-(III), diethyl ether and methanol were research grade or AnalaR reagents. *N*-Methyl-pyrrolidine and -piperidine (Koch–Light Ltd.) were purified by distillation and dried over molecular sieve (type 4A, B.D.H. Ltd.). Quinuclidine (Ralph N. Emanuel Ltd.) and triethylenediamine (Kodak) were purified by sublimation. Triethylenediamine monomethiodide (Maybridge Chemical Co. Ltd.) was recrystallised before use. The other tertiary amines used in kinetic studies, with the exception of *N*-n-butylaziridine, *N*-deuteriomethyldi-n-butylamine and *trans*-1,2,6-trimethylpiperidine, were prepared by methylation of commercially available secondary amines by the method of Clarke, Gillespie, and Weisshaus.[21] The *N*-n-butylaziridine was prepared from *N*-n-butylethanolamine (Ralph N. Emanuel Ltd.) and chlorosulphonic acid following Elderfield and Hageman.[22] *N*-Deuteriomethyldi-n-butylamine was prepared by reduction of ethyl *NN*-di-n-butylcarbamate with lithium aluminium deuteride following the procedure of Marshall and McMahon [23] and had b.p. 158—160° (lit.,[24] 161—162°). Mass spectral analysis showed the deuterium content was >98%. *trans*-2,6-Dimethylpiperidine was prepared by the reduction of 2,6-lutidine with sodium in ethanol following Hill, Chan, and Joule.[25] The *trans*-isomer was purified by distillated using a Buchi 'Abegg' spinning-band column, b.p. 132—134° (lit.,[26] 133—134°). The best fraction containing 93 and 7% of *trans*- and *cis*-isomers, respectively (estimated by g.l.c. and ^1H n.m.r.) was methylated by the method of Clarke, Gillespie, and

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Weisshaus.[21] Final purification by preparative g.l.c. gave *trans*-1,2,6-trimethylpiperidine (>99% by g.l.c., τ 7·33 (2H, m, α-H), 7·85 (3H, s, *N*-Me), 8·55 (6H, m, β- and γ-H), and 9·05 (6H, d, α-Me); *cf. cis*-1,2,6-trimethylpiperidine, τ 7·88 (3H, s, *N*-Me), 8·10 (2H, m, α-H), 8·60 (6H, m, β- and α-H), and 8·98 (6H, d, α-Me).

All solutions for kinetic studies were prepared from distilled and deionised water (conductance $<1\cdot0\ \mu\Omega^{-1}$).

For experiments in the absence of air, nitrogen (British Oxygen Co. White Spot) was deoxygenated and dried by passing it successively, through a solution of chromous chloride, concentrated sulphuric acid, and potassium hydroxide pellets.

Product Studies.—The *N*-methyl- or *N*-deuteriomethyl-di-n-butylamine was placed in a tared reaction flask, which was then stoppered and weighed. A weighed amount of potassium hexacyanoferrate(III) dissolved in 2M-KOH (25 ml) was added. The reaction flask was then flushed with oxygen-free nitrogen (2 min), restoppered, and shaken until the mixture became colourless. The reaction mixture was then cooled, acidified, and extracted with ether (4 × 75 ml). Diaminoethane (5 ml) was added to the acidified reaction mixture to remove formaldehyde and it was then cooled, basified, and extracted with ether (4 × 75 ml). The ether solutions were dried ($MgSO_4$) and the ether was removed by fractional distillation with a column packed with Fenske helices. The residues were analysed by g.l.c. For quantitative chromatographic studies an internal standard was employed.

Kinetic Studies.—An aqueous methyl alcohol solution (30% v/v) containing 0·5M-potassium hydroxide and 1·84mM-potassium hexacyanoferrate(III) was prepared and stored in a thermostatted bath (±0·2°). Equal amounts of this solution were then pipetted into two glass cells in the thermostatted cell-block (±0·2°) of the spectrophotometer. They were allowed to equilibrate before the amine substrate in methanol (30 μl) was added to one cell which was shaken vigorously and replaced in the spectrophotometer. The kinetics were then examined by following the difference in absorption at 420 nm between the two cells with time.

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