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Intramolecular Nucleophilic Attack of the Tertiary Amine Group on the Carbonyl Group in 3,3-Dimethyl-4-dimethylaminobutanal

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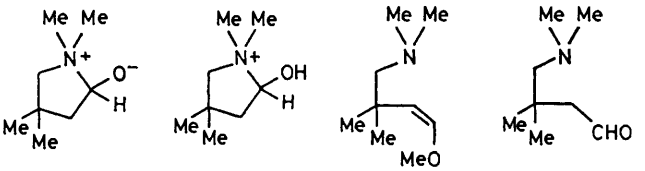
^{1}H N.m.r. spectroscopy indicates that 3,3-dimethyl-4-dimethylaminobutanal is largely in a cyclic form in D_2O, as is its conjugate acid in both $CDCl_3$ and D_2O.

There have been reasonably extensive studies of the interaction in acid solutions of tertiary amines with formaldehyde[1] or intramolecularly with a ketone in medium-sized rings,[2] and the results have been pertinent to the mechanisms of various carbonyl reactions including certain enzymic processes and acyl transfer reactions. Surprisingly, one of the simplest possible cases of this type of interaction, namely within 4-dialkylaminobutanals, has received no attention. We now report that 3,3-dimethyl-4-dimethylaminobutanal exists in a cyclic form, as the free base (**1**) and the conjugate acid (**2**) in aqueous solution. This provides the first opportunity of determining directly the acidity constant for an α-ammonio alcohol where the equilibrium is not complicated by carbon–nitrogen bond cleavage.

The hydrochloride of 3,3-dimethyl-4-dimethylaminobutanal was first obtained[3] from the reaction of di-μ-chlorobis-[3-(dimethylamino)-1-formyl-2,2-dimethylpropyl-*C*,*N*]dipalladium(II) with excess of phenylacetylene, but was most conveniently prepared by treatment of the enol ether[4] (**3**) with excess of hydrochloric acid in aqueous methanol. The resulting deliquescent, colourless, solid could be purified by either sublimation (110 °C at 0.02 mmHg) or preparative t.l.c. (methanol–dichloromethane, 1:9). ^{1}H N.m.r. spectra (see Table 1) of this compound in $CDCl_3$ or D_2O show an absence (<1%) of low-field resonances attributable to an aldehydic proton. However, they do contain resonances attributable to the methine proton in an aldehyde hydrate or in an ammonio alcohol (**2**). It is evident that the latter is correct, since, in both spectra, most of the various geminal proton and methyl pairs are non-equivalent.

In the presence of a trace of potassium carbonate, the non-equivalence is lost in both solvents, presumably because of rapid equilibration with the small amount of free base generated, at least some of which must be in the open chain form (**4**). Indeed, upon stirring a $CDCl_3$ solution of the hydrochloride with an excess of anhydrous potassium carbonate, the methine resonance suffers a very marked downfield shift, while the N–CH_3 and N–CH_2 resonances shift upfield. When the free base thus formed is dissolved in D_2O, the ^{1}H n.m.r. spectrum returns to a peak pattern which more closely resembles that of the conjugate acid in D_2O to which only a trace of potassium carbonate has been added. The upfield shift of the methine resonance and the downfield shifts of the N–CH_3 and N–CH_2 (relative to the $CDCl_3$ spectrum) suggest that, in this situation also, the nitrogen atom is interacting with the carbonyl group to give (**1**), although the lack of non-equivalence in the spectrum suggests



(1) (2) (3) (4)

Table 1. ^{1}H N.m.r. data (δ values) for 3,3-dimethyl-4-dimethylaminobutanal and its hydrochloride at 60 MHz.

Compound	Solvent	NMe	NCH_2	CMe	$2H^2$	H^1	$J(H^1–2H^2)$/Hz
Base	D_2O[a]	2.67	3.12	1.14	1.83(d)	5.43(t)	7.3
Base	$CDCl_3$	2.21	2.11	1.03	2.13(d)	9.62(t)	3.2
Hydrochloride	D_2O[a]	2.93, 2.80	3.34, 3.24[b]	1.17, 1.14	2.03(m)	5.13(dd)	ABX[c]
Hydrochloride	$CDCl_3$	3.27, 3.00	3.50, 3.39[b]	1.27	2.12(m)	5.42(dd)	ABX[d]

[a] External tetramethylsilane; [b] J = 13 Hz; [c] $J_{AX} + J_{BX}$ = 14.8 Hz; [d] $J_{AX} + J_{BX}$ = 14.5 Hz.

that (**1**) must be in rapid equilibrium with some of the open-chain aldehyde (**4**). However, a comparison (see Table 1) of the magnitude of the spin–spin coupling constant observed for the methine proton in this case with the corresponding ones for the hydrochloride [$(J_{AX} + J_{BX})/2$] and the free base (**4**) in $CDCl_3$ appears to indicate that the cyclic form (**1**) predominates very heavily. This conclusion gains firm support from u.v. measurements which suggest that little (<5%) free aldehyde is present in aqueous solution. The pK_a of (**2**) was measured as 8.70 (±0.04) by titrating an aqueous solution (*ca.* 0.1 mol dm^{-3}) of the free base with hydrochloric acid (*ca.* 0.1 mol dm^{-3}) at 20 °C.

For comparison, 2,2-dimethyl-3-dimethylaminopropanal (Aldrich) and 4-dimethylaminobutanal[5] were also studied. As expected, the former exists (^{1}H n.m.r. evidence) in open-chain forms in D_2O and $CDCl_3$ for both the free base and its hydrochloride. However, the spectra of the conjugate acid are complicated by features not present in those of the base. In $CDCl_3$, the N–CH_2 and N–CH_3 resonances are cleanly split by spin–spin coupling to the NH while, in D_2O, resonances for both the free aldehyde and the aldehyde hydrate are present. The surprisingly large proportion (*ca.* 75%) of the latter probably owes its existence to the proximity of the ammonio and aldehyde functions, which presumably also affects the magnitude of the pK_a (measured as 8.68 ± 0.03) for this compound. The hydrochloride of 4-dimethylaminobutanal exists (^{1}H n.m.r.) in the cyclic form [*cf.* (**2**)] in both $CDCl_3$ and D_2O. The free base, which was generated by stirring a solution of the hydrochloride in CH_2Cl_2 with anhydrous potassium carbonate, gives the expected ^{1}H n.m.r. spectrum for the free aldehyde in $CDCl_3$. However, in D_2O, it gives a very complicated one, exhibiting peaks ascribable to a cyclic form [*cf.* (**1**)], aldehyde hydrate, and products of aldolisation. Thus, not unexpectedly, the lack of the geminal dimethyl substituents at C-3 results in a smaller amount of ring closure[6] and in addition opens up the α-methylene for aldol reactions.

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References

1 J. Hine and F. C. Kokesh, *J. Am. Chem. Soc.*, 1970, **92**, 4383 and references therein.
2 N. J. Leonard and J. A. Klainer, *J. Org. Chem.*, 1968, **33**, 4269 and references therein.
3 R. McCrindle and A. J. McAlees, unpublished work.
4 R. McCrindle, G. Ferguson, M. A. Khan, A. J. McAlees, and B. L. Ruhl, *J. Chem. Soc., Dalton Trans.*, 1981, 986.
5 M. Takahara and R. Yoshida, Jap. P. 68 09, 529 (*Chem. Abs.*, 1968, **69**, 107070Z).
6 N. L. Allinger and V. Zalkow, *J. Org. Chem.*, 1960, **25**, 701.