

## Switch from O- to N-Protonation of 1-Methoxycarbonylpiperidine as the Acidity Increases

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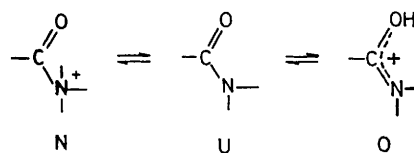
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**Summary** Evidence is presented for predominant *N*-protonation at high acidities, but substantial *O*-protonation at low acidities, of the title compound.

AMIDES are protonated predominantly on oxygen.<sup>1,2</sup> The extent of the minor *N*-protonation has been estimated in several cases;<sup>3,4</sup> the  $pK$ 's of the *O*- and *N*-protonated forms [ $pK(O)$  and  $pK(N)$ ] differ by 6–7 units. From the reported rate constant for proton exchange of ethyl *N*-methylcarbamate<sup>5</sup> we calculate, similarly,<sup>3,4d</sup> that  $pK(N) = -5.5$ . For predominant<sup>6</sup> *O*-protonation  $pK(O)^7 = -3.4$ . The basicities of the nitrogen and carbonyl oxygen are clearly much closer in carbamates than in amides. With ethyl *NN*-di-isopropylcarbamate, *N*-protonation, perhaps for steric reasons, is preferred.<sup>8,9</sup>

We now report that the title carbamate (**2**) in fluoro-sulphuric acid is also protonated predominantly on nitrogen. The <sup>1</sup>H n.m.r. spectrum shows the appearance, as the temperature is lowered to  $-74^\circ\text{C}$ , of a broad peak at  $\delta$  6.7 (1 H) and an increase in the complexity of the C(2)-proton signals. In contrast, the amide (**1**) gives a sharp peak at 9.2 (1 H), characteristic of *O*-protonation,<sup>6</sup> and no change in the C(2)-proton signals. The extent of protonation in aqueous sulphuric acid increases with acidity less rapidly with oxygen bases than with nitrogen bases.<sup>10</sup>

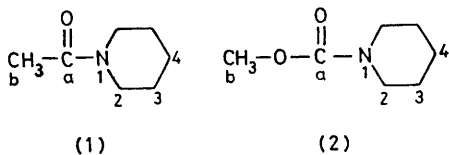
Thus, we wondered whether or not a switch to predominant *O*-protonation of (**2**) occurs at lower acidities. The following evidence indicates that it does.



SCHEME

The variation of the chemical-shift difference (<sup>13</sup>C n.m.r.) between C(a) and C(4),  $D_{a,4}$ , of (**2**) goes through a maximum at about 60%  $\text{H}_2\text{SO}_4$ . For the amide (**1**),  $D_{a,4}$  behaves quite differently (Figure). *O*-Protonation increases the positive charge on C(a), increasing  $D_{a,4}$  for both (**1**) and (**2**). The difference in behaviour can be understood if (**2**) only undergoes a switch to *N*-protonation at high acidities, which moves the positive charge entirely to the nitrogen and causes an upfield shift of C(a), a downfield shift of C(4), and a consequent reduction in  $D_{a,4}$ .

The chemical-shift differences  $D_{b,4}$  and  $D_{2,4}$  of (**2**) both increase sigmoidally with acidity as expected if protona-



tion is occurring.<sup>7</sup> However the two curves are not superimposable by scaling. If both the equilibria of the Scheme are important, an observed chemical-shift difference  $D$  at a particular acidity is an average of those characteristic of the U, O, and N forms ( $E$ ,  $F$ , and  $G$ , respectively) weighted by the fractions U, O, and N, respectively, of each present at that acidity, equation (1). We have used

$$D = EU + FO + GN \quad (1)$$

the Marziano function,<sup>11</sup> renamed  $X$  and recalculated by Cox and Yates<sup>10</sup> to estimate  $pK(O)$  and  $pK(N)$  from  $D_{b,4}$  and  $D_{2,4}$  at 20 acidities. Ionisation ratios,  $I$ , vary with  $X$  as in equation (2),<sup>10</sup> from which equations (3) and (4) follow, where  $S = [H^+] \times 10^{mX}$ ,  $T = [H^+] \times 10^{nX}$ ,

$$\log I - \log [H^+] = m^*X + pK \quad (2)$$

$$O/U = SP; N/U = TQ \quad (3)$$

$$D = (E + FSP + GTQ)/(1 + SP + TQ) \quad (4)$$

$P = 10^{pK(O)}$ ,  $Q = 10^{pK(N)}$ ;  $m$  and  $n$  are the slopes [ $m^*$  of equation (2) and ref. 10] for  $O$ - and  $N$ -protonation, respectively. For each chemical-shift difference, values of  $E$  and  $G$  were those measured at the lowest and highest acidities, respectively. Values of  $F$ ,  $pK(O)$ , and  $pK(N)$  were then derived by computer, from a least-squares fit between the calculated [equation (4)] and observed values of  $D$ . Both  $D_{2,4}$  and  $D_{b,4}$  were fitted simultaneously. The slope  $m$  was taken as 0.54, the mean of values for 10 previously investigated carbamates for which  $O$ -protonation has either been demonstrated<sup>6</sup> or can be assumed because of the low basicity of the nitrogen atom. The best fit was obtained with  $n$  1.05. This is a typical value of  $m^*$  for nitrogen bases.<sup>10</sup> The standard deviation for 20 values of each chemical-shift difference  $D_{2,4}$  and  $D_{b,4}$  was 0.1 p.p.m., comparable with the error of the measurements.

Values of  $pK(O)$  and  $pK(N)$  so derived were  $-2.8$  and  $-4.9$ , respectively. These and equations (3) gave U, O,

and N as functions of the acidity, see the Figure. The maximum extent of  $O$ -protonation derived in this independent way occurs at an acidity close to the maximum in  $D_{a,4}$  (Figure).

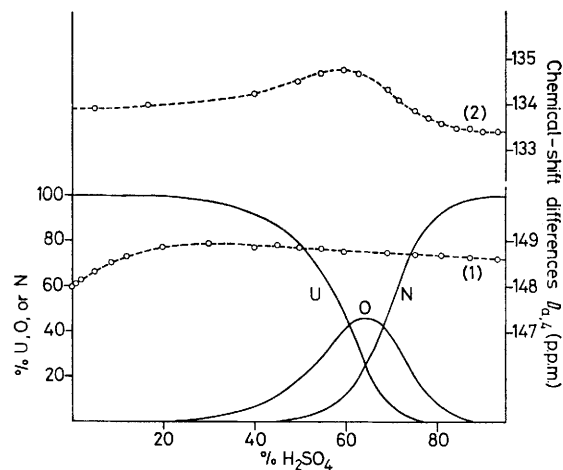


FIGURE. Variation with acidity of (a) the calculated percentages of (2) present in the unprotonated (U),  $O$ -protonated (O), and  $N$ -protonated (N) forms (full lines, left-hand ordinate); and (b) the chemical-shift differences between C(a) and C(4) in the amide (1) and the carbamate (2) (dashed lines, right-hand ordinate).

We conclude that (2) is predominantly  $O$ -protonated in dilute acid, but  $N$ -protonation is favoured in more concentrated acid. The derived  $pK_a$ 's are necessarily approximate because of uncertainties with regard to the slopes,  $m^*$ .

It is likely that other carbamates with unusually basic nitrogen will show similar behaviour. This work also supports the view<sup>2,4b</sup> that with amides a switch in the reverse direction, from nitrogen to oxygen protonation with increasing acidity, as has been suggested,<sup>12</sup> is unlikely to occur.

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