Methyl Basicity and Nucleophilicity: the *N*- and *O*-Alkylation of Carbamates

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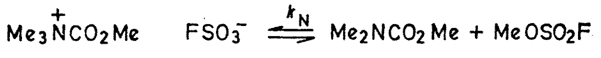
Summary In complete contrast to protonation, thermodynamically-controlled alkylation of two simple carbamates with methyl fluorosulphonate occurs on nitrogen: the reasons for this and the results of kinetically-controlled alkylation are discussed.



$\overset{+}{Me_3NCO_2Me}\ FSO_3^- \overset{k_N}{\rightleftharpoons} Me_2NCO_2Me + MeOSO_2F$

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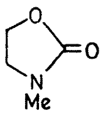

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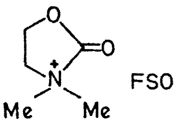

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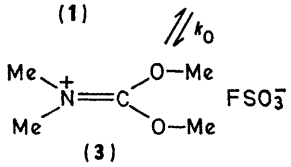

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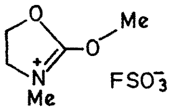

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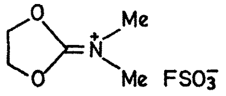

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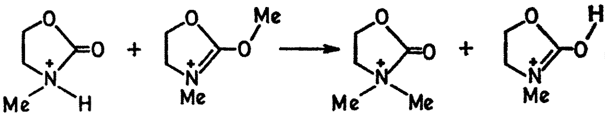
WE report here a study of the alkylation of two simple carbamates, methyl *NN*-dimethylcarbamate (**1**) and *N*-methyl-2-oxazolidone (**4**). Reaction of (**1**) with a ten-fold excess of methyl fluorosulphonate[1] at 25° was followed by n.m.r.; (**1**) absorbs at τ 6·38 (OMe) and 7·13 (NMe_2), (**2**) at τ 5·98 (OMe) and 6·70 (NMe_3), while (**3**) absorbs at τ 5·84 [$(OMe)_2$] and 6·92 (NMe_2). Initially k_O and k_N are about 6×10^{-6} and 3×10^{-6} moles l.$^{-1}$ sec.$^{-1}$ respectively but after 33·5 hr. the solution contained 76% (**2**), 11·5% (**3**), and 12·5% (**1**). Shortly after this, crystallisation of (**2**) began. Crystalline (**2**) was isolated and redissolved in acetonitrile. The 3% of (**3**) in this solution diminished to

1% after 2 days at room temp., therefore the *N*-alkylation product (**2**) is favoured by at least 99 : 1 at equilibrium. Protonation of (**1**), however, in fluorosulphonic acid is >95% on carbonyl oxygen as is normal for carbamates,[2] one exception being ethyl *NN*-di-isopropylcarbamate.[3] One explanation for this striking contrast might be the presence of an $A^{(1,3)}$ interaction[4] between two methyl groups in either planar conformation of (**3**). We therefore examined the alkylation of (**4**), since one conformation of its *O*-alkylation product (**6**) lacks an $A^{(1,3)}$ interaction. (**6**) is in fact formed rapidly from (**4**) and an excess of methyl fluorosulphonate to the exclusion of (**5**) (<5%), reaction being complete in 1 min. The rate of *O*-alkylation of (**4**) is, therefore, at least 1000 times that for (**1**). Nevertheless, after 24 hr. at 100° (**5**) is formed. It was isolated and shown not to revert into (**6**) during 24 hr. at 100° [>10% (**6**) formed]. (**7**), another possible rearrangement product, is not formed. Therefore the *N*-alkylation product is strongly favoured at equilibrium but protonation is >95% on oxygen.


(1)

At least in the case of *N*-methyl-2-oxazolidone (**4**) the steric explanation is inadequate. Qualitatively, the HSAB principle[5] points in the right direction, the softer acid (CH_3^+) favouring the softer basic centre (nitrogen). Semi-quantitatively, one may consider the formal reaction (equation 1) and calculate ΔH to be -4 kcal./mole from the bond dissociation energies given by Benson.[6] Although other factors[7] such as the hydrogen-bonding capabilities of the two proton adducts are likely to be important, the calculated enthalpy change for the reaction (equation 1) is close to that needed to account for protonation being 95% on oxygen at 25° (ΔG 1·7 kcal./mole) and methylation being 90% on carbon at 100° (ΔG 1·6 kcal./mole).

These results illustrate the need to distinguish nucleophilicity and basicity towards methyl carbon and point the way, by intra- and intermolecular comparisons using an anion of suitable nucleophilicity to effect transfer alkylation, to the development of scales of these quantities for comparison with a scale of hydrogen basicity.

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