The Regiospecific Alkylation of Amides. MNDO SCF-MO Calculations

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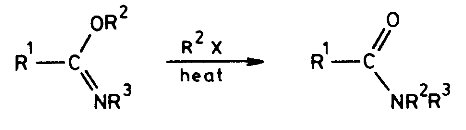
MNDO SCF-MO calculations are reported for neutral amides and the formamide anion. Consideration of the overall charge distribution and the atomic electron densities of the two highest MOs shows that frontier-orbital theory does not explain the known regiospecific alkylation of these compounds, but it can be rationalised in terms of a product-like transition state. Product control results from stabilisation by delocalisation of the nitrogen lone-pair electrons into the π-system of the amide C=O group. Significantly, in neutral amides where this is precluded, alkylation is calculated to occur on the nitrogen atom, in line with experiment.

Recent studies [1] of the alkyl halide catalysed rearrangement of imidates [equation (1)] support the hypothesis [2] that the nucleophilic reactivity of neutral amides resides at the oxygen atom. It follows that the alkylation of neutral amides may proceed initially at the oxygen atom to give an *O*-alkyl imidate, with the *N*-substituted amide arising from ensuing rearrangement catalysed by R^2X [equation (2)]. Subsequently, Beak *et al.* have shown that the alkylation of amides by methyl fluorosulphonate is regiospecific to give only *O*-alkylated products [3] and the acylation of both tertiary amides [4] and hydroxamic derivatives [5] follows a similar course. Thus regiospecific reactivity at the oxygen atom appears to be a general property of neutral amides. In contrast, the amide anion [*e.g.* (2)] reacts exclusively at the nitrogen atom to give *N*-substituted amides.[2] To account for this difference in the site of substitution, Challis and Challis [2,6] argued that the regiospecificity of neutral amides could be explained by consideration of the expected transition states for *O*- and *N*-substitution [(3) and (4), respectively]. Since delocalisation of the nitrogen lone-pair electrons should dissipate charge, transition-state (3) ought to be of lower energy than (4). No explanation of *N*-substitution in amide anions was given other than the generally accepted view that the negative charge preferentially resides at the nitrogen atom [implicit in structures such as (2)].

As a further test of this hypothesis, we have made SCF-MO calculations for the alkylation and protonation of amides and their derivatives using the semi-empirical MNDO method.[7] These model studies refer to molecules in the gas phase.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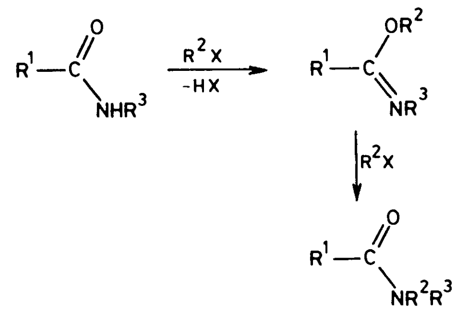
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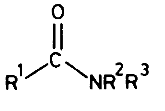
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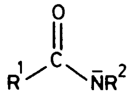
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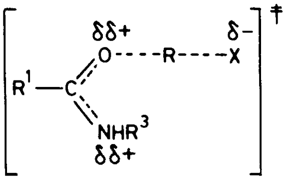
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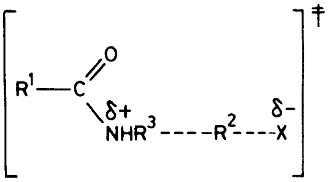
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Computational Procedure

The standard MNDO program (known to give good calculated values for ionisation potentials and relative molecular energies [7]) was used. The nuclear co-ordinates of all the systems studied were optimised with respect to the energy using the Davidon–Fletcher–Powell method.[7] In those cases where symmetry permitted, rotational barriers were calculated with an enforced plane of symmetry. Otherwise rotational barriers were calculated by minimising the sum of the squared scalar gradients using a variation of the Broyden–Levenberg–Marquardt method to locate the stationary point in the potential energy surface.[8]

Results and Discussion

Frontier Orbital Approach.[9]—It is conceivable that the alkylation and protonation of neutral amides on oxygen and of amide anions on nitrogen may be explained in terms of charge and orbital control of the reactions. In principle, charge control could explain all the findings since oxygen is the most electronegative element and therefore the most negatively charged atom in the neutral species, whereas the predominance of the negative charge on the nitrogen atom would account for *N*-substitution of the amide anion. Little is known about the direction of reactivity of amides under orbital control, but within the zero differential overlap approximation, the atom with the highest coefficient of electron density (Σc_i^2, where c_i is the corresponding LCAO coefficient) in the highest occupied molecular orbital (HOMO) ought to be the more reactive.[9]

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Table 1. Oxygen and nitrogen atomic charges (q_i) and HOMO and NHOMO coefficients of electron densities (Σc_i^2) for some representative amides

			π-orbital			n_O orbital		
Amide	q_O	q_N	E/eV	Σc^2(O)	Σc^2(N)	E/eV	Σc^2(O)	Σc^2(N)
(1; $R^1 = R^2 = R^3 = H$)	−0.37	−0.43	−10.70	0.29	0.70	−11.09	0.78	0.09
(1; $R^1 = R^2 = H, R^3 = CH_3$)	−0.36	−0.46	−10.40	0.22	0.66	−11.11	0.77	0.10
(1; $R^1 = CH_3, R^2 = R^3 = H$)	−0.34	−0.34	−10.76	0.43	0.50	−11.42	0.57	0.29
(1; $R^1 = HO, R^2 = R^3 = H$)	−0.36	−0.44	−11.03	0.36	0.62	−11.48	0.84	0.06
(1; $R^1 = F, R^2 = R^3 = H$)	−0.36	−0.41	−11.43	0.32	0.67	−12.22	0.87	0.05
(1; $R^1 = Cl, R^2 = R^3 = H$)	−0.30	−0.39	−11.52	0.29	0.71	−11.94	0.88	0.05
(2; $R^1 = R^2 = H$)	−0.64	−0.59	−2.81	0.36	0.62	−3.71	0.68	0.22

Table 2. Heats of formation, ΔH^f_{298} (kJ mol^{-1}), and π-bond orders of alkylated and protonated amide cations

	(4)			(5)		
Substituents	ΔH^f_{298}	π_{C-O}	π_{C-N}	ΔH^f_{298}	π_{C-O}	π_{C-N}
$R^1 = R^2 = R^3 = R^4 = H$	523.8	0.55	0.76	595.8	0.96	0.11
$R^1 = R^2 = R^3 = H, R^4 = CH_3$	537.6	0.57	0.74	603.8	0.96	0.11
$R^1 = R^2 = H, R^3 = R^4 = CH_3$	521.7	0.55	0.75	611.3	0.96	0.12
$R^1 = F, R^2 = R^3 = R^4 = H$	360.7	0.52	0.71	450.2	0.92	0.12
$R^1 = H, R^2, R^3 = (CH_2)_5, R^4 = CH_3$	505.8			623.4		
	(7a) [a]			(7b) [b]		
Substituents	ΔH^f_{298}	π_{C-O}	π_{C-N}	ΔH^f_{298}	π_{C-O}	π_{C-N}
$R^1 = R^2 = R^3 = R^4 = H$	636.0	0.77	0.25	645.6	0.79	0.24
$R^1 = R^2 = R^3 = H, R^4 = CH_3$	638.9	0.78	0.24			
$R^1 = R^2 = H, R^3 = R^4 = CH_3$	637.2	0.78	0.25			
$R^1 = F, R^2 = R^3 = R^4 = H$	448.6	0.68	0.23	453.5	0.71	0.23

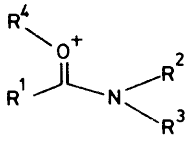
[a] Lone pair *anti* to the C–O bond. [b] Lone pair *syn* to the C–O bond.

Table 1 lists the electronic charge distribution given by the MNDO method for representative amides. Contrary to expectation, the nitrogen atom of neutral amides bears the greater atomic charge which implies this atom should undergo substitution in charge controlled reactions. This conclusion agrees with experimental findings for the reactions of Bu^{t}Cl and PhCH$_2$Cl with formamides,[10] but the severe reaction conditions used allow alternative explanations.[1] It does not agree, however, for other reactions under conditions which do not offer alternatives, *e.g.* $Et_3O^+BF_4^-$–0° C,[11] $MeSO_3F$–25 °C,[3] where the oxygen atom undergoes alkylation. Further, the atomic charge distribution in the formamide anion shows the oxygen atom bears the greater part of the negative charge. This is also incompatible with the experimental evidence that the nitrogen atom is substituted.[2,6] Thus the frontier orbital approach to amide regiospecificity under charge controlled conditions is not convincing.

The electron density coefficients (Σc_i^2) at the oxygen and nitrogen atoms for the HOMO and the next highest MO (NHOMO) are also listed in Table 1. These show that the nitrogen atom bears the greater electron density in the highest occupied amide π-orbital. Our calculations also show that, for all but acetamide, the highest occupied π-orbital lies only 0.4—0.8 eV in energy above the n_O orbital which corresponds to an oxygen lone-pair of electrons. This conclusion agrees with photoelectron spectroscopic studies for *N*-substituted amides,[12] but not for unsubstituted amides where the first ionisation is in fact from the n_O orbital located on the oxygen atom.[12,13] Nevertheless, within the accuracy of the MNDO method (±0.3 eV)[7] the antisymmetric π-orbital and the n_O orbital can be considered to be almost degenerate, a situation borne out by experiment.[13] It is extremely difficult therefore to ascertain whether it is the oxygen atom or the nitrogen atom of neutral amides that will undergo substitution under orbital controlled conditions. This is particularly apparent if one inspects the relevant term in the Klopman–Salem relationship (3)[9] where a,b are atomic orbitals, r are molecular orbitals on

$$\Delta E \propto \sum_{r}^{occ}\sum_{s}^{unocc} - \sum_{s}^{occ}\sum_{r}^{unocc} \frac{2(\Sigma_{ab}C_{ra}C_{sb}\beta_{ab})^2}{E_r - E_s} \qquad (3)$$

one molecule and s those on the other. E_r is the energy of molecular orbital r, and C_{ra} is the coefficient of atomic orbital a in molecular orbital r. Equation (3) gives the change in energy (ΔE) when the filled orbitals of one reactant interact with the empty orbitals of the other. This interaction depends not only on the molecular orbital coefficient C_{ra} but also on $\Delta\beta$, the change in the resonance integral as the interaction develops. Since the antisymmetric π-orbital and the n_O orbital of amides have different symmetries the change in $\Delta\beta$ will be different for each case. Consequently, frontier orbital theory cannot easily explain the regiospecific alkylation of neutral amides in oxygen and amide anions on nitrogen.



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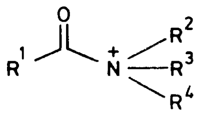


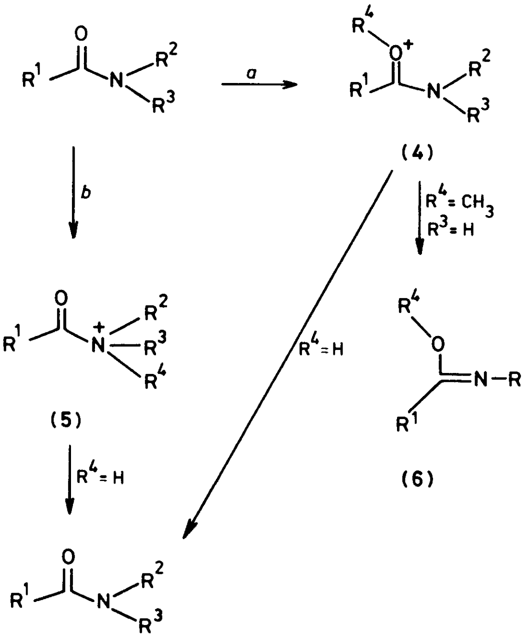
(5)

Product Control of the Transition State.—Alkylation of neutral amides at the oxygen or nitrogen atoms gives rise to the cations (4) and (5), respectively, and product-like transition

Table 3. Heats of formation (kJ mol^{-1}) and π-bond orders for amides and the isomeric imidates

	(2)			(6a)[a]			(6b)[b]		
	ΔH^f_{298}	π_{C-O}	π_{C-N}	ΔH^f_{298}	π_{C-O}	π_{C-N}	ΔH^f_{298}	π_{C-O}	π_{C-N}
$R^1 = R^2 = R^3 = R^4 = H$	−165.3	0.85	0.47	−151.0	0.36	0.92	−147.3	0.33	0.94
$R^1 = R^2 = H$, $R^3 = R^4 = CH_3$	−170.7	0.85	0.45	−98.3	0.33	0.94	−118.0	0.32	0.94
$R^1 = Cl$, $R^2 = R^3 = R^4 = H$	−210.5	0.82	0.48	−174.9	0.34	0.92	−175.3	0.32	0.93
$R^1 = F$, $R^2 = R^3 = R^4 = H$	−383.7	0.81	0.44	−352.3	0.33	0.90	−359.8	0.32	0.90

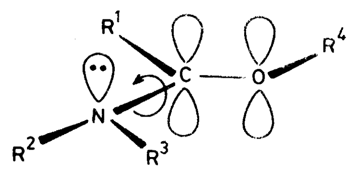
[a] Oxygen lone pair *syn* to C=N bond. [b] Oxygen lone pair *anti* to C=N bond.



Scheme 1.

states will resemble them. Comparison of the energies of formation of such species (Table 2) calculated by the MNDO method (when R^4 = H or CH_3) shows that cations of type (4), derived from *O*-substitution, are *ca.* 80—105 kJ mol^{-1} more stable, for either protonation or methylation, than those cations (5) derived from *N*-substitution. The results for protonation are similar to those for *ab initio* calculations [14] which show *O*-protonated formamide to be *ca.* 25 kJ mol^{-1} more stable than the *N*-protonated tautomer.

Scheme 1 shows alkylation or protonation of an amide to occur at either the O (path *a*) or N (path *b*) atoms. The results in Table 2 suggest that attack proceeds preferentially by path *a* to give the more stable intermediate (4), and that the transition state for path *a*, if product like, is favoured by *ca.* 90 kJ mol^{-1}. Deprotonation of (5) leads to an amide product whereas deprotonation of (4) will give the thermodynamically less stable imidate (6). The MNDO calculations successfully predict that the imidate is the thermodynamically less stable product as can be seen by comparison of the calculated heats of formation in Table 3.



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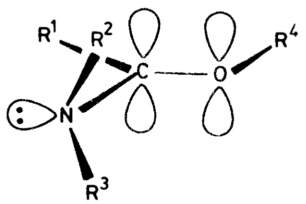
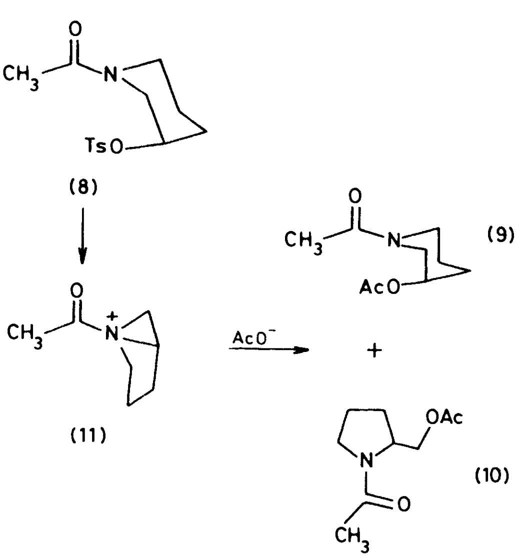


(7a)

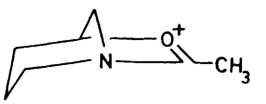
Stabilisation of the Transition State.—Exactly why the *O*-substituted amide (4) is more stable than the *N*-substituted species (5) lies, as anticipated, in delocalisation of the π-system. Inspection of Table 3 shows that amides exhibit substantial π_{C-N} bond development in the neutral molecule, indicating a delocalisation of the nitrogen lone pair of electrons into the π_{C-O} system. *N*-Alkylation or protonation, which precludes this type of interaction, reduces the π_{C-N} value drastically and localises the π-system almost entirely between the carbon and oxygen atoms, making this process an energy-demanding one. The π_{C-N} bond order in (5) is due entirely to hyperconjugative delocalisation and as such depends on the rotational conformation of the $-\overset{+}{N}R_3$ group. In contrast, *O*-alkylation or protonation increases the π_{C-N} bond order and despite a concomitant reduction in the π_{C-O} bond order, significant π_{C-O} bond character is retained.

That delocalisation of the nitrogen lone-pair electrons alone is responsible for the increased stability of the *O*-substituted compounds and was tested as follows. Rotation about the C−N bond in (4) gives the orthogonal structure (7) in which the nitrogen lone pair is either *anti* to the C−O bond (7a) or *syn* to the C−O bond (7b). The nitrogen lone pair is now incapable of delocalisation into the π_{C-O} bond. The calculated energies of (7a and b) are compared with those of (4) and the *N*-alkylated (or protonated) structure (5) in Table 2. These results clearly show that the orthogonal *O*-substituted structures (7a and b) are either less stable or no more stable than the *N*-substituted species, supporting the proposal that the stabilisation of the product from *O*-attack arises from delocalisation of the nitrogen lone-pair electrons. It must be noted, however, that some π_{C-N} bond character is retained in the orthogonal structures, and that the C−O bond does not attain full π-bond character. This may be due to a hyperconjugative effect. Nonetheless, significant loss of delocalisation of the nitrogen lone pair is observed, enough to destabilise the molecule.

There is reliable experimental evidence that some amides do react *via* the nitrogen atom alone [15,16] and these examples require comment. For example, acetolysis of *N*-acetyl-3-



Scheme 2. Acetolysis of *N*-acetyl-3-tosylpiperidinol



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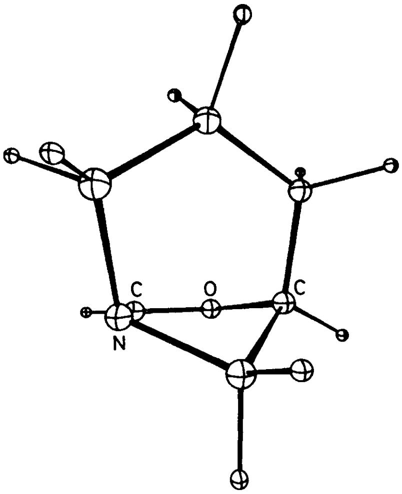
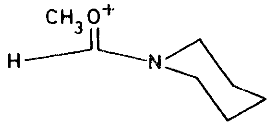


Figure. ORTEP diagram of the 1-aza-3-oxabicyclo[3.2.1]octyl cation (12)

tosylpiperidinol (8) gave (9) and (10), and the intermediate was shown to be (11), *i.e.* the product of intramolecular nitrogen-attack (Scheme 2). Molecular models of this system indicate that the corresponding *O*-intermediate (12) is unlikely to be stabilised by lone-pair π-bond interaction. This is reflected in the relative heats of formation of the formyl analogues (11; H for CH$_3$) and (12; H for CH$_3$) calculated by the MNDO method to be 665.7 and 681.6 kJ mol^{-1} respectively, suggesting that the *O*-alkylated intermediate (13) is *ca.* 16 kJ mol^{-1} *less* stable than the *N*-substituted analogue. Inspection of the ORTEP plot of (12; H for CH$_3$) (Figure) also shows that the nitrogen lone-pair electrons are unable to interact strongly with the $\pi_{\mathrm{C-O}}$ system. That this is a real effect is proved by considering intermolecular alkylation of *N*-formylpiperidine, where the *O*-methylated cation (13) is 117 kJ mol^{-1} (*cf.* Table 2) more stable than the *N*-methylated form (14).



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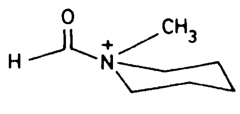

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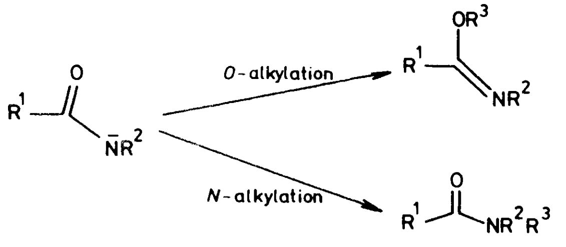

Scheme 3. Alkylation of an amide anion

So far we have considered alkylation of neutral amide molecules. However, alkylation of amide anions may be explained in similar terms. Alkylation can give rise to either a neutral amide or a neutral imidate (Scheme 3). By considering the stabilisation of the product, *viz.* imidate or amide (Table 3), it is obvious that a product-like transition state leading to the amide is the more stable. Again, this results from greater delocalisation in the amide system compared with the corresponding imidates (*cf.* Table 3). Hence *N*-alkylation of amide anions is also favoured by product control of the transition-state.

Conclusions

Most neutral amide molecules are regiospecifically alkylated on the oxygen atom, whereas most amide anions are regiospecifically alkylated on the nitrogen atom. The MNDO MO calculations bear out, and give a quantitative basis to, the previous intuitive arguments that alkylation of neutral amides gives rise to the thermodynamically more stable transition state, and that *N*-alkylation of amide anions arises from the formation of a product-like transition state. These arguments offer a more satisfactory explanation to the nucleophilic reactivity of amides than does frontier orbital theory.

Acknowledgements

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