

Nucleophilic Reactivity of Some Nitrogen Heterocycles

P. FRØYEN* and R. F. HUDSON

University Chemical Laboratory, Canterbury, Kent, England

The rates of reaction of 1,4-diazabicyclo[2.2.2]octane and quinuclidine with various substrates are explained by through bond coupling of the lone pairs in the diaza-compound. The relative reactivity of 1,2-oxazolidine and tetrahydro-1,2-oxazine towards *p*-nitrophenyl acetate indicates *weak* interaction between the lone pairs on adjacent nitrogen and oxygen atoms. The reactivities of piperidine and pyrrolidine are used as reference compounds to obtain a measure of steric hindrance. Comment is made on the high energy barrier to inversion of cyclic hydroxylamines.

Nucleophilic reactivity is usually discussed¹ in terms of polarisability and basicity (*i.e.* the pK_a of the conjugate acid of the nucleophile), although solvation energies are particularly important in the reactions of anionic reagents.² In addition, steric hindrance frequently dominates a reaction sequence, as for example in the reactions of amines.³

It is now evident that reactions must be considered in orbital terms⁴ rather than in terms of empirical parameters (*e.g.* free energy relationships), since orbital diagrams give a more detailed, albeit approximate, description of the reaction process. This approach has been developed recently⁵ to explain

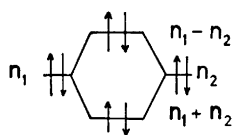


Fig. 1.

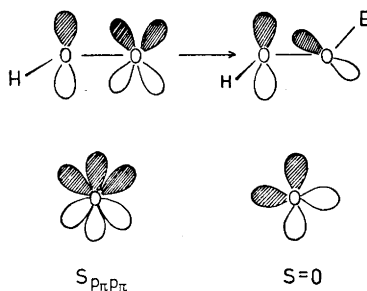


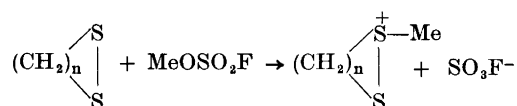
Fig. 2.

* Present address: Kjemisk Institutt, Universitetet i Bergen, Bergen, Norway.

the anomalously high reactivity of certain nucleophiles (*e.g.* HO_2^- , ClO^-) towards electrophilic centres. According to this explanation, lone pairs of the correct symmetry on adjacent atoms combine to give bonding and anti-bonding molecular orbitals as shown in Fig. 1.

For example, in the case of the hydroperoxide ion, $p\pi-p\pi$ overlap leads to electron repulsion* which is partially removed on formation of a σ -bond with an electrophile, E (Fig. 2).

This orbital splitting, and hence the repulsion energy is conformation dependent. We have demonstrated this by following the reactions of cyclic disulphides⁶ with methyl fluorosulphonate in dimethyl sulphate solution,



Sulphur compounds are particularly suitable for study because, unlike nitrogen, the lone pair electrons are in pure p orbitals, orthogonal to the C_{sv} σ -bond framework.⁷ Accordingly, the reactivity, k , of the disulphide depends on the dihedral angle, θ , between the $p\pi$ orbitals, and on the extent of bond formation,** β , in the transition state as follows,

$$RT \ln k \simeq 2\beta E_\pi S \cos \theta$$

where E_π is the orbital splitting energy (given directly by photoionisation spectra⁷), and S_π the $p\pi-p\pi$ overlap integral for a disulphide bond.

In further work,⁸ aromatic nitrogen heterocycles (*e.g.* pyrazine and isothiazole) were found to be considerably more reactive towards activated esters than predicted from their basicity. Here again lone-pair repulsions (in essentially sp^2 orbitals) lead to orbital splitting with consequent destabilisation of the molecule and increased nucleophilic reactivity. The situation with nitrogen compounds is by no means simple, owing to the combination of "lone-pair" orbitals with orbitals used in σ -bonding.⁹ This modifies the behaviour of the nitrogen lone pair such that in certain molecules it may effectively "disappear" into the molecular structure.

In the present study we have measured the rate of reaction of some nitrogen heterocycles which may show through space or through bond coupling¹⁰ of lone pair orbitals, with various electrophiles. In the present work we show that through space interaction of the lone pairs on adjacent oxygen and nitrogen atoms of cyclic hydroxylamines can lead to small increases in reactivity, when bond formation in the transition state is extensive. On the other hand, through bond coupling in 1,4-diazabicyclo[2.2.2]octane (DBCO) can lead to small rate enhancements when bonding in the transition state is very weak (low Brønsted β), but in most reactions the more basic homomorph³ quinuclidine (Q) is more reactive than DBCO.

* Given by $4(\beta - \alpha S)/(1 - S^2)$ according to Hückel MO theory.

** This is given approximately by the Brønsted exponential coefficient, β .

EXPERIMENTAL

Materials. Methyl tosylate was synthesized from tosyl chloride and methanol. Before use it was recrystallized several times from ether-petrol ether, m.p. 28°. *p*-Nitrophenyl acetate was prepared from acetic anhydride and *p*-nitrophenol, and was recrystallized from benzene-petrol ether, m.p. 78°. 4,4'-Tetramethyldiaminotriphenylmethane chloride (malachite green) a commercial product from B.D.H. Ltd. was used without further purification. The hydrochlorides of 1,2-oxazolidine and tetrahydro-1,2-oxazolidine and tetrahydro-1,2-oxazine were prepared according to King,¹¹ and were repeatedly recrystallized before use.

1,4-Diazabicyclo[2.2.2]octane and quinuclidine hydrochloride were obtained from R. H. Emanuel, Ltd. and were recrystallized from ethanol. Piperidine hydrochloride was prepared by treatment of piperidine with dry HCl. The product was crystallized twice from ethanol, m.p. 246°. Pyrrolidine (Fisons Chemicals) was dried over KOH pellets and distilled before use.

Kinetic methods. The rates of reaction were followed colourimetrically using a Unicam S.P. 800 spectrophotometer and a cell held at $25 \pm 0.1^\circ$. The appearance of 4-nitrophenol and 4-nitrophenolate ion was followed at 330 and 400 nm, respectively, and the disappearance of malachite green was followed at 625 nm. The reactions of methyl tosylate were followed at 272 nm. Freshly prepared, aqueous, solutions were used in all cases, and a large excess of nucleophile ensured that the reactions proceeded under pseudo-unimolecular conditions. The bases thus served as buffer and nucleophile, and the concentration of free base was calculated from the pK_a and pH of the solution used in each case. The rate constants, calculated by Guggenheim's method are given in Tables 1 and 2.

Table 1. Rates of reaction of several substrates with 1,4-diazabicyclo[2.2.2]octane and with quinuclidine in aqueous solution at 25°. (Second order rate constants are given as $l \text{ mol}^{-1} \text{ min}^{-1}$).

Substrate	β^a	1,4-Diazabicyclo- [2.2.2]octane* ^b	Quinu- clidine	Relative reactivity
<i>p</i> -Nitrophenyl acetate	0.83	1.1	148.3	135
Malachite green	0.41	5.6×10^{-2}	4.0	71
Methyl tosylate	0.10	4.3	10.7	2.5
2,4-Dinitrophenyl phosphate ¹²	≈ 0	5.11×10^{-2}	1.68×10^{-2}	0.3

^a β is the Brønsted coefficient for reactions with a series of amines. ^b Half of observed values.

Table 2. Reaction of *p*-nitrophenyl acetate and methyl phosphate with some cyclic amines and hydroxylamines. (Second order rate constants $l \text{ mol}^{-1} \text{ min}^{-1}$).

Nucleophile	<i>p</i> -Nitrophenyl acetate	<i>p</i> -Nitrophenyl methylphosphonate ¹³
Pyrrolidine	9200	285
Piperidine	3180	48
1,2-Oxazolidine	1.89	0.14
Tetrahydro-1,2-oxazine	0.21	0.075

RESULTS AND DISCUSSION

The initial studies involved the reactions of 1,4-diazabicyclo [2.2.2]octane (DBCO) and quinuclidine (Q) with several electrophiles in aqueous solution (Table 1). Molecules of the same general structure, *e.g.* tertiary amines, normally show the same reactivity order to all substrates † as given quantitatively by the Brønsted equation, Hammett equation or similar linear free energy relationship.⁴ The data of Table 1, however, show that DBCO is more reactive than Q towards 2,4-dinitrophenyl phosphate,¹² but less reactive towards the other reagents.

This change in reactivity order may be attributed to the unusual electronic structure of DBCO since the pK_a is very low for a tertiary amine, but the ionisation potential is also low (7.52 eV; *cf.* 8.6 eV for quinuclidine).¹⁰ Usually a low pK_a is associated with a high ionisation potential for molecules of a given structure. In the case of DBCO, the combination of the lone pair orbitals with σ and σ^* orbitals of the C–C bonds gives delocalised orbitals⁹ as shown in Fig. 3.

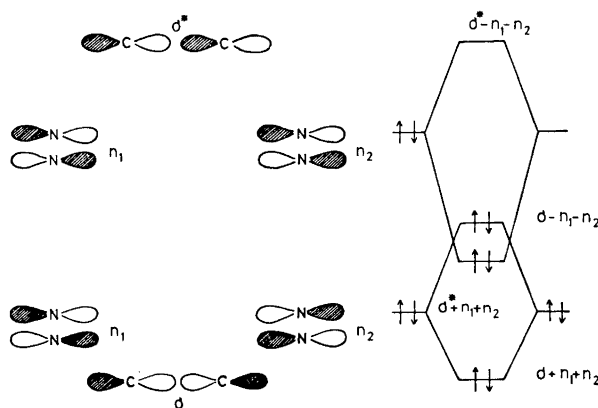


Fig. 3.

This orbital interaction has been confirmed elegantly by a study of the photoelectron spectrum by Heilbronner,¹⁰ from which it may be concluded that in spite of the high energy occupied (symmetric) orbital (I.P. 7.52 eV), the molecule is more stable than quinuclidine (I.P. 8.6 eV).^{††}

We can now explain the change in the reactivity order in the following way. For small interactions, as in the reaction of 2,4-dinitrophenyl phosphate ($\beta \approx 0$), the electronic structure of the nucleophile is essentially unaltered, and the electrophilic L.U.M.O. (σ^* orbital) interacts primarily with n_1 and n_2 of DBCO. (Fig. 4).

† Providing that differences in steric hindrance are negligible.

†† Hence a greatly reduced pK_a (8.8) compared to a tertiary amine, *e.g.* 11.2 for Et_3N and 10.95 for quinuclidine.¹⁴

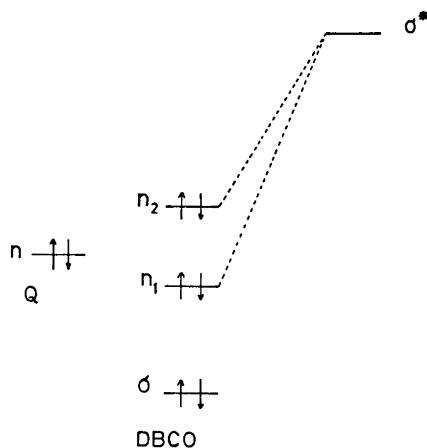


Fig. 4.

As predicted by Hoffmann,⁹ and shown later by Heilbronner,¹⁰ the average energy of n_1 and n_2 is less than the energy of n (for quinuclidine). Hence under these conditions the perturbation of DBCO is greater than that of Q, and the former is the more reactive. As the interaction in the transition state increases, the electrophile interacts more strongly with the available orbitals, n_1 , n_2 and σ . In the limit, when the bond is (almost) fully formed in the transition state, *e.g.* as in acylation ($\beta = 0.83$), the reactivity is determined by the stability of the nucleophile (*i.e.* the total electronic energy), and quinuclidine is more reactive than DBCO (Table 1).

In further work we have compared the reactivity of cyclic hydroxylamines and cyclic amines. As shown by the data in Table 2 the relative reactivity of pyrrolidine and piperidine towards *p*-nitrophenyl methyl phosphonate (6.0) is greater than the relative reactivity towards *p*-nitrophenyl acetate (2.9). This is in line with greater steric hindrance towards phosphorylating agents than towards acylating agents.¹⁵ Moreover, the relative reactivity of 1,2-oxazolidine and tetrahydro-1,2-oxazine towards *p*-nitrophenyl methyl phosphonate is appreciably less than the relative reactivity of the two cyclic amines. According to Edwards *et al.*¹³ the rate differences are due to differences in steric hindrance produced mainly by the 3 and 5 axial H-atoms, and hence the cyclic hydroxylamines are expected, on this basis, to exert less steric hindrance than the corresponding cyclic amines.

On the other hand 1,2-oxazolidine is *ca.* 9 times more reactive than tetrahydro-1,2-oxazine towards *p*-nitrophenyl acetate, where steric hindrance differences are expected to be negligible (*i.e.* less than for the methylphosphonate). This rate increase is therefore probably due to the interaction of lone-pairs on adjacent nitrogen and oxygen atoms. The effect, however, is small compared with reactivity increases found for other α -nucleophiles, and this reduced effect may be due to the different symmetries of the lone pair orbitals on oxygen and nitrogen. Because of the (local) C_3 symmetry of the nitrogen atom, the lone pair orbital will combine with the σ -bond orbitals and the lone pair is effectively delocalised throughout the σ -bond framework.

This will reduce the repulsion exerted towards the lone pairs in the p_π orbital of the oxygen atom.

In this connection it is found that isoxazolidines and tetrahydro-1,2-oxazines undergo nitrogen inversion slowly with barriers of the order of 14–17 kcal/mol.¹⁶ The barriers for simple acyclic amines are of the order of 5 kcal/mol. The difference can be attributed to strong $p_\pi-p_\pi$ repulsions of the lone pairs in the transition state where the nitrogen atom adopts the trigonal configuration. An estimate of the repulsion energy, ΔE , may be obtained from a simple Hückel treatment for the interaction of two p orbitals,

$$\Delta E \simeq 4[(\beta - \alpha S)/(1 + S)][S/(1 - S)] \simeq 2E_\pi[S/(1 - S)]$$

where E_π is the π -bond energy of a N–O single bond and S the corresponding overlap integral. For $E_\pi \simeq 50$ kcal/mol* and $S_{N-O} \simeq 0.1$ we have a value of 11 kcal/mol for the inversion barrier. This is similar to the difference in energy barriers for cyclic N–O compounds and cyclic amines, and is in agreement with the assumption of a small lone-pair lone-pair repulsion energy in the ground state. Molecules of this kind therefore can exhibit only small rate enhancements (α -effects) in nucleophilic substitutions.

REFERENCES

1. Pearson, R. G. and Edwards, J. O. *J. Am. Chem. Soc.* **84** (1962) 16; Hudson, R. F. *Chimia* **16** (1962) 173.
2. Parker, A. J. *Quart. Rev.* **16** (1962) 163; *Advan. Phys. Org. Chem.* **5** (1967) 173.
3. Brown, H. C. *J. Am. Chem. Soc.* **67** (1945) 503.
4. Hudson, R. F. *Angew. Chem.* **85** (1973) 63; *Int. Ed.* **12** (1973) 36; Salem, L. *Chem. in Britain* **5** (1969) 449.
5. Aubort, J.-D. and Hudson, R. F. *Chem. Commun.* **1970** 937.
6. Filippini, F. and Hudson, R. F. *Chem. Commun.* **1972** 726.
7. Filippini, F. and Hudson, R. F. *Chem. Commun.* **1972** 522; Zoltewicz, J. A. and Jacobsen, H. L. *Tetrahedron Letters* **1972** 189; Zoltewicz, J. A. and Deady, L. W. *J. Am. Chem. Soc.* **94** (1972) 2765.
8. Hoffmann, R. *Accounts Chem. Res.* **4** (1971) 1.
9. Hoffmann, R., Inamura, A. and Hehre, J. W. *J. Am. Chem. Soc.* **90** (1968) 1499.
10. Heilbronner, E. and Muszkat, K. A. *J. Am. Chem. Soc.* **92** (1970) 3818.
11. King, H. *J. Chem. Soc.* **1943** 43.
12. Kirby, A. J. and Varvoglis, A. G. *J. Chem. Soc. A* **1968** 135.
13. Brass, H. J., Edwards, J. O. and Fina, N. J. *J. Chem. Soc. Perkin Trans. 2* **1972** 726; Brass, H. J., Edwards, J. O. and Biallas, M. J. *J. Am. Chem. Soc.* **92** (1970) 4675.
14. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*, 1965, p. 260.
15. Hudson, R. F. and Keay, L. *J. Chem. Soc.* **1956** 2463.
16. Griffith, D. L. and Olsen, B. L. *Chem. Commun.* **1968** 1682; Riddell, F. G., Lehn, J. M. and Wagner, J. *Ibid.* 1403.

Received June 29, 1973.

* Estimated from the value for a N–O double bond, and from double and single bond distances.