1,3-Dipolar Character of Six-membered Aromatic Rings. Part XX.[1] Preparation and Dimerisation of 1-(5-Nitro-2-pyridyl)- and 1-(4,6-Dimethylpyrimidin-2-yl)-3-oxidopyridinium

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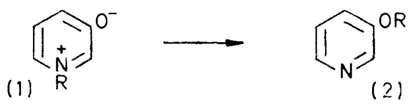
The title betaines form dimers, the structures and stereochemistry of which are elucidated. The regio- and stereoselectivity of dimer formation are rationalised and the variation of reactivity of 3-oxidopyridinium betaines with their substitution patterns is discussed in MO terms.

STUDY[2] of 1-(2,4-dinitrophenyl)-3-oxidopyridinium (1a) showed the superior dipolar reactivity of a compound possessing a strong electron-withdrawing group on the nitrogen atom compared[3] with (1b). However, work with (1a) is difficult because of the ease[2] of rearrangement (1a) ⟶ (2). We have therefore sought other betaines with electron-withdrawing groups in the 1-position.


(1) (2)

a; R = 2,4-$(NO_2)_2C_6H_3$
b; R = Me
c; R = H
d; R = Ph
e; R = C_6H_4X-*p*

1-(5-Nitro-2-pyridyl)-3-oxidopyridinium (7).—Our work on this compound is summarised in Scheme 1. The salt (5), formed as expected, gave on treatment with bases under most conditions the dimer (6). However the monomeric betaine (7) could be isolated, albeit in impure form; (7) readily dimerises, but does not rearrange to the 3-pyridyloxypyridine (8) which was prepared independently as shown in Scheme 1. The structure and stereochemistry of the dimer (6) were elucidated from spectral evidence; the n.m.r. spectrum [Supplementary Publication No. SUP 21794 (3 pp.)] † is especially significant and the assignments were confirmed by double irradiation experiments.[4] The spectrum (Table 1) in $(CD_3)_2SO$ shows two clear AMX systems in the aromatic region assignable to the two nitropyridyl groups situated in different environments. In the olefinic region, the down-field quartet at δ 7.55 was assigned to H-8 and irradiation at this frequency simplified the absorptions of H-7 (δ 5.97) and H-9 (δ 6.29). Irradiation at the H-6 absorption frequency (δ 3.49) confirmed the coupling of H-6 to H-7 by 2.5 Hz and the coupling of H-6 to H-5 by 6.5 Hz, and as H-5 is in turn coupled to H-4 by 7.7 Hz, the positional sequence H-4 to H-9 was thus unambiguously established. The signal of the bridgehead proton H-6 not located α to a nitrogen atom occurs at higher field than those of the other three bridgehead protons.

The *exo*-configuration ‡ of the dimer is supported by the similarity of the observed coupling constants to those calculated using the Karplus relationship[5] (see Table 2). Further, H-6 is coupled to H-2 by 2.5 Hz. Molecular models demonstrate that only in the *exo*-structure does the four-bond system connecting the two protons H-6 and H-2 assume a planar configuration necessary for W-type long-range coupling; the system deviates sharply from planarity in the *endo*-structure.

The dimer (6) showed a marked tendency to Michael additions at C=C–C=O, and the adducts (9), (10), and (11) were prepared in this way. Their i.r. spectra show no $\alpha\beta$-unsaturated carbonyl absorption. The n.m.r. spectra of the Michael adducts (Table 1) are characterised by the disappearance of the vinylic absorption due to H-8 and H-9 and the presence of new high field ABX absorptions due to H-8, H-9a, and H-9b. Mass spectra gave molecular ions at *m/e* 452, 466, and 451 for (9), (10), and (11), respectively.

Dimer (6) appears to be in thermal equilibrium with monomer (7) at elevated temperatures. This equilibrium is comparable to that reported by Holland and Jones[6] between 1,3-diphenylinden-2-one and its dimer.

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† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1975, Index issue.

‡ In the dimers the *exo* terminology is used when the single atom bridges (*i.e.* CO or NR) are *trans*.

[1] A. R. Katritzky and H. Wilde, *J.C.S. Chem. Comm.*, 1975, 770 is regarded as Part XIX.

[2] N. Dennis, B. Ibrahim, A. R. Katritzky, I. G. Taulov, and Y. Takeuchi, *J.C.S. Perkin I*, 1974, 1883.

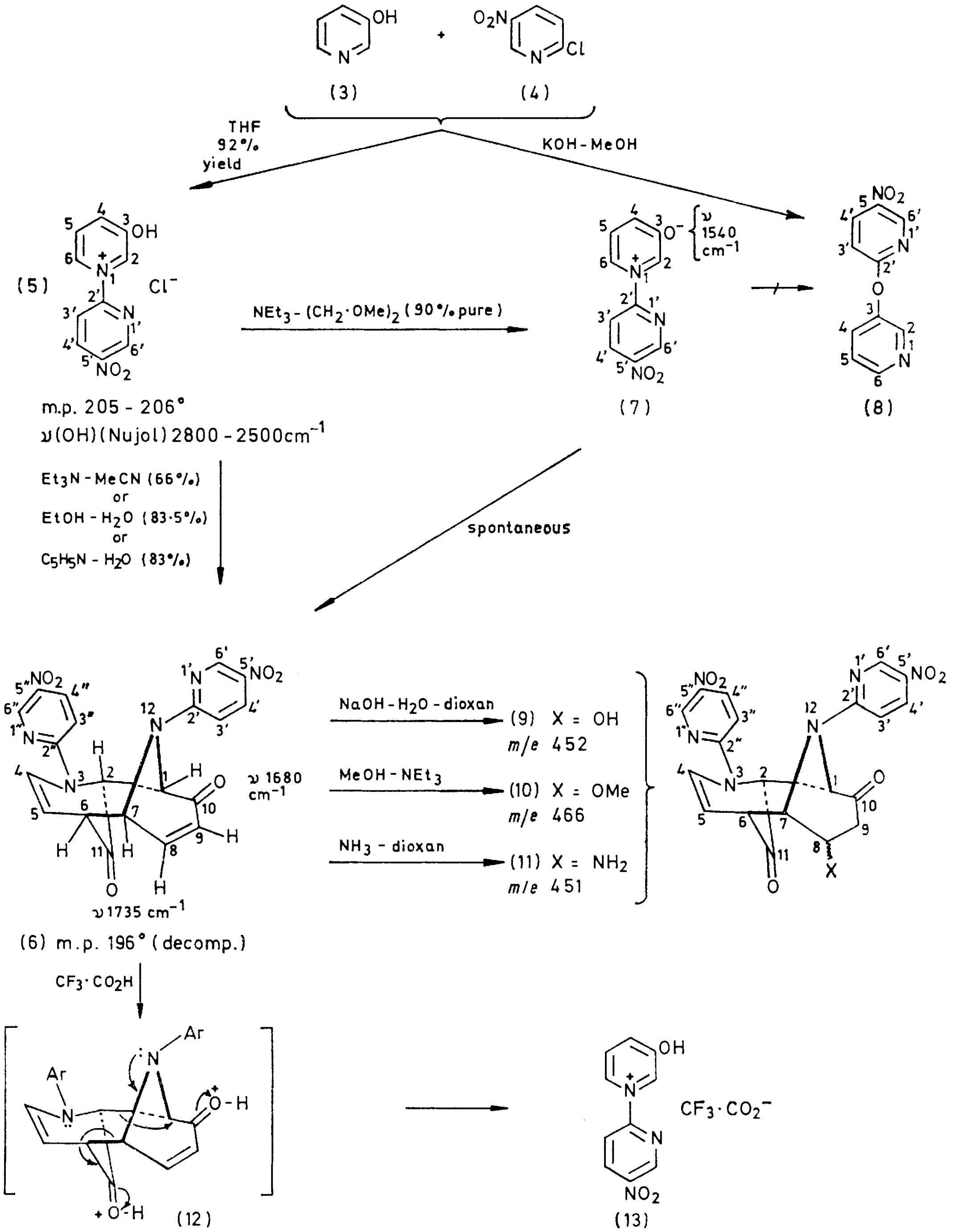
[3] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (*C*), 1971, 874.

[4] For full details see B. Ibrahim, Ph.D. Thesis, University of East Anglia, 1975.

[5] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

[6] J. M. Holland and D. W. Jones, *Chem. Comm.*, 1969, **587**; *J. Chem. Soc.* (*C*), 1971, 608.

The instability of (6) towards dissociation is underlined by the complete absence of the corresponding dimer molecular ion in the mass spectrum. The dissociation is also catalysed by strong acids, thus the n.m.r. spectrum taken in CF_3CO_2H is that of the salt (13) and not of the dimer (6). By contrast, dissociation of (6) is slow in acetic acid. Presumably, protonation of the carbonyl oxygen atoms initiates dissociation (Scheme 1).



SCHEME 1 1-(5-Nitro-2-pyridyl)-3-oxidopyridinium and its dimer

Rationalisation of Dimerisation (7) ⟶ (6).—A 3-oxidopyridinium betaine is to be regarded as belonging to the $4n$ π-electron class of electrocyclic components for addition across the 2- and 6-positions, but to the $(4n + 2)$ π-electron class of components for the reaction across the 2- and 4-positions (Scheme 2).

The normal thermal reactions of 3-oxidopyridinium betaines with olefins across the 2- and 6-positions are thus readily rationalised by the general theories[7-9] of pericyclic reactions. Moreover, it is clear that dimerisation of the betaines should involve the 2- and 4-positions of one molecule reacting with the 2- and 6-positions of the other, as already found [(7) $\longrightarrow$ (6)]. Satisfying though rationalisation is, successful prediction is fundamental to an assessment of the value of theory; the succeeding paper[10] demonstrates that other 4 π-electron components will add across the 2- and 4-positions of pyridinium betaines, while 6 π-electron components react at the 2- and 6-positions.[11] Recently, 1-methyl-3-oxidoquinolinium betaine (14) has been shown to react as a ($4n + 2$) π-electron component with a number of 1,3-dienes.[12]

TABLE 1

Proton n.m.r. spectra (δ values) of dimers and derivatives[a]

Proton	(6) *	(9) †	(10) †	(11) *	(18) ‡	(19) ‡	(22/23) ‡
1	6.13[b]	5.60[b]	5.65[b]	4.70[b]	6.53[c]	6.74[d]	5.75,[c] 5.75[d]
2	5.16[c]	5.38[c]	5.36[c]	4.90[c]	5.25[c]	5.22[c]	4.92,[c] 4.90[d]
3							4.87[c]
4	7.22	7.05[b]	7.11[b]	7.08[b]	7.47[b]	7.42[b]	7.70[b]
5	5.22[c]	5.75[c]	5.80[c]	5.00[c]	4.83[c]	4.85[c]	4.87[c]
6	3.49[e]	4.86[d]	4.78[d]	*ca.* 5.0	3.25[d]	3.25[d]	2.95,[d] 2.90[c]
7	5.97[c]	5.60[d]	5.65[d]	5.40[d]	6.25[d]	5.97[c]	5.60[c]
8	7.55[c]	3.60[d]	3.84[d]		7.27[c]		
9	6.29[c]				6.25[b]	6.30[b]	
9a		3.15[c]	3.30[c]	*ca.* 3.0			2.95[d]
9b		3.08[c]	3.10[c]	*ca.* 3.0		7.27[c]	2.95[d]
10							3.14[d]
6′, 6″	9.12, 8.58[b]	9.2, 9.0[b]	9.46, 9.10[b]	9.03, 8.73[b]			
4′, 4″	8.40, 8.18[c]	8.84, 8.75[c]	8.91, 8.80[c]	8.40, 8.20[c]			
3′, 3″	7.14, 6.97[b]	7.50, 7.46[b]	7.56, 7.53[b]	7.08, 6.90[b]			
5′, 5″					6.55, 6.24[f]	6.55, 6.24[f]	6.45, 6.16[f]
Me			3.54[f]		2.35[f]	2.35[f]	2.30[f]

[a] Me_4Si as internal standard. [b] Doublet. [c] Double doublet. [d] Multiplet. [e] Double triplet. [f] Singlet.

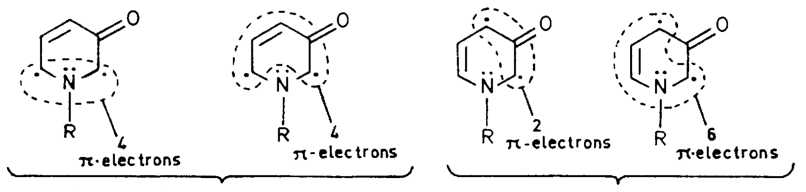
* In $(CD_3)_2SO$. † In CF_3CO_2H. ‡ In $CDCl_3$.

TABLE 2

Observed and calculated coupling constants (Hz) of dimers and their derivatives

J	Φ[a]	$J_{calc.}$[b]	(6)	(9)	(10)	(11)	(18)	(19)	(22/23)
1, 2	60	2.0	2.5				3.0	3.0	3.0
1, 7							*ca.* 1.0	*ca.* 1.0	
1, 10								5.5	
2, 3	25	6.4							
2, 6			2.5				2.5	2.5	2.5
4, 5			7.7	8.0	8.0	8.0	8.0	8.0	8.5
5, 6	25	6.4	6.5	6.0	6.3	6.3	6.5	6.3	6.5
6, 7	60	2.0	2.5				2.5	2.5	
7, 8	40	5.0	5.3				5.5		2.7
7, 9								*ca.* 1.0	
8, 9			9.5				9.5		
8, 9a				4.0	4.0	4.0			7.3
8, 9b				*ca.* 0.0	*ca.* 0.0	*ca.* 0.0			*ca.* 0.0
4′, 6′			2.8	2.8	2.8	2.8			
3′, 4′			9.2	9.2	9.2	9.2			
9a, 9b				17.0	17.0	17.0			
9, 10								9.7	

[a] Observed dihedral angles for the *exo*-structure. [b] Calculated coupling constants from a modified Karplus equation: S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.



(a) Reaction at the 2- and 6-positions: behaviour as a $4n$ π-component

(b) Reaction at the 2,4-positions: behaviour as a $(4n+2)$ π-component

SCHEME 2 3-Oxidopyridinium betaines as pericyclic components

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[7] Reviews: R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie/Academic Press, Weinheim, Germany, 1970; *Accounts Chem. Res.*, 1968, **1**, 17; *Angew. Chem. Internat. Edn.*, 1969, **8**, 781.

[8] M. J. S. Dewar, 'The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.

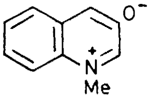
[9] H. E. Zimmerman, *Accounts Chem. Res.*, 1971, **4**, 272.

[10] N. Dennis, B. Ibrahim, and A. R. Katritzky, following paper.

[11] For preliminary communications see N. Dennis, B. Ibrahim, and A. R. Katritzky, *J.C.S. Chem. Comm.*, (*a*) 1974, 500; (*b*) 1975, 425.

[12] K. L. Mok and M. J. Nye, *J.C.S. Chem. Comm.*, 1974, 608.

Variation in Cycloaddition Reactivity of Pyridinium Betaines.—1-Methyl-3-oxidopyridinium [3] (1b) and 3-hydroxypyridine [13] [as its zwitterionic tautomer (1c) [14]] react slowly with dipolarophiles. This reactivity is increased in the 1-phenyl [15] (1d) and still more in the 1-(2,4-dinitrophenyl) analogues [2] (1a), but the spontaneous dimerisation and remarkable reactivity [10] of the 1-(5-nitro-2-pyridyl) betaine (6) put it in a class above the other betaines listed. Perturbation molecular orbital theory (PMO) [8,16,17] used at the level of the frontier molecular orbital approximation (FMO) [18,19] explains this variation in reactivity. The magnitudes of the interactions between specific frontier orbitals when two addends approach are inversely proportional to their energy separation, while the total interaction energy ΔE of equation (1) (see Appendix) is a measure of the stabilisation of the transition state during the process of bond formation. Thus ready ability of a 3-oxidopyridinium betaine to dimerise demands a small energy separation of the interfrontier levels within the molecule. Since extended conjugation is known to narrow this separation, 1-aryl betaines are more reactive than 1-alkyl betaines.



(14)

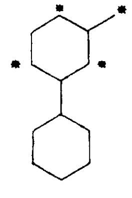
1-Aryl-3-oxidopyridinium betaines are isoconjugate with the cross-conjugated [8] benzyl anion (15). The HOMO of the betaine corresponds to the NBMO of (15) in which non-starred positions as well as all atoms in the aryl substituent are inactive, *i.e.* occur at nodes. CNDO/2 calculations (Appendix) have indicated a pseudo-non-bonding character in the HOMO of 1-methyl-3-oxidopyridinium betaine. First order PMO theory [20,21] predicts that substitution at inactive positions will not affect the HOMO level of the betaine, and in agreement the ionisation potentials of 1-aryl-3-oxidopyridinium betaines (1e) [22] are insensitive towards the *para*-substituent (Table 3). Strong electron withdrawal produced by electronegative groups including aza-substituents at inactive positions, will exert considerable lowering effect on the LUMO, resulting in a small energy separation between the frontier levels of the betaine. Thus the nitropyridyl betaine (7) dimerises and is more reactive than the phenyl betaine (1d).

TABLE 3

Ionisation potentials (eV) of 1-*p*-(substituted phenyl)-3-oxidopyridiniums [22]

para-Substituent	MeO	H	Cl
I.P. (eV)	7.4	7.55	7.60

However, for such electronic conjugative effect to be assessed, secondary steric effects must be considered. The ring planes are inclined at about 30° in the biphenyl system,[23] and at 83.5° in 2,4,6-trimethyl-1-phenylpyridinium perchlorate,[24] but are coplanar in 3,6-diphenyl-*s*-tetrazine.[25] By analogy the rings in the dinitrophenyl betaine (1a) are expected to deviate sharply from coplanarity, resulting in inefficient conjugation. Therefore (1a) does not dimerise but rearranges.



(15)

3-Oxido-1-(pyrimidin-2-yl)- (20) and the 3-oxido-1-(*s*-triazinyl)-pyridinium betaines (24) are expected to assume complete coplanarity, and should therefore be superior to (7) towards dimerisation and cycloadditions.

1-(4,6-*Dimethylpyrimidin*-2-*yl*)-3-*oxidopyridinium* (20).—In the present investigation, the pyrimidin-2-yl betaine (20) has indeed been observed to possess exceptionally high activity towards dimerisation and cycloadditions in general, and the transformations shown in Scheme 3 lend strong support to the above reasoning. The quaternary salt (17) was prepared from 3-hydroxypyridine and 2-chloro-4,6-dimethylpyrimidine. The i.r. spectrum of (17) shows ν(OH) at 2 800—2 500s cm^{-1}. The n.m.r. spectrum (Table 4) gave a normal ABXY pattern for the pyridinium ring, in which the downfield shifts of the 2- and 6-proton signals relative to the other betaines reflects the influence of the pyrimidine nitrogen atoms.

On treatment with cold alkali, or on melting, the salt decomposes. However, treatment of (17) with triethylamine in 1,2-dichloroethane results in a clear solution the yellow colour of which fades within a few seconds with precipitation of triethylamine hydrochloride. Evaporation of the filtrate within 15 min affords the crystalline betaine dimer (18), m.p. 160—161 °C (90%). However,

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[13] J. Banerji, N. Dennis, J. Frank, A. R. Katritzky, and T. Matsuo, *J.C.S. Perkin I*, 1976, 2334.

[14] M. Ramaiah, Ph.D. Thesis, University of East Anglia, 1974.

[15] N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, and Y. Takeuchi, *J.C.S. Perkin I*, 1974, 746.

[16] M. J. S. Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.

[17] W. C. Herndon, *Chem. Rev.*, 1972, **72**, 157.

[18] K. Fukui, 'Molecular Orbitals in Chemistry, Physics, and Biology,' ed. P.-O. Löwdin and B. Pullman, Academic Press, New York, 1964, pp. 513—537; K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, 1969, **42**, 3399.

[19] R. Sustmann, *Tetrahedron Letters*, 1971, 2717, 2721.

[20] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (*A*), 1947, **191**, 39; H. C. Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

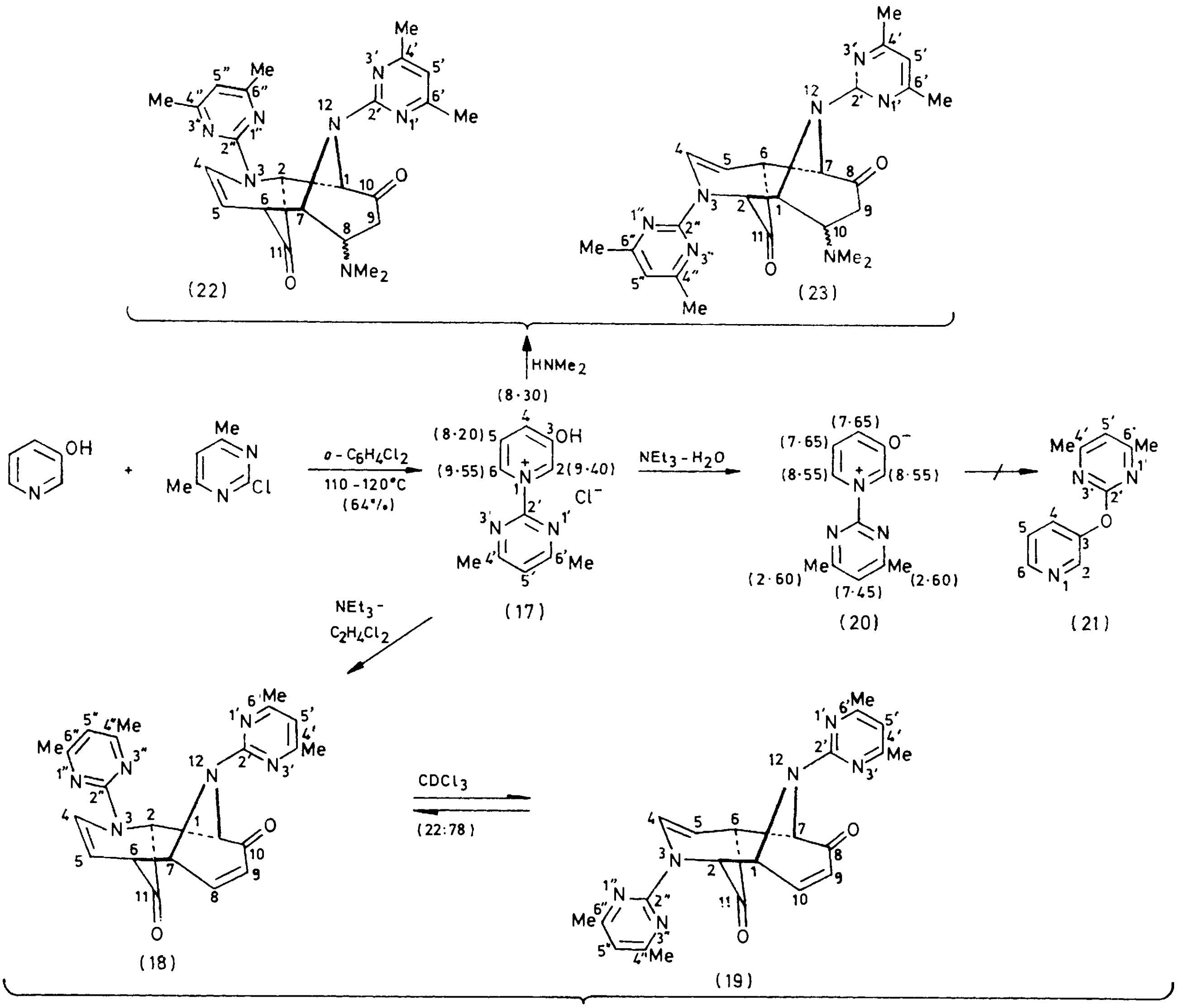
[21] K. N. Houk, J. Sims, R. E. Duke, jun., R. W. Strozier, and J. K. George, *J. Amer. Chem. Soc.*, 1973, **95**, 7287.

[22] K. Undheim and P. E. Hansen, *Org. Mass Spectrometry*, 1973, **7**, 635.

[23] K. Yakushi, I. Ikemoto, and H. Kuroda, *Acta Cryst.*, 1971, **B27**, 1710.

[24] A. Camerman, L. H. Jensen, and A. T. Balaban, *Acta Cryst.*, 1969, **B25**, 2623.

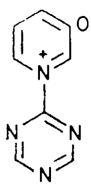
[25] N. A. Ahmed and A. I. Kitaigorodsky, *Acta Cryst.*, 1972, **B28**, 739.



Mixture shows $\nu_{C=O}$ at 1 735 cm^{-1} and 1 680 cm^{-1} and N–C=C at 1 640 cm^{-1}; *m/e* 404, 202

SCHEME 3 1-(4,6-Dimethylpyrimidin-2-yl)-3-oxidopyridinium and its dimers

if the filtrate is kept for 1 h before work-up, a mixture of the dimeric regioisomers (18) and (19) in the ratio 67 : 33 results.



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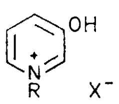


(25)

a; R = 2,4-$(NO_2)_2C_6H_3$, X = Cl
b; R = Me, X = I
c; R = Ph, X = Cl

Structures (18) and (19) were assigned from elemental analysis and spectra. The i.r. spectra showed strong conjugated and nonconjugated carbonyl bands at 1 680 and 1 735 cm^{-1}, respectively, and a medium enamine ν(C=C) band at 1 640 cm^{-1}. The ^{1}H n.m.r. spectrum of (18) in $CDCl_3$ immediately after preparation (Figure 1) shows characteristic vinylic proton pairs H-8,H-9 and H-4,H-5 and similar to those of the spectrum of (6) (Table 1). Double resonance experiments (Figure 1) allowed unambiguous assignment of the rest of the spectrum. Thus, irradiation at the frequency of H-6 (δ 3.25) caused the H-5 signal to collapse to a doublet by eliminating the coupling $J_{5,6}$ (6.5 Hz). The triplet due to H-2 (δ 5.25) also collapses to a doublet. Irradiation at δ 6.53 simplified the H-6 multiplet to a double doublet ($J_{6,7}$ 2.5 Hz), and also simplified the signals of H-8 ($J_{7,8}$ 5.5 Hz) and H-1. Irradiation at the H-5 frequency confirmed the 5,6- and 4,5-coupling ($J_{4,5}$ 8.0 Hz). These experiments demonstrate the positional sequence H-4 to H-8 on one side of the

TABLE 4

Proton n.m.r. spectra (δ values) of salts, betaines, and ethers ^{a}

Proton	Salts						Betaines					Ethers		
	(5) ^{b,c}	(25a) ^{b,f}	(25a) ^{b,c}	(25b) ^{f,h}	(25c) ^{f,j}	(17) ^{b,c}	(1a) ^{f,b}	(1a) ^{b,k}	(1b) ^{f,h}	(1d) ^{f,j}	(20) ^{b,k}	(2a) ^{b,l}	(8) ^{b,l}	(21) ^{b,l}
2	9.10	9.00 ^{g}	8.73 ^{g}	8.63	8.91	9.40	7.59 ^{g}	7.93 ^{g}	7.30	7.50—7.65	8.55 ^{g}	8.53 ^{l}	8.44	8.40 ^{d}
4	8.34	8.45 ^{g}	8.39 ^{g}	8.16	8.35	8.30 ^{g}	7.18 ^{g}	7.76 ^{g}	6.90	7.08	7.65 ^{g}	7.50 ^{g}	7.45	7.40 ^{e}
5	8.23	8.20 ^{e}	8.24 ^{e}	8.16	8.08	8.20 ^{g}	7.50 ^{e}	7.76 ^{g}	7.21	7.40	7.65 ^{g}	7.45 ^{e}	7.35	7.36 ^{d}
6	9.10	9.00 ^{g}	8.73 ^{g}	8.63	8.78	9.55 ^{e}	7.59 ^{g}	7.93 ^{g}	7.35	7.50—7.65	8.55 ^{g}	8.60 ^{e}	8.44	
6′	9.62 ^{d}	9.10 ^{d}	9.40 ^{d}				9.0 ^{d}	9.28 ^{d}				8.86 ^{d}	8.93 ^{d}	8.82 ^{d}
4′	9.13 ^{e}	8.96 ^{e}	8.98 ^{e}				8.79 ^{e}	8.87 ^{e}				8.38 ^{e}	8.44	8.36 ^{e}
3′	8.38 ^{d}	8.40 ^{d}	8.29 ^{d}				8.25 ^{d}	8.17 ^{d}				7.08 ^{d}	7.04 ^{d}	7.05 ^{d}
5′						7.65					7.45			
NMe				4.48 ^{i}					3.73 ^{i}					
NPh					*ca.* 7.75 ^{g}					*ca.* 7.50				
CMe						2.70					2.60 ^{i}			2.60 ^{i}

^{a} Me_4Si as internal standard. ^{b} This study. ^{c} In D_2O. ^{d} Doublet. ^{e} Double doublet. ^{f} In $(CD_3)_2SO$. ^{g} Centre of broad band. ^{h} Ref. 3. ^{i} Singlet. ^{j} Ref. 15. ^{k} In D_2O–$NaHCO_3$. ^{l} In $CDCl_3$.

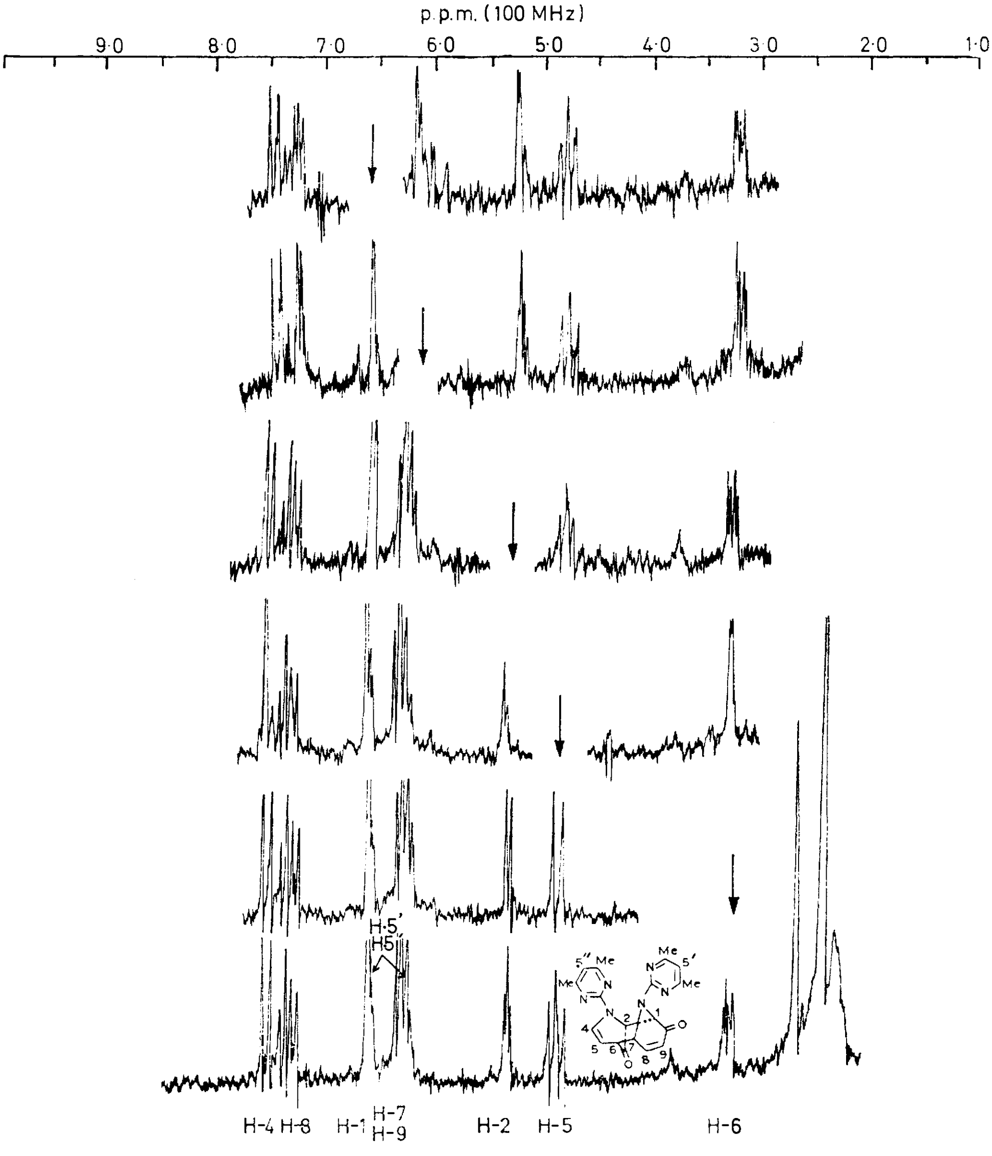


FIGURE 1 Double resonance n.m.r. experiments on the dimer (18)

molecule. The coupling of H-1 to H-2 by 3.0 Hz on the other side of the molecule was revealed by similar double irradiation at the frequencies of H-1 and H-2. The regio-structure of (18) is confirmed by the shift towards higher δ values of the signals of H-2 and to a lesser extent H-1 compared to H-6 and H-7; H-2 and H-1 are affected by the anisotropy of the nitrogen atom at the 3-position.

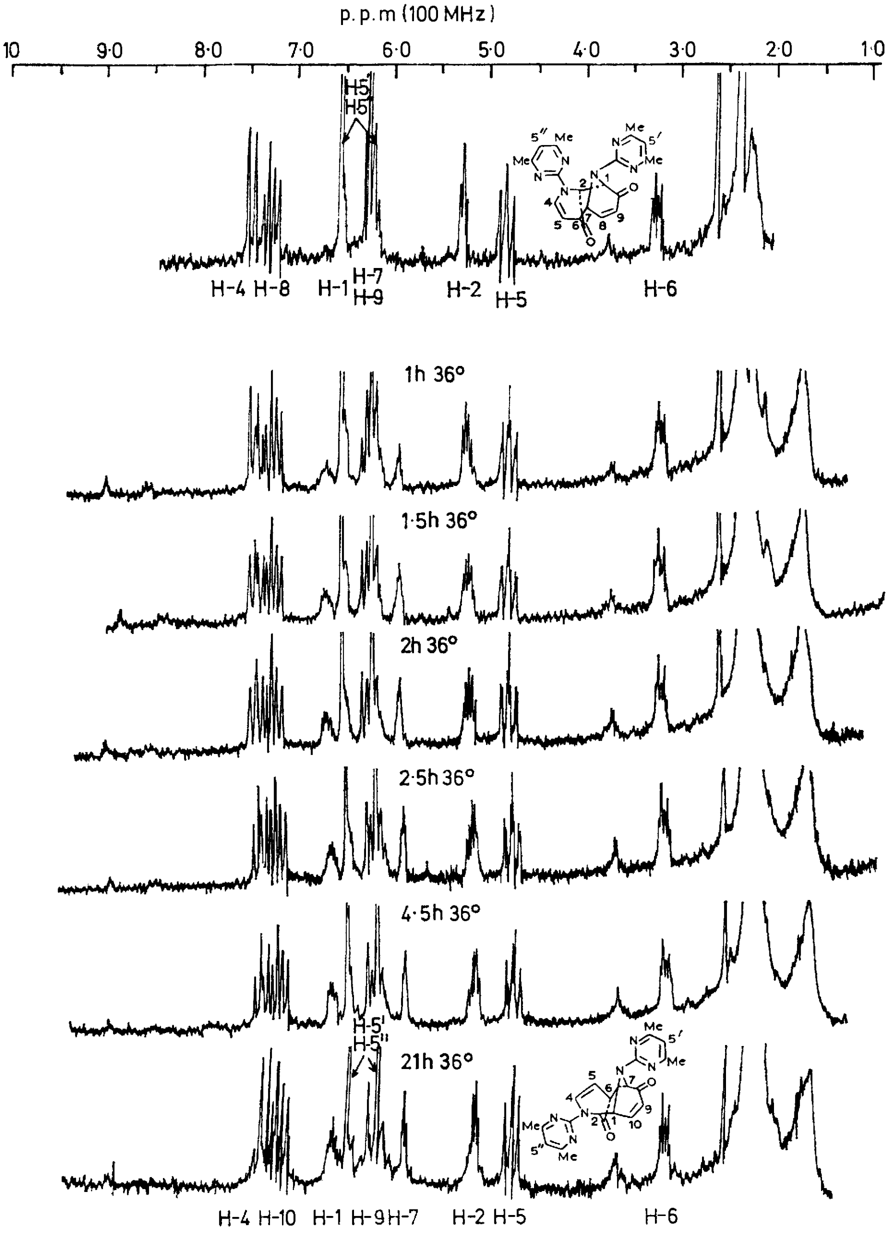


FIGURE 2 N.m.r. spectra of the mixture of dimers of 1-(4,6-dimethylpyrimidin-2-yl)-3-oxidopyridinium [(18) and (19)] showing variation of equilibrium (18) $\rightleftharpoons$ (19) with time

The ^{1}H n.m.r. spectrum of the solution of the dimer (18) soon started to show new peaks which grew steadily at the expense of those of (18). A steady transformation of (18) to a new product was followed at 36 °C by recording the spectrum at intervals (Figure 2): the system attained equilibrium after 21 h, and was then invariant over several days. The spectral similarity shows that the new product (19) found to the extent of 78% at equilibrium is isomeric with (18). The signals due to the vinylic protons of (19) are almost superposed on those of (18). The bridgehead protons are significantly more sensitive to the regio-structure, and the carbonyl bridgehead proton signals almost exactly exchange positions with each other. Double resonance studies (Figure 3) demonstrated the regioisomeric structure (19): H-6 is coupled to the vinylic H-5, and H-1 to the vinylic H-10 on the other side of the molecule. However no coupling occurs between H-1 and H-6 or between H-2 and H-7. The nitrogen atom at the 3-position now exerts a downfield shift on H-1 and particularly on H-2.

The *exo*-configuration of the dimers (18) and (19) is demonstrated by fair agreement between the observed and the calculated coupling constants[5] (Table 2), as well as by the substantial W-type long-range coupling constants in both (18) and (19) [for (18), $J_{1,7}$ 1.0, $J_{2,6}$ 2.5 Hz], as also found for (6). The dimers (18) and (19) do not complex appreciably with the lanthanide shift reagents $Eu(fod)_3$ and $Pr(fod)_3$, evidently owing to crowding at the carbonyl groups in the *exo*-adducts. The bridge carbonyl groups exhibit some strain in the *exo*-adducts relative to the *endo*-adducts: (6), (18), (19), and the *exo*-cyclopentadiene adducts show ν(C=O) at 1 735—1 740 whereas typical *endo*-adducts[10] of 3-oxidopyridiniums with butadienes show absorptions at 1 710—1 720 cm^{-1}.

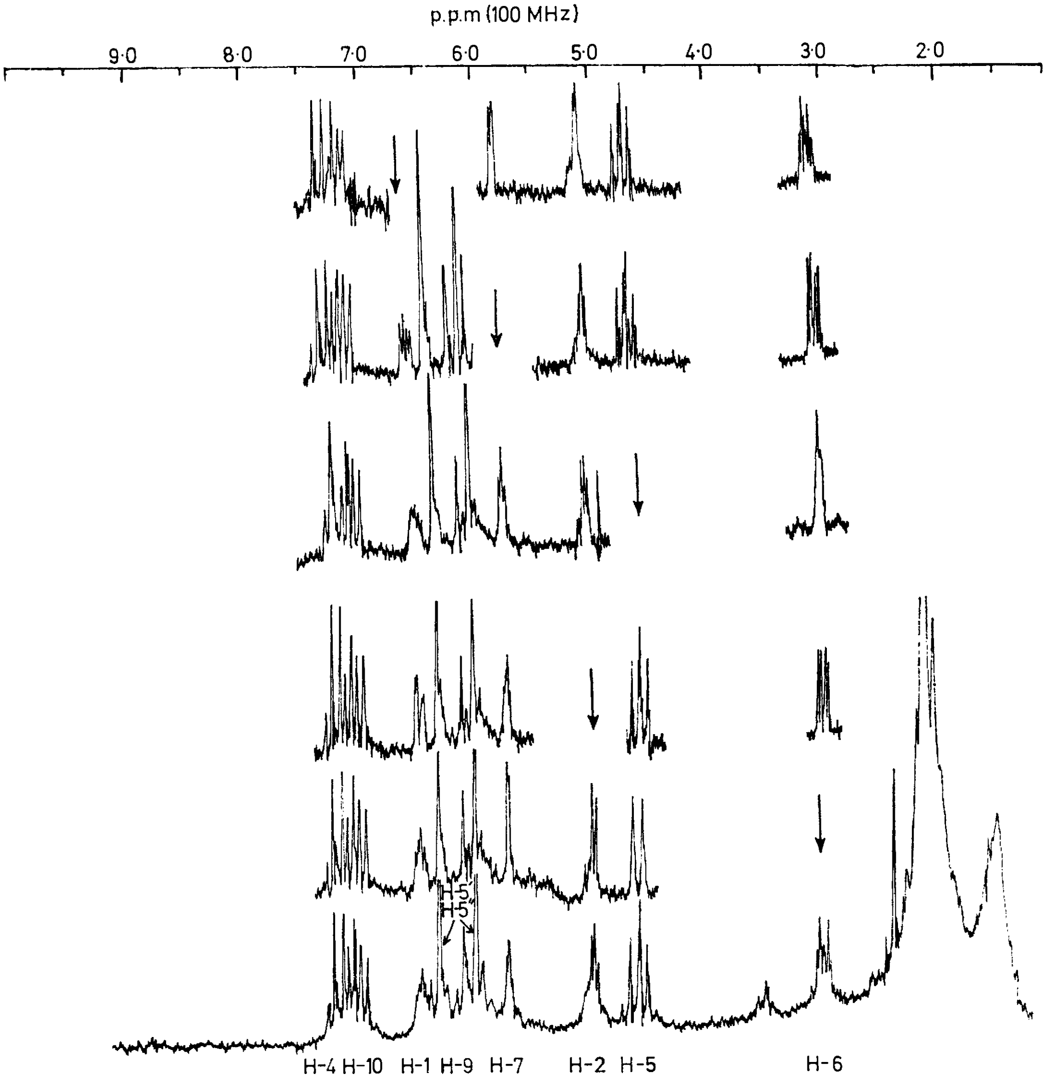
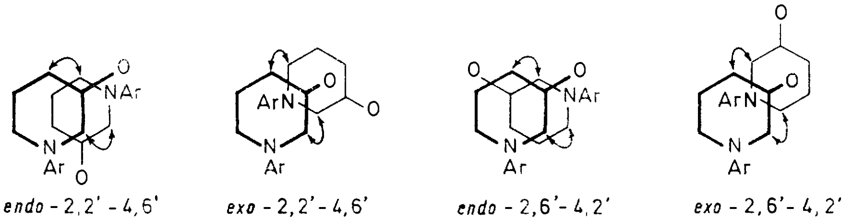


FIGURE 3 Double resonance n.m.r. experiments on the dimer (19)

The equilibrium composition of 22 : 78 in favour of (19) was found by expanding the H-4 region, where the peaks due to (18) and (19) are well separated. The ^1H n.m.r. spectra (Figure 2) consistently show initial weak peaks at δ 9.0, 8.6, and 2.61 with intensities gradually decreasing with time, which are assigned to the monomeric betaine (20). The system involves a dynamic process, (18) $\rightleftharpoons$ (20) $\rightleftharpoons$ (19), ultimately ending in an equilibrium. Generation of the betaine (20) from the salt is followed by a fast kinetically controlled dimerisation to (18). The energy barrier for dimerisation to (18) is lower than that to (19) but the stabilisation of (18) with respect to (20) is not so great. Accordingly at the early stages of the equilibration process (18) predominates, but with an appreciable concentration of the monomeric betaine (20). Dimerisation of the betaine is a bimolecular process while the retro-breakdown of the dimer is a unimolecular process, and the concentration dependence of these reactions differs.

Whereas dimerisation is favoured at high concentrations, dissociation to the betaine is favoured at low concentrations: the u.v. spectrum given by dissociation of the dimer (18) [$\lambda_{max.}$ (EtOH) 230 (log ε 4.38), 245 (4.43), and 368 (3.81) nm] is that of the monomeric betaine [$\lambda_{max.}$ (H_2O) 223 (log ε 4.30), 240 (4.28), and 343 (3.71) nm]. The observed solvent shift is reasonable for this highly polar species. By analogy to the 2,6- and 2,4-adducts of this betaine, which gave bands near 240 and 280 nm, respectively, due to a $n \longrightarrow \pi^*$ transition of the arylamine chromophores, the dimer (18) or (19) should have given the latter peak as the longest wavelength maximum. By comparison the nitropyridyl dimer (6) did not show any appreciable dissociation to the monomeric betaine under u.v. conditions. Its u.v. spectrum is markedly different from that of the betaine and shows characteristic bands of the arylamine chromophore at 354 nm (log ε 4.20).



endo - 2,2′ - 4,6′ *exo* - 2,2′ - 4,6′ *endo* - 2,6′ - 4,2′ *exo* - 2,6′ - 4,2′

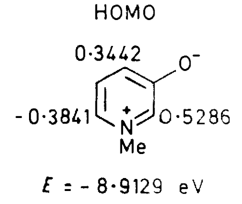
A B C D

SCHEME 4 Regio- and stereo-selectivity of dimer formation

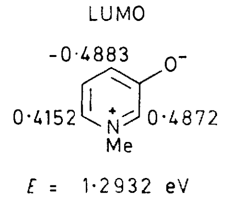
That the betaine (20) can exist in a substantial concentration in equilibrium with the dimers at 36 °C is reflected in the fast reactions of this system with various dipolarophiles at room temperature. However, all attempts to isolate the monomeric betaine (20) have failed: the i.r. spectrum measured immediately for a sample of the salt (17) crushed in Nujol with a drop of triethylamine showed the strong characteristic peaks of the dimer and triethylamine hydrochloride. The appreciable stability of (20) in water allowed the measurement of its ^{1}H n.m.r. spectrum (Table 4). The H-2 and H-6 signals shifted by nearly 1.0 p.p.m., while those of H-4 and H-5 shifted by nearly 0.6 p.p.m. with respect to their absorptions in (17).

As in the case of dimer (6), the αβ-unsaturated carbonyl system of the dimer (18) or (19) is active towards nucleophilic addition. The salt (17) when treated with aqueous dimethylamine at 20 °C gave a mixture of adducts (22) and (23). The structures were supported by the i.r. spectrum: ν(C=O) 1 750 and enamine ν(C=C) 1 660 cm^{-1}. The ^{1}H n.m.r. spectrum (Table 1) indicates the replacement of the vinylic signals by high-field ABX signals; integration demonstrates the presence of six methyl groups.

Regio- and Stereo-selectivity of Dimer Formation.—Regioisomerism (2,2′-4,6′ or 2,6′-4,2′) and stereoisomerism (*exo* or *endo*) together allow four possible modes of dimerisation (Scheme 4). We have not observed any formation of either of the *endo*-isomers. It has previously been predicted[26] that [$_\pi4_s + _\pi6_s$] pericyclic reactions should lead to *exo*-adducts on the basis of secondary orbital overlap, and *exo*-products were indeed observed in the dimerisation of 1*H*-azepines[27] and addition of cyclopentadiene to tropone.[28] Inspection of secondary orbital overlap between corresponding pairs of interacting frontier orbitals [*cf.* (26a and b)] in the *endo*-transition state indicates equal number of positive and negative overlaps, positive at 6-4′ and 5-3′; negative at 1-3′ and 3-1′. Furthermore the fully eclipsed transition states needed for *endo*-addition (Scheme 4) are more crowded than those for the *exo*-addition.



(26a)



(26b)

Whereas the *exo*-2,2′-4,6′ regioisomer (6) only is found for the pyridyl betaine dimer, in the pyrimidinyl series both *exo*-regioisomers are found. As discussed above, the mixture initially contains mainly the *exo*-2,2′-4,6′ dimer (18), but is converted spontaneously into a mixture in which the *exo*-2,6′-4,2′ dimer (19) predominates. Evidently (18) is formed under kinetic control, but (19) is thermodynamically more stable. Second-order intermolecular PMO calculations[17,29] correctly predict the preferential formation of the *exo*-2,2′-4,6′ dimer as the orbital interactions in the transition state are greater. Frontier orbital energies and coefficients at a number of positions in the 3-oxidopyridinium betaine (Appendix) are shown in formulae (26a and b). Since the orientation 2,2′-4,6′ results in a larger interaction energy (ΔE —3.51 × 10^{-2} ν^{2}eV) than the 2,6′-4,2′ orientation (—3.41 × 10^{-2} ν^{2}eV), the expected kinetically controlled product is the *exo*-2,2′-4,6′ dimer.

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[26] R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, 1965, **87**, 4388.

[27] I. C. Paul, S. M. Johnson, J. H. Barrett, and L. A. Paquette, *Chem. Comm.*, 1969, 6; L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, 1969, **91**, 3616.

[28] R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Comm.*, 1966, 15.

[29] (*a*) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, 1968, **24**, 2575; O. Eisenstein, J.-M. Lefour, and Nguyen Trong Anh, *Chem. Comm.*, 1971, 969; (*b*) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Amer. Chem. Soc.*, 1973, **95**, 7301.

EXPERIMENTAL

M.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer 257 grating i.r. spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100 n.m.r. spectrometer. Compounds were purified until they were observed as single spots on t.l.c. (silica gel PF 254).

3-Hydroxy-1-(5-nitro-2-pyridyl)pyridinium Chloride (5).—3-Hydroxypyridine (20 g, 0.21 mol) and 2-chloro-5-nitropyridine (33.2 g, 0.21 mol) were heated under reflux in tetrahydrofuran (THF) (150 ml) for 24 h with stirring to give the *salt* (5) as buff plates (from EtOH–Et$_2$O), m.p. 205—206 °C (49 g, 92%) (Found: C, 47.3; H, 3.4; Cl, 13.9; N, 16.6. $C_{10}H_8ClN_3O_3$ requires C, 47.3; H, 3.2; Cl, 14.0; N, 16.6%); $\nu_{max.}$ (Nujol) 2 800—2 200, 1 600, 1 530, and 1 345 cm^{-1}; $\lambda_{max.}$ (H_2O) 211 (log ε 4.11), 225 (4.18), 250 (4.16), 280 (4.01), and 350 nm (3.57); *m/e* 217 (*M* − HCl).

1-(*5-Nitro-2-pyridyl*)-*3-oxidopyridinium* (7).—To a cooled (10—15 °C) suspension of (5) (25.3 g, 0.1 mol) in 1,2-dimethoxyethane (150 ml), triethylamine (10.1 g, 0.1 mol) was added with stirring. The mixture soon became homogeneous and a greenish-yellow solid separated. Ether (100 ml) was added and the solid filtered off and washed with ether (50 ml) to afford a mixture (*ca.* 1 : 1) of the betaine (7) and triethylamine hydrochloride (32 g, 90%); $\nu_{max.}$ (Nujol) 2 700—2 500 (Et_3N,HCl), 1 615, 1 600 (aromatic), 1 545, 1 505 (antisym. NO_2), and 1 340 cm^{-1} (sym. NO_2). The product is fairly stable at room temperature but in organic solvents (*e.g.* chloroform) is slowly converted into the dimer (6) when warmed above 40 °C.

3,12-*Bis*-(*5-nitro-2-pyridyl*)-3,12-*diazatricyclo*[5.3.1.1^{2,6}]-*dodeca*-4,8-*diene*-10,11-*dione* (6).—Three methods are described. (*a*) To a well stirred suspension of the salt (5) (25.3 g, 0.1 mol) in acetonitrile (250 ml) at 0 °C, triethylamine (10.1 g, 0.1 mol) was added. After stirring for 3 h more, the solid was filtered off and washed with $CHCl_3$ (50 ml) to give the dimer (6) as pale yellow prisms (from THF), m.p. 196 °C (decomp.) (13.6 g, 66%). (*b*) Triethylamine (2 g, 2 × 10^{-2} mol) was added at 20 °C to the salt (5) (5 g, 2 × 10^{-2} mol) in EtOH (40 ml). The mixture was stirred for 12 h to give a dark green solid which after treatment with charcoal in THF gave the dimer (6) (3.6 g, 83.5%), m.p. 196 °C (decomp.). (*c*) Pyridine (25 ml) was added to (5) (25.3 g, 0.1 mol) in water (100 ml). The solution was stirred at 60 °C for 10 min, NaCl (*ca.* 10 g) was added in portions, and stirring was continued for 1 h. The product was cooled, filtered, washed several times with distilled water, and dried (80 °C). Crystallisation from THF gave the pure *dimer* (6) (18 g, 83%) as pale yellow prisms, m.p. 196 °C (decomp.) (Found: C, 55.2; H, 3.3; N, 19.0. $C_{20}H_{14}N_6O_6$ requires C, 55.3; H, 3.3; N, 19.4%); $\nu_{max.}$ (Nujol) 1 735 (C=O), 1 680 (C=C–*C*=*O*), 1 590, 1 580 (aromatic ring), 1 505 (antisym. NO_2), and 1 340 cm^{-1} (sym. NO_2); $\lambda_{max.}$ (EtOH) 210 (log ε 4.10), 227 (4.16), 250 (4.00), and 354 nm (4.20); *m/e* 217 (*M*/2).

8-*Methoxy*-3,12-*bis*-(*5-nitro-2-pyridyl*)-3,12-*diazatricyclo*-[5.3.1.1^{2,6}]*dodec*-4-*ene*-10,11-*dione* (10).—The dimer (6) (1 g, 0.002 3 mol), MeOH (10 ml), and Et_3N (1 ml) were heated at 100 °C for 5 min and cooled to give the *methoxy-dimer* (10) (0.97 g, 90%) which crystallised from THF–MeOH as yellow needles, m.p. 232—233 °C (decomp.) (Found: C, 54.5; H, 4.1; N, 17.5. $C_{21}H_{18}N_6O_7$ requires C, 54.1; H, 3.9; N, 18.0%); $\nu_{max.}$ (Nujol) 1 730, 1 600, 1 575, 1 510, 1 350, and 1 120 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (log ε 4.30), 226 (4.28), 244 (4.23), and 369 nm (4.55); *m/e* 466.

8-*Hydroxy*-3,12-*bis*-(*5-nitro-2-pyridyl*)-3,12-*diazatricyclo*-[5.3.1.1^{2,6}]*dodec*-4-*ene*-10,11-*dione* (9).—The dimer (6) (1 g, 0.002 3 mol), dioxan (5 ml), and 10% NaOH (5 ml) were heated at 100 °C for 5 min, then cooled and neutralised with dilute H_2SO_4. The *hydroxy-dimer* (9) precipitated and after drying crystallised as yellow prisms ($CHCl_3$), m.p. 227 °C (0.88 g, 85%) (Found: C, 53.3; H, 3.7; N, 18.2. $C_{20}H_{16}N_6O_7$ requires C, 53.1; H, 3.5; N, 18.6%); $\nu_{max.}$ (Nujol) 3 580, 1 720, 1 640, 1 600, 1 570, 1 505, 1 345, and 1 120 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (log ε 4.31), 227 (4.28), 244 (4.23), and 368 nm (4.55); *m/e* 452.

8-*Amino*-3,12-*bis*-(*5-nitro-2-pyridyl*)-3,12-*diazatricyclo*-[5.3.1.1^{2,6}]*dodec*-4-*ene*-10,11-*dione* (11).—The dimer (6) (1 g, 0.002 3 mol), dioxan (5 ml), and conc. ammonia (5 ml) were heated at 100 °C for 5 min. On cooling, the *amino-dimer* (11) separated; it crystallised from THF–EtOH as yellow prisms, m.p. 252—253 °C (decomp.) (0.8 g, 77%) (Found: C, 53.5; H, 3.7; N, 21.4. $C_{20}H_{17}N_7O_6$ requires C, 53.2; H, 3.8; N, 21.7%); $\nu_{max.}$ (Nujol) 1 730, 1 595, 1 575, 1 510, and 1 340 cm^{-1}; $\lambda_{max.}$ (EtOH) 209 (log ε 4.34), 227 (4.36), 245 (4.30), and 367 nm (4.67); *m/e* 451.

3-(*5-Nitro-2-pyridyloxy*)*pyridine*.—3-Hydroxypyridine (1 g, 1 × 10^{-2} mol) and 2-chloro-5-nitropyridine (1.7 g, 1 × 10^{-2} mol) were treated with methanolic KOH (15 ml, 3.7%) to give the ether (8) as prisms (from Et_2O), m.p. 94 °C (lit.,[30] 95 °C) (1 g, 47%) (Found: C, 55.3; H, 3.5; N, 19.4. Calc. for $C_{10}H_7N_3O_3$: C, 55.3; H, 3.3; N, 19.4%); $\nu_{max.}$ (Nujol) 1 610, 1 580, 1 560, 1 520, 1 355, and 1 120 cm^{-1}; *m/e* 217.

1-(*4,6-Dimethylpyrimidin-2-yl*)-*3-hydroxypyridinium Chloride* (17).—3-Hydroxypyridine (19 g, 0.2 mol), 2-chloro-4,6-dimethylpyrimidine (28.5 g, 0.2 mol), and 1,2-dichlorobenzene (80 ml) were heated at 110—120 °C with stirring until precipitation was complete (*ca.* 2 h). The solid was filtered off, washed with acetone (*ca.* 100 ml), and recrystallised three times from 95% EtOH (animal charcoal) to give the *salt* (30.5 g, 64%) (17) as rods, m.p. 224—225 °C (decomp.) (Found: C, 55.7; H, 5.0; Cl, 15.0; N, 17.7. $C_{11}H_{12}ClN_3O$ requires C, 55.6; H, 5.1; Cl, 14.9; N, 17.7%); $\nu_{max.}$ (Nujol) 2 800—2 500, 1 600, 1 565, 1 500, 1 335, 1 250, 1 120, 1 020, 810, and 770 cm^{-1}; $\lambda_{max.}$ (H_2O) 205 (log ε 4.20), 223 (4.30), and 240 nm (4.28); *m/e* 201 (*M* − HCl).

3,12-*Bis*-(*4,6-dimethylpyrimidin-2-yl*)-3,12-*diazatricyclo*-[5.3.1.1^{2,6}]*dodeca*-4,8-*diene*-10,11-*dione* and 3,12-*Bis*-(*4,6-dimethylpyrimid-2-yl*)-3,12-*diazatricyclo*[5.3.1.1^{2,6}]*dodeca*-4,9-*diene*-8,11-*dione* [(18) *and* (19)].—Triethylamine (4.8 g, 0.05 mol) was added to a suspension of the salt (17) (11 g, 4.64 × 10^{-2} mol) in 1,2-dichloroethane (70 ml) and the mixture stirred at 20 °C for 0.5 h. The Et_3N,HCl was filtered off, and the filtrate diluted to 150 ml with 1,2-dichloroethane, washed twice with water (60 ml), dried (Na_2SO_4; animal charcoal), and evaporated to give a 2 : 1 mixture of compounds (18) and (19) (2 : 1) as prisms (from $ClCH_2{\cdot}CH_2Cl$), m.p. 160—161 °C (decomp.) (7.5 g, 80%) (Found: C, 65.5; H, 5.7; N, 21.1. Calc. for $C_{22}H_{22}N_6O_2$: C, 65.7; H, 5.5; N, 20.9%); $\nu_{max.}$ (Nujol) 1 735 (C=O), 1 680 (C=C–*C*=*O*), 1 640 (C=C–N) 1 590, and 1 570 cm^{-1} (aromatic); $\lambda_{max.}$ (EtOH) 208 (log ε 4.11), 230 (4.38), 245 (4.43), and 368 nm (3.81); *m/e* 402.

8-*Dimethylamino*-3,12-*bis*-(*4,6-dimethylpyrimidin-2-yl*)-3,12-*diazatricyclo*[5.3.1.1^{2,6}]*dodec*-4-*ene*-10,11-*dione* (22) *and* 10-*Dimethylamino*-3,12-*bis*-(*4,6-dimethylpyrimidin-2-yl*)-

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[30] F. Yoneda, *J. Pharm. Soc. Japan*, 1957, **77**, 944.

3,12-diazatricyclo[5.3.1.1^{2,6}]*dodec-4-ene-8,11-dione* (23).—The salt (1 g, 4.3 × 10^{-2} mol) was dissolved in 30% aqueous dimethylamine (15 ml) and the solution was stirred at room temp. for 3 h. The precipitate was crystallised from toluene–Et$_2$O to give compounds (22) and (23) as needles, m.p. 185 °C (decomp.) (0.6 g, 31%) (Found: C, 64.6; H, 6.6; N, 19.8. Calc. for $C_{24}H_{29}N_7O_2$: C, 64.4; H, 6.5; N, 21.9%); $\nu_{max.}$ (Nujol) 1 750 and 1 660 cm^{-1}.

APPENDIX (with G. P. FORD)

Preliminary CNDO/2 Calculations on the Regioselectivity in the 1,3-Dipolar Addition Reactions of 1-Methyl-3-oxidopyridinium.—For the CNDO/2 molecular orbital calculation on 1-methyl-3-oxidopyridinium (1b) we used a CNDO/2 program[31] modified to bond order convergence,[32] carried out on an I.C.L. 1905E computer to a convergence limit of ±1 × 10^{-4} in the elements of the bond order matrix.

The ring geometry was derived from an *X*-ray crystallographic study[33] of the 3-carbamoyl-1-(2,6-dichlorobenzyl)pyridinium cation. The CH bond lengths were taken as 1.08 Å as in pyridine[34] and the bonds were assumed to bisect the angle formed by the carbon atom to which the hydrogen was attached and the two atoms on either side. The parameters for the $\overset{+}{\mathrm{N}}\text{–}\mathrm{CH_3}$ and C–O$^-$ groups were taken from data on the methylammonium ion[35] and *N*-(*p*-bromophenyl)sydnone,[36] respectively. The final geometry is shown in Figure 4.*

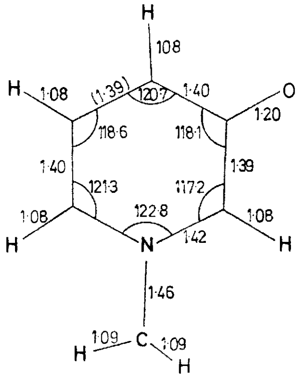

FIGURE 4 Geometry of 1-methyl-3-oxidopyridinium adopted for the CNDO/2 calculation

The calculated electron distribution (Figures 5 and 6) shows substantial delocalisation of the oxygen $2p_\pi$ electrons. The energy levels (Figure 7) and orbital coefficients from the CNDO calculation were combined with data for olefins for the calculation of the perturbation expressions. The dipolar additions of the olefins to the betaine are all controlled by the interaction of the betaine HOMO with the olefin LUMO as the betaine HOMO is of high energy owing to the strong interaction between the oxygen $2p_\pi$ orbital and the ring.

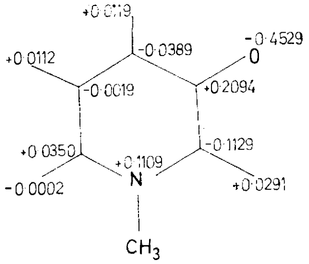

FIGURE 5 Total atom charges

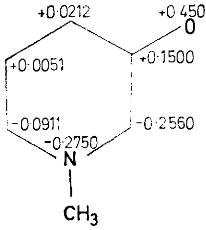

FIGURE 6 Calculated π charges

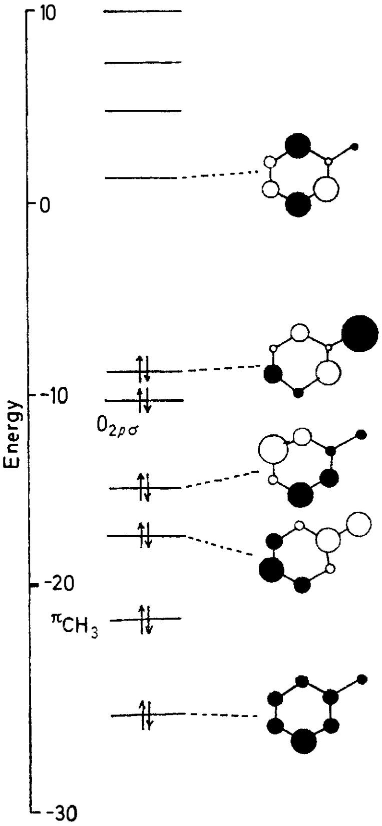

FIGURE 7 Energy levels and some orbital coefficients calculated from CNDO/2 MO theory

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* The bond lengths were unfortunately quoted[33] to only 2 places of decimals and the cumulative error inevitably leads to a final (redundant) bond length different from the expected. Thus the inadequacy in the present data leads to a value of 1.39 Å for the C(4)–C(5) bond rather than the expected 1.36 Å.

[31] P. A. Dobosh, Quantum Chemical Program Exchange, Program 141, Indiana University, Bloomington, Indiana, U.S.A.

[32] J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970, p. 72.

[33] C.-I. Brändén, I. Lindqvist, and M. Zeppezauer, *Arkiv Kemi*, 1969, **30**, 41.

[34] B. Bak, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectroscopy*, 1958, **2**, 361.

[35] 'Tables of Interatomic Distances and Configuration in Molecules and Ions,' eds. H. J. M. Bowen, J. Donohue, D. G. Jenkin, O. Kennard, P. J. Wheatley, and D. H. Whiffen, Chem. Soc. Special Publ. No. 11, 1958, p. M175.

[36] H. Bärnighausen, F. Jellinek, J. Munnik, and A. Vos, *Acta Cryst.*, 1963, **16**, 471.

Prediction of the Regioselectivity in the 1,3-*Dipolar Additions.*—We have used a second-order perturbation expression (1) for the change in energy which accompanies the interaction of two molecules involved in the cycloaddition, considering only the frontier orbitals.[29b] Equation (1) was

$$\Delta E = 2\left[\frac{(\mathrm{C}_r{}^{\mathrm{HO}}\,\mathrm{C}_s{}^{\mathrm{LU}} + \mathrm{C}_{r'}{}^{\mathrm{HO}}\,\mathrm{C}_{s'}{}^{\mathrm{LU}})^2\gamma^2}{E_{\mathrm{R}}{}^{\mathrm{HO}} - E_{\mathrm{S}}{}^{\mathrm{LU}}} + \frac{(C_r{}^{\mathrm{LU}}\,\mathrm{C}_s{}^{\mathrm{HO}} + \mathrm{C}_{r'}{}^{\mathrm{LU}}\,\mathrm{C}_{s'}{}^{\mathrm{HO}})^2\gamma^2}{E_{\mathrm{S}}{}^{\mathrm{HO}} - E_{\mathrm{R}}{}^{\mathrm{LU}}}\right] \quad (1)$$

previously applied successfully in a qualitative sense to rationalise reactivity,[37] regioselectivity, and periselectivity in 1,3-dipolar cycloadditions.[29b] Each term describes a specific frontier orbital interaction between the two addends, the magnitude of which is inversely proportional to their energy separation. The total interaction energy ΔE is a measure of the stabilisation of the transition state during the process of bond formation and larger values of ΔE therefore indicate more ready reactions.

Application to the reactions of 1-methyl-3-oxidopyridinium with itself and electron-deficient and electron-rich olefins using the energy levels and coefficients obtained by the CNDO method correctly predicts the preferred orientation for 1,3-dipolar addition. However the results are at variance with observation in that the addition is predicted on this basis to occur more readily with methyl vinyl ether than with either methyl acrylate or acrylonitrile. More precise calculations are in progress.

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[37] R. Sustmann and H. Trill, *Angew. Chem. Internat. Edn.*, **1972**, **11**, 838.