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Theoretical Interpretations of Some Experimental Observations in Reactions of Triazolopyridines and their Quaternary Salts

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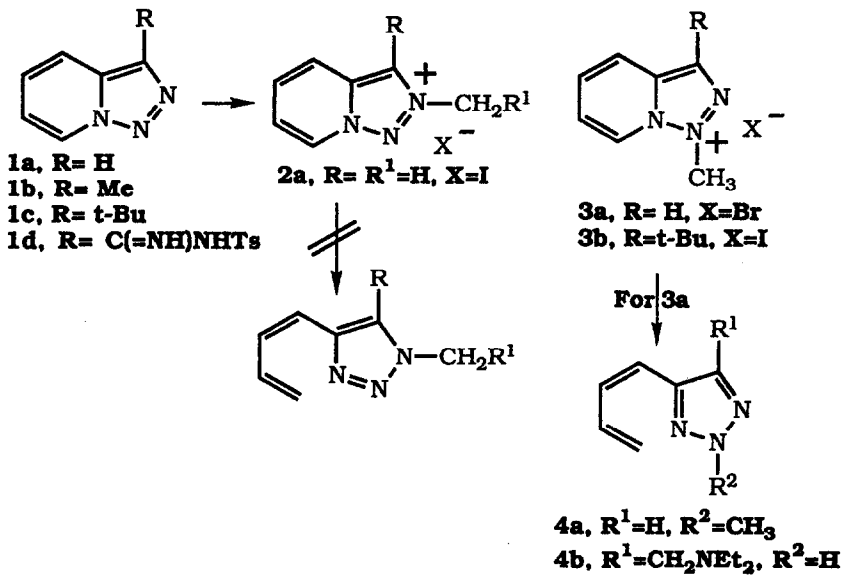
Abstract *The site of alkylation of triazolopyridines (1a), (5), and (6) has been interpreted using semi-empirical and ab initio molecular orbital calculations. Attack by hydride on the methyl triazolopyridinium salt (3a) has been shown to give the triazolylbutadiene (4a), while the isomeric salt (2a) is unaffected by nucleophiles. These observations are interpreted by consideration of the mechanisms of reaction, and calculation of appropriate energy levels.*

Previous studies have shown[1] that alkylation of 1,2,3-triazolo[1,5-a]pyridines (**1**) invariably form 2-alkyltriazolopyridinium salts (**2**), except when a t-butyl substituent in position 3 provides considerable steric hindrance at N2; some 1-methyltriazolopyridinium salt (**3b**) is then formed. We have now subjected the isomeric triazolopyridinium salts (**2a**) and (**3a**) to borohydride reduction, when the 1-methyl derivative (**3a**) (prepared unambiguously by cyclization of pyridine-2-carboxaldehyde N-methylhydrazone) forms 4-(2-methyl-4-triazolyl)butadiene (**4**). The N2 methylated salt is resistant to hydride and to other nucleophiles. The butadiene (**4**) was fully characterized by analysis, mass spectrum, and n.m.r spectra. The ^{1}H n.m.r. spectrum showed an N-methyl singlet at δ4.18, alkene signals at δ5.30 - 5.45 (2H, m, H4 and H4'), 6.22-6.33 (2H,m, H2 and H3), 7.22-7.36(1H,m,H1), and 7.54 (1H, s, triazole H). The ^{13}C n.m.r. spectrum showed signals at δ33.52 (CH_3), 118.57 (d, C2'), 121.42 (t, C4'), 133.13 (d, C3'), 135.82 (d, C5), 148.57 (d, C1), and 155.18 (s, C4). We have previously reported[2] that a 3-carbamoyltriazolopyridine is converted by lithium aluminium hydride reduction into a triazolylbutadiene (**4b**), and had expected that both salts, (**2a**) and (**3a**), would undergo similar reaction. There seems no simple explanation for their differing behaviour, and we report in this paper molecular orbital calculations which provide explanations for the preferred site of alkylation in triazolopyridines (**1a**), (**5**), and (**6**), and also for the difference between salts (**2a**) and (**3a**) in their behaviour towards nucleophiles.

Dedicated to Dr. A. Messmer for his 70th birthday.



SCHEME 1

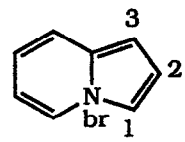
One of us has been involved in the development of semi-empirical MO calculations as a means of predicting the site of alkylation in multinitrogen heterocycles.[3-5] The underlying assumption was that S_N2 attack on the halide was related to electron density at the nitrogen atoms, and that the most appropriate measure of the nucleophilicity would be the electron density in the highest occupied molecular orbital which is of σ symmetry. The n-HOMO as the authors named it was not the highest molecular orbital, which is always a pi orbital. The values used were c_n^2 (the square of the coefficient, where n represents the principal quantum number of the highest occupied shell). We have used this method to explain the alkylation pattern of triazolopyridine (**1a**) and its isomer (**5**), and to predict the site of alkylation in the isomer (**6**), confirming this prediction with experiment. We have also extended the theory to provide an explanation of the differing behaviour of salts (**2a**) and (**3a**) towards nucleophiles.

The previous papers[3,5] used semi-empirical calculations AM1; the calculated values of c^2 in the n-HOMO for the two non-bridgehead nitrogen atoms in compounds (**1a**), (**5**), and (**6**) are given in Table 1. Also given, for comparison are c^2 values for the HOMO (pi), and calculated values for c^2 (n-HOMO) obtained by using the *ab initio* method using GAUSSIAN 86 with the STO-3G basis set. The molecular dimensions first used were a combination of those of pyridine and triazole. Subsequently crystal data on a triazolopyridine (**1d**) became available, but recalculation showed negligible change in the results.

TABLE 1

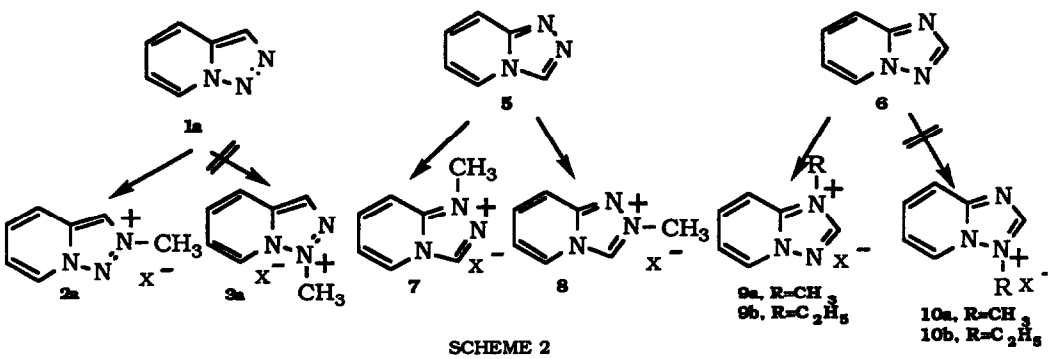
C^2 Values for Triazolopyridines (1), (5) and (6)

(n-HOMO and pi-HOMO).



		n-HOMO		pi–HOMO
Compound	N	Semi-Empirical	*Ab Initio*	(semi-empirical)
(1a)	N2	0.561	0.53	0.013
	N1	0.060	0.37	0.160
	Nbr		0.16	
(5)	N3	0.329	0.17	0.144
	N2	0.296	0.16	0.306
(6)	N3	0.518	0.24	0.220
	N1	0.256	0.12	0.134

From Table 1 it can be seen that the alkylation of compound (**1a**) is in accord with the c^2 (n-HOMO) but not with the c^2 (pi-HOMO) figures; the *ab initio* calculations confirm the semi-empirical results. For compound (**5**) the calculated c^2 figures for the two non-bridgehead nitrogen atoms are closer, but favour N3; the reported experimental results[6] show preference for N3 over N2 (compounds (**7**) and (**8**)) by 2:1. Again the pi-HOMO calculations predict the wrong result. No literature information was available on the alkylation of triazolopyridine (**6**) but our calculations show a considerable preference for N3. We have treated triazolopyridine (**6**) with dimethyl sulphate and with triethyloxonium fluoroborate, the products being the N-3 methyltriazolopyridinium salt (**9a**) and the N-ethyltriazolopyridinium salt (**10a**) exclusively, with no sign of the isomers (**9b**) and (**10b**). Confirmation of structure was by DIFNOE on compound (**9a**), irradiating at the 4H signal with NOE effect on the N-methyl signal. These results are summarized in Scheme 2.



SCHEME 2

The interpretation of the differing reaction of salts (**2a**) and (**3a**) with hydride required further calculations and a consideration of the probable mechanisms. Our calculations on the salts (**2a**) and (**3a**) used the 6-31G basis set, which is superior for charged species, since it allows for orbital interaction to occur when a centre develops a more positive charge.[7] The overall charge distribution (Figure 1) shows that C7 carries the highest positive charge (apart from bridgehead carbon 3a) in both salts, so that preferred site of attack by hydride in the case of compound (**3a**) is in accord with calculation.

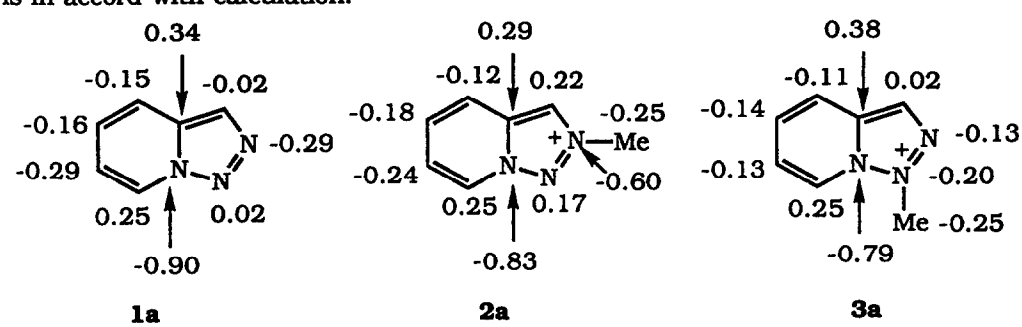
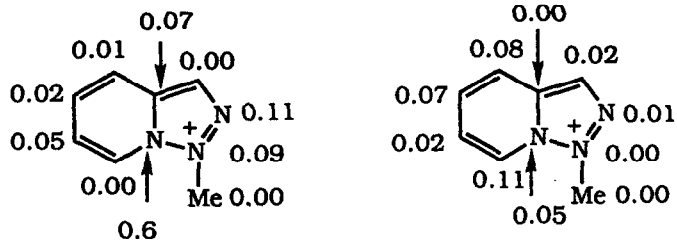


Figure 1: Electron Densities for Compounds 1a, 2a, and 3a
(Carbon Charges only)

Turning to the mechanisms, attack on compound (**2a**) should occur with displacement of the N-C7 electron pair and should be *anti*, using a LUMO of σ-symmetry - route (a). On the other hand attack on compound (**3a**) can be via a LUMO of pi-symmetry, to give an intermediate set up for 6π cyclo-reversion - route (b).



LUMO; Eigenvalue -0.091a.u. LUMO+1; Eigenvalue -0.087a.u.

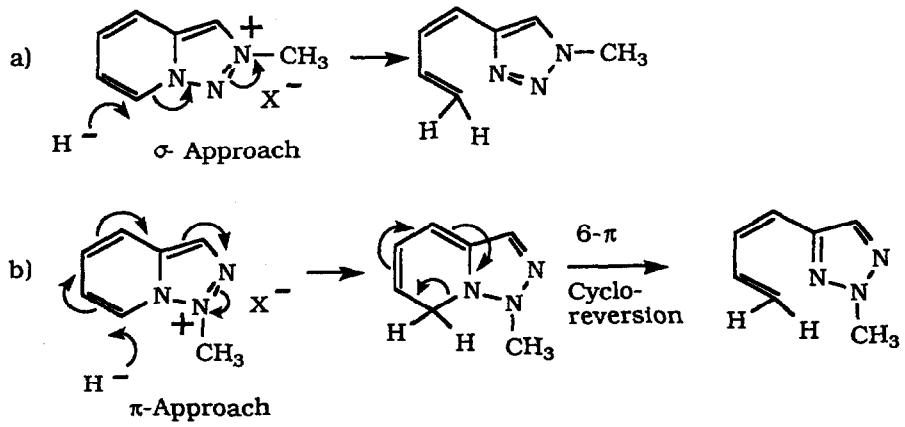
Figure 2: Electron Densities for LUMO and LUMO+1 orbitals of Compound (**3a**) (both have pi-symmetry)

As can be seen from the calculations (Figure 2) the coefficient for the LUMO for compound (**3a**) at C7 is zero; but there is a LUMO + 1 of very similar energy which can be used. On the other hand, the lowest unoccupied orbital of σ-symmetry in compound (**2a**) is of appreciably higher energy than the LUMO (pi) (Table 2) and reaction by the mechanism shown in (a) does not occur.

TABLE 2

LUMO Energy Levels

	Given value (atomic units)		
	Compound (**1**)	Compound (**3a**)	Compound (**2a**)
LUMO (pi)	0.08	-0.09	-0.11
LUMO + 1 (pi)		-0.087	
LUMO (sigma)	0.22	0.07	0.08

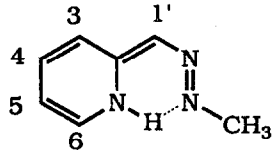


SCHEME 3

EXPERIMENTAL

Mps were determined on a heated stage, and are uncorrected. Nmr spectra were determined for solutions in $CDCl_3$, unless otherwise stated.

*1-Methyl[1,2,3]triazolo[1,5-a]pyridinium Bromide (**3a**):* a) Pyridine-2-carboxaldehyde (10 g) was added slowly to methylhydrazine (20 cm^3), with ice cooling, then the mixture was heated at 80-90°C (30 min.). Sodium hydroxide solution (30%, 20 cm^3) was added to the cooled solution, which was extracted with ether. The ethereal extracts were dried (KOH pellets), filtered, and evaporated, to give the crude hydrazone (12 g), which was used without purification for the next stage. ^1H nmr δ2.65 (3H, NMe), 6.0-6.5 (1H, br, NH), 6.75-6.80 (1H, ddd, J=7.33, 5.12, and 1.22 Hz, H5), 7.23 (1H, s, CH=N) 7.25-7.32 (1H, d of t, J=7.40 and 1.71 Hz, H3), 8.16-8.19 (d of q, J=4.88 and 0.98 Hz, H6). ^{13}C nmr δ41.47 (CH_3N), 117.10 (d, C1'), 120.63 (d, C3), 131.81 (d, C4), 133.66 (d, C5), 133.87 (d, C6), 144.92 (s, C2) *; this spectrum is in accord with the enamine structure



b) The N-methylhydrazone (17.35 g) in ethylacetate (50 cm^3, dried over mol. sieves) was added with stirring, under nitrogen, to a solution of N-bromophthalimide (50 g) in ethylacetate (1275 cm^3). The mixture was heated to 50-60°C (1 h.) then to 75°C (30 min). A solid precipitate was obtained on cooling, and was filtered off and washed with ethyl acetate. The weight of almost pure *1-methyltriazolopyridinium bromide* was 20 g (72.7%). A sample was purified by repeated precipitation from absolute ethanol solutions, using ethyl acetate. (Found: C, 37.58; H, 3.53; N, 18.99. $2C_7H_8N_3Br.\ H_2O$ requires C, 37.67; H, 3.38; N, 18.83%). ^1H nmr (d_4 methanol) 4.40 (3H, N^+CH_3), 7.99-8.05 (1H, t of d, J=8.05 and 0.72 Hz, H5), 8.51-8.55 (1H, d of t, 8.79 and 1.22 Hz, H4), 8.8 (1H, d, J=1 Hz, H3), 9.46-9.48 (1H, d(br), J=7.08 Hz, H7). ^{13}C nmr δ40.45 (q, CH_3N^+), 121.72 (d, C4), 123.94 (d, C6), 125.55 (d, C5), 130.79 (d, C7), 133.99 (d, C3), 137.69 (s, C3a).

1-Methyl[1,2,4]triazolo[1,5-a]pyridinium Tetrafluoroborate (**9a**); A solution of [1,2,4]triazolo[1,5-a]pyridine[8] (0.3 g, 2.4 mmol) and dimethylsulphate (0.2 g, 1.7 mmol) in acetonitrile (2 cm^3) was boiled under reflux (4 h). The solvent was removed in vacuo and the residue dissolved in water (3 cm^3) and mixed with 40% fluoroboric acid. The *N-methyltriazolopyridinium tetrafluoroborate* had m.p. 123-127° (from ethanol) (0.30 g, 82%). (Found: C, 37.83; H, 3.68; N, 19.22. $C_7H_8N_3BF_4$ requires C, 38.05; H, 3.64; N, 19.02%. ^1H nmr (d_6-DMSO) 4.18 (3H, NMe), 8.05 (1H, dd, H6), 8.34 (1H, d, H8), 8.36 (1H, dd, H7), 9.23 (1H, d, H5), 9.50 (1H, s, H2).

1-Ethyl[1,2,4]triazolo[1,5-a]pyridinium Fluoroborate (**10a**); A solution of triazolopyridine (**6**) (0.2 g, 1.7 mmol) in anhydrous dichloromethane (5 cm^3) with triethyloxonium fluoroborate (0.4 g, 2.2 mmol) was stirred at 20°C for 24 h. The solution was treated with absolute ether, and the precipitated salt filtered off (0.32 g, 80%). Recrystallised from ethanol the *triazolopyridinium salt* (**10a**) had m.p. 124-126°C. (Found: C, 40.62; H, 4.25; N, 17.87. $C_8H_{10}N_3BF_4$ requires C, 40.86; H, 4.13; N, 17.71). ^1H nmr 1.55 (3H, t, $CH_2\mathbf{CH_3}$), 4.45 (2H, q, CH_2N^+), 7.80 (1H, dd, H6), 8.25-8.40 (2H, m, H7 and H8), 8.10 (1H, d, H5), 9.15 (1H, s, H2).

1-(2-Methyltriazol-4-yl)-1,3-butadiene (**4a**); Sodium borohydride (6.3 g) was added to a solution of 1-methyltriazolopyridinium bromide (**3a**) (7 g) in methanol (100 cm^3). The mixture was stirred at room temperature overnight, then evaporated. The solid residue was extracted with ether; evaporation of the ethereal extracts gave an orange oil (2.2 g). Purification on a Chromatotron, eluting with ethyl acetate/60-80° petrol (1:9) gave almost pure *triazolylbutadiene* (1.7 g, 38.5%), b.p. 60°/0.01 mm Hg (bulb tube). (Found: C, 61.93; H, 6.78; N, 30.8. $C_7H_9N_3$ requires C, 62.22; H, 6.67; N, 31.11%).

Calculations

Ab initio molecular orbital calculations were performed with the GAUSSIAN 86[9] program on the Amdahl 5890 computer at Manchester Computer Centre, using the STD-3G basis set.[10]

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