Tetrahedron Letters,Vol.30,No.30,pp 4013-4016,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

A GENERAL ANIONIC MECHANISM FOR THERMODYNAMIC CONTROL OF REGIOSELECTIVITY IN N-ALKYLATION AND ACYLATION OF HETEROCYCLES

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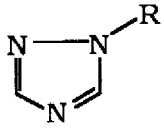
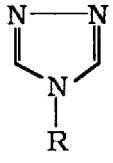
Abstract. Regioselective alkylation of 1,2,4-triazole (Ia, IIa) to 1-alkyl derivatives (Ib) may occur by nucleophilic displacement of the triazole anion, is thermodynamically-controlled (shown by a free energy diagram), and the position of equilibrium is relatively insensitive to the nature of the alkyl group.

Selective alkylation of 1,2,4-triazole (Ia, IIa) to 1-alkyl-1,2,4-triazoles (Ib) in preference to the 4-isomer (IIb) can be attributed to various kinetically-controlled mechanisms: *e.g.* statistical factors are favourable (2 : 1) and two adjacent nitrogen atoms may show an α-effect;[1a] also there may be complexation by silicon reagents,[2] control of ambident nucleophilic reactivity by dipolar aprotic solvents or a radical mechanism.[3] Using kinetic data to construct a free energy diagram, we now show that the most important (and initially unexpected) factor is thermodynamic control.



(I)



(II)

(a) R =H (b) R = alkyl (c) R = $CH_2C(OH)R'R''$

(d) R = $CH_2C(OH)Ph_2$ (e) R = $CH_2C(O^-)Ph_2$ (f) R = $CH_2C(O^-)R'R''$

(g) R = $(CH_2)_3Ph$ (h) R = $COCH_3$

ß-Hydroxyethyl-(1,2,4-triazole) derivatives (Ic) are of considerable current interest because they possess plant growth and fungicidal activities.[4] Syntheses directly from triazole are preferred on economic grounds, and control of regioselectivity has been studied intensively both by us and others.[2-6] Typically, conditions as mild as possible were initially chosen to try to improve the regioselectivity of the reaction. Such kinetically-controlled reactions are successful for reactive α-halo-oxiranes [5a] and α-haloketones.[5b] For alkylations of triazole using less reactive electrophiles (*e.g.* epoxides or 3-phenylpropyl bromide), we obtained isomer ratios of 85-90 / 15-10. There are examples in aromatic substitution where high temperatures lead to greater regioselectivity by thermodynamic control.[7] These, and other examples for ambident nucleophiles,[8] may be regarded as exceptional. However alkyl halides are known to catalyse isomerisations of N-alkylated heterocycles, by thermodynamically-controlled processes involving formation of quaternary salts.[9] We now provide evidence for an additional mechanism involving nucleophilic displacement of the triazole anion, and we comment on more general implications.

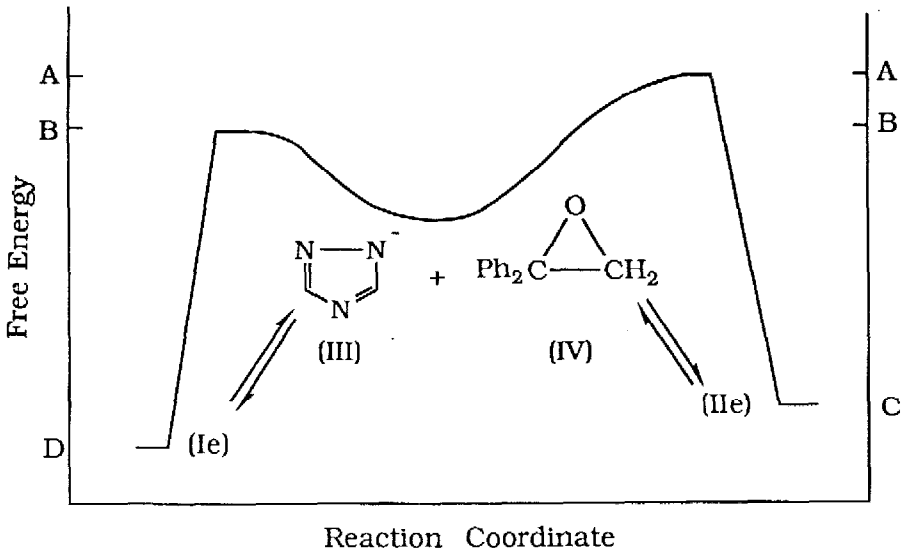


Figure. Free energy diagram for the production of 1-alkyl-1,2,4-triazole (Ie) from triazole anion (III) and epoxide (IV), and from rearrangement of the 4-isomer (IIe).

Following reports of high temperature, base-catalysed isomerisations of ß-hydroxyethyl triazoles (IIc),[3] we studied the kinetics and equilibria involved in the formation and decomposition of the ß,ß-diphenyl derivatives (Id and IId). Rate constants were determined by aliquot sampling combined with reversed phase high performance liquid chromatography (HPLC). First order rate constants for decompositions of 0.1M solutions of the anions (Ie, and IIe) under strongly basic conditions gave the free energy differences **BD** and **AC** respectively (see figure). Under these conditions, the initial decomposition products should be the triazole anion (III) and diphenyloxirane (IV) - structures shown in the figure. Although these initial products cannot be detected directly, their presence as intermediates is supported by observations that the triazole anion can be trapped by other oxiranes and that diphenylacetaldehyde is formed during decomposition of the 1-isomer (Ie), presumably by isomerisation of the epoxide (IV). Decomposition of the 4-isomer (IIe) occurs more readily, yielding the 1-isomer (Id) after protonation. The product ratio for the second order reaction between the triazole anion (III) and diphenyloxirane (IV), giving initially a mixture of anions (Ie, IIe), provided the free energy difference between the transition states for product formation (**AB**, see figure).

From the kinetic data alone, the difference in free energy between the 1- isomer (Ie) and the 4-isomer (IIe) is calculated to be 4.31 kcal/mol (see Table). A completely independent measure of this difference in free energy can be obtained by quenching an equilibrium mixture of these anions, followed by HPLC analysis of the two alcohols (Id, IId). At 150 °C the equilibrium mixture approached from both sides was 99.3 ± 0.1% of (Id) and 0.7% of (IId); hence $\Delta G = 4.17$ kcal/mol, in satisfactory agreement with the value of 4.31 kcal/mol calculated from the kinetic data. These results provide strong evidence that base-catalysed isomerisations of the ß-hydroxyethyl compounds (IIc, d) occur via the triazole anion (III) by a dealkylation/alkylation process (see Figure) under thermodynamic control. Other examples (Table) show that the position of equilibrium is relatively independent of the alkyl group, including data for (I, IIg) in which the ß-hydroxyethyl group is absent. Similarly, high equilibrium isomer ratios are likely for N-acyltriazoles (Ig),[10] for which the 4-isomer (IIg) has not been detected.

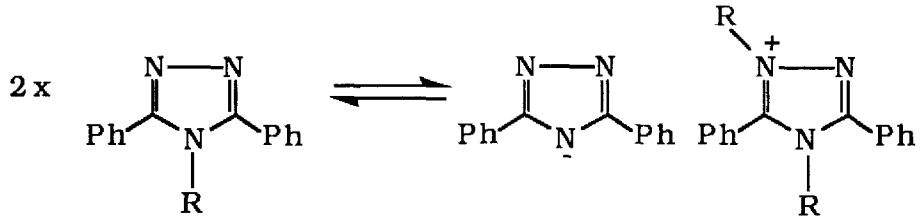
Table. Free energy differences (kcal/mol) at 150 °C for isomerisations of triazole isomers (I, II, e, f, g) in N-methyl-pyrolidinone - see figure.

Substrates [a]	AB	BD	AC	CD (calc)[b]	CD (obsd)[c]
(I, IIe)	2.05	32.48	30.22	4.31	4.17
R'=Ph, R"=Bu^n	2.31	32.65	30.64	4.32	4.45
R'=*p*-ClPh, R"=Bu^n	2.19	32.48	30.71	3.96	4.05
R'=R"=$Ph(CH_2)_3$	2.16	33.41	31.52	4.05	4.45
R'= $Ph(CH_2)_3$, R"=Pr^n	2.17	33.46	31.47	4.16	4.30
(I, IIg)	2.36	33.10	31.28	4.18	4.64

[a] Refer to structure (If), unless stated otherwise. [b] From rate and product data: **CD = AB + BD - AC** (see text). [c] From equilibrium data.

The base-catalysed isomerisations of the ß-hydroxyethyl compounds (IIc, d) occur in a variety of solvents (*e.g.* PEG 400, excess triazole, or in neat solutions). Iodide can initiate similar isomerisations of the alkylated triazole (IIg) probably by displacement of the triazole anion (III) giving the alkyl iodide, which would then catalyse the reaction.[9]

A recent report of liquid phase rearrangements from 4- to 1-alkyl-3,5-diphenyl-1,2,4-triazoles (V) can be explained by a similar displacement of the corresponding substituted triazole anion, rather than by an alkyl-shift process.[11] Heating the neat compounds (V) at 350 °C may lead to a bimolecular dealkylation of one molecule by another, leading to the salt or ion pair (VI). If, as shown above, the reaction were thermodynamically-controlled, the observed preference for isomerisation to the 1-alkyl-isomer could be explained. Supporting this proposal is the expectation that the S_N2 dealkylation would be unfavourable for 4-phenyltriazoles,[1b] consistent with the observations that no rearrangement products were observed.[11] The 3- and 5-phenyl groups in (V) are not essential for this rearrangement, because we have found that the 4-isomer of the alkylated triazole (IIg) rearranges to the 1-isomer (Ig) at 350 °C. Although these are reactions in the condensed phase at relatively high temperatures, much higher temperatures (*ca.* 700 °C) are required for flash vacuum pyrolyses of related compounds.[11,12]



(V) (VI)

Conclusion. A new general mechanism, requiring nucleophilic displacement of the heterocyclic anion, is proposed for thermodynamically-controlled N-alkylation and acylation of heterocycles. This mechanism is expected to be more favourable for acylation than for alkylation and could apply to various heterocycles; *e.g.* hydrolyses of acetyl triazole in water,[13] and of acetylimidazole in base[14] show the ease of displacement of these

heterocyclic groups, and the high reactivity of these acylated derivatives. Both experimental [15] and theoretical studies [16] of tautomeric equilibria (Ia, IIa) of 1,2,4-triazole show that tautomer (Ia) is strongly preferred to tautomer (IIa). Hence a predictive approach based on theoretical studies of tautomeric heterocycles may generalise these results further.

Experimental. Illustrative descriptions of formation and isomerisation/decomposition of substrates are given:
Preparation of 1,1-diphenyl-(1,2,4-triazol-4-yl) ethanol (IIc) and the 1-isomer (Ic) . A mixture of 1,1-diphenyloxirane (IV) (5.00g, 0.026 mol), 1,2,4-triazole (1.79g, 0.026 mol), and potassium carbonate (3.59g, 0.026 mol) in dimethyl formamide (13 ml) was stirred at 86 °C for 1 hr. After evaporating the solvent, the solid residue was treated with water (100 ml) and extracted with dichloromethane (100 ml). The organic layer was dried and then evaporated to give a white solid (6.38g, 94%), an 87/13 mixture of Ic and IIc. This solid (5g) was extracted with boiling toluene (2 x 200 ml) and was filtered hot; on cooling the filtrates gave Ie (3.35g, 67%), which was recrystallised from toluene and then methanol (m.p. 132 °C). The material insoluble in toluene was dissolved in dichloromethane (50 ml) and extracted with 0.1M HCl (50 ml). Neutralisation of the aqueous layer with 1M NaOH gave white crystals, which were isolated by extraction into dichloromethane; recrystallisation from methanol gave white crystals (m.p. 253 °C) of IIc (0.34g, 7%).
Decomposition of the 1-isomer (Ic) . To a solution of Ic (0.0795g, 0.00043 mol) in N-methylpyrrolidinone (3 ml) at 150 °C was added solid NaOH (0.24g). Small samples were removed at various time intervals, quenched (liquid nitrogen), filtered, and then analysed directly by HPLC (15 cm. x 1/4", 5μ ODS2, eluent 60% MeOH/water).

Acknowledgements. We thank SERC for the award of a CASE studentship (to PJW) and for a research grant to purchase HPLC equipment.

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(Received in UK 24 May 1989)