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CYCLIZATION OF IMIDOYL AZIDES STABILIZED BY INTERNAL HYDROGEN BONDING

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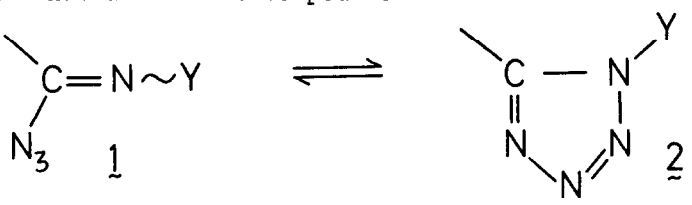
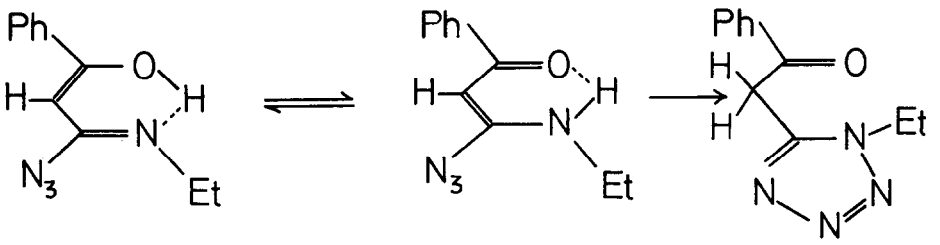
Ring-chain isomerism between imidoyl azides 1 and their cyclic analogues, the tetrazoles 2, has been widely observed.[1] In most cases the tetrazole form 2 is the more stable (consistent with theoretical calculations[2]) and it has been pointed out[3] that all of the compounds which are stable in the azido form 1



also have a lone pair on the group Y (= -$\ddot{O}$R, $\ddot{N}R_2$, $\ddot{S}$R), a feature which is known to slow EZ isomerisation about the C=N bond. A puzzling exception to this general rule is the observation by Woodward, Olfson[4] and others[5] that labile azido forms can be detected in the adducts of ketoketenimes with azide ion; the substituent Y is an alkyl or aryl group in this case so that (in the absence of other factors) nitrogen inversion should be rapid. We wish to report that the relative stability of the azido form is due to the existence of an internal hydrogen bond and that these azides show a unique response to catalysts in the cyclization to the tetrazole.

The azide 3 was prepared on reaction of the ketoketenimine, PhCOCH=C=NEt (formed in situ from the N-ethyl-5-phenylisoxazolium cation)[3] with azide ion in aqueous solution. The azide was extracted with CCl_4 and precipitated, m.p. 30-31°, on evaporation of the solvent and treatment with petroleum ether at -60°. The nmr showed that the azide was uncontaminated by the isomeric tetrazole 4 and is consistent with either an enol (3a) or enamine (3b) structure (with singlets assigned to =CH- at δ5.64 (1H) and -NH (or OH) at δ11.05 (1H)). The configuration of 3a is assigned as Z (N_3 and Et groups cis) on the basis of previously observed stereoelectronic control of reactions involving nucleophiles and nitrilium ions.[6]



3a 3b 4

Clearly hydrogen bonding to the imidoyl nitrogen (3a) and/or rapid tautomerism to 3b are the key factors which inhibit cyclisation to 4 and thus permits the isolation of 3.

The azide 3 cyclises to 4 on heating in an inert solvent; in water cyclisation occurs at 25° and is strongly catalysed by both acid and base. The pH dependency of the rate of cyclization is unusually complex (see Figure); base catalysis is observed from pH 8-13 and acid catalysis at intermediate (3-6) pH. However acid inhibition is also observed at higher acid concentrations (pH < 2). In addition, strong general acid catalysis (by species such as HOAc or $H_2PO_4^-$) is also observed.

This kinetic behaviour can be rationalised in terms of structure(s) 3. At high pH, proton removal gives the anion 6 which, deprived of the OH (or NH) group, can undergo rapid nitrogen inversion and thus cyclize to 4. The fact that the rate of cyclization of 3 does not become pH independent even at high pH indicates that the pKa of 3 is > 13 and that cyclization of the anion is very rapid indeed ($t_{\frac{1}{2}}$ < 1s).

Under acidic conditions protonation (to give 5) disrupts the H-bonded system present in 3 so that C-N bond rotation can occur (5→7); this can lead to an azide 8 which is correctly oriented for cyclization when deprotonation occurs. At sufficiently low pH however the equilibrium shifts towards the protonated form 5 or 7 (this is clear from the uv spectrum of 3 which shows the equilibrium loss of the characteristic azide absorption in the uv at 348 nm in acid). The protonated azide 7 does not itself cyclize and since the equilibrium concentration of the free base form 8 is low at pH < 2, the overall rate of cyclization of 3 to 5 is again slow at low pH. The solid lines drawn in the Figure are theoretical, assuming such a reaction scheme.

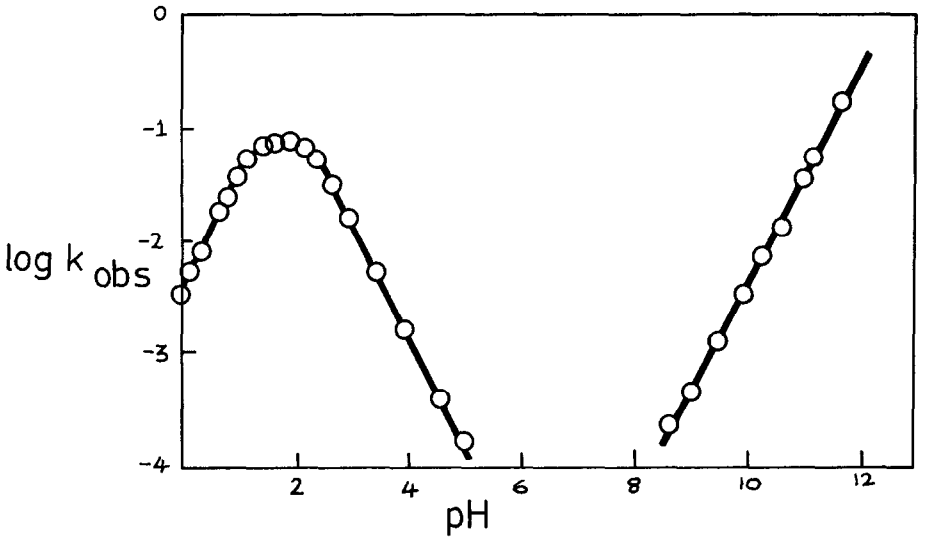
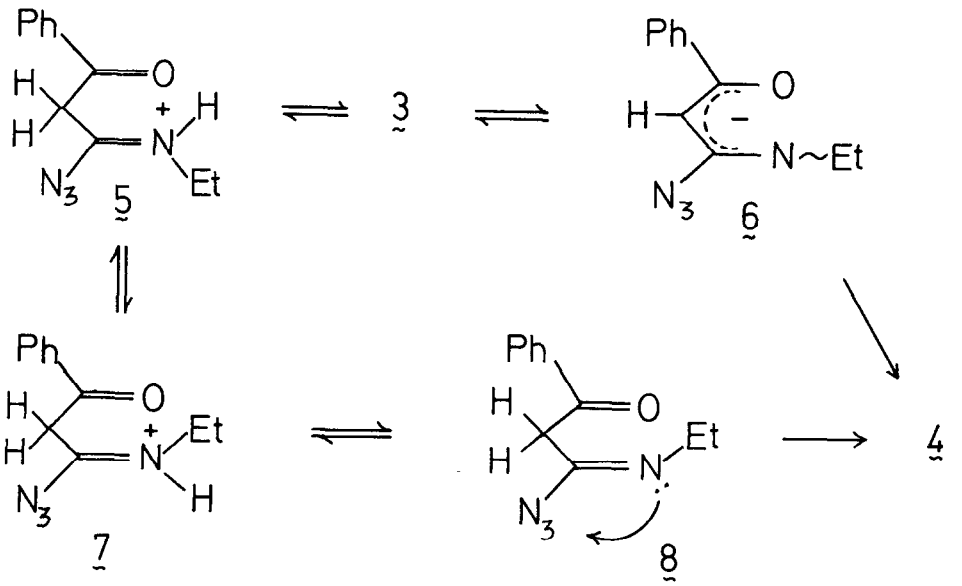


FIGURE Plot of the log of the observed rate constant for cyclization of 3 to 4 in water as a function of pH; conditions: 25°, μ=1.0 ($NaClO_4$), {buffer}=0.



Addition of CD_3CO_2D to a $CDCl_3$ solution of 3 causes rapid cyclization to 4. The tetrazole 4 formed was shown (by nmr) to contain just one deuterium (in the methylene group). This confirms the acid catalysed mechanism outlined in the scheme, with cyclization of the azide occuring rapidly subsequent to protonation at carbon.

REFERENCES

1. See W. Lwowski, "The Chemistry of the Azido Group", S. Patai, Ed., Interscience, New York, N.Y. 1971, p.503 for a general discussion of this problem.

2. L.A. Burke, J. Elguero, G. Leroy and M. Sana, J.Amer.Chem.Soc., 98, 1685 (1976).

3. K.J. Dignam, A.F. Hegarty and P.L. Quain, J.Org.Chem., 43, 388 (1978).

4. R.B. Woodward and R.A. Olofson, J.Amer.Chem.Soc., 83, 1007 (1961).

5. D.S. Kemp and R.B. Woodward, Tetrahedron, 21, 3019 (1965).

6. The ketenimine reacts in aqueous solution to initially abstract a proton from H_2O or H_3O^+ to give a nitrilium ion $R\text{-}CH_2\text{-}C{\equiv}\overset{+}{N}\text{-}R^1$ (D.G. McCarthy and A.F. Hegarty, unpublished results); reaction of such nitrilium ions with nucleophiles are stereospecific (M.T. McCormack and A.F. Hegarty, J.Chem.Soc.Perkin II, 1701 (1976).