The Kinetics and Stereochemistry of Pyrazoline-ring Formation. Evidence for Stereoselective Enamine–Imine Tautomerism

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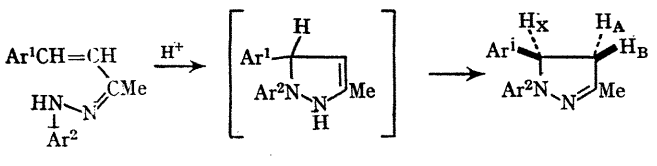
THE kinetics of cyclisation of a series of αβ-unsaturated phenylhydrazones (I), with differing substitutents in the Ar^1 and Ar^2 rings, have been studied in acetic acid solution. A least-squares analysis of the relationship between log k_{56} and σ- or σ$^+$-values for each reaction series showed that while σ$^+$-values were more successful in correlating substituent effects in the Ar^1 ring (ρ −1·44), σ$^+$-values gave only a slightly better correlation than σ-values for substituents in Ar^2 (ρ = −2·54). The ρ-values are consistent with a mechanism involving protonation at the imine nitrogen with subsequent cyclisation leading to an intermediate Δ^3-pyrazoline (II), which tautomerises to the stable Δ^2-pyrazoline (III).[1] The n.m.r. spectrum of 2-methyl-1,5-diphenyl-2-pyrazoline (III; Ar^1 = Ar^2 = Ph) showed that the H_A and H_B protons, which are diastereotopic because of the chiral centre at C-5, formed an ABX system with the H_X proton: H_A τ 6·6 (J_{AX} 12·2, J_{AB} 17·5 Hz.); H_B τ 7·3 (J_{BX} 8·25 Hz.); H_X τ 4·95. The stereochemical assignments are necessarily tentative because of the limited value of the Karplus equations in a strained five-membered ring,[2] but examination of molecular models and assumption of a relationship between cos^2(dihedral angle) and coupling constant leads to the assignment of H_A as *cis* to H_X.



(I) (II) (III)

Rearrangement of 4-phenylbut-3-en-2-one phenylhydrazone (I; Ar^1 = Ar^2 = Ph) in AcOD showed only a small kinetic isotope effect, k_H/k_D varied from 1·036 to 1·053 for kinetic runs at three temperatures. Isolation of the product from a rearrangement at *ca.* 70° for 5 min. and determination of its n.m.r. spectrum showed that *ca.* twice as much deuterium had been incorporated into the H_A proton into the H_B position. A sample of 2-methyl-1,5-diphenyl-2-pyrazoline was stable under these conditions in AcOD but when the mixture was heated under reflux for longer periods the H_A and H_B protons underwent exchange at the same rate.

The stereoselectivity exhibited in the kinetically controlled enamine–imine tautomerism [(II) ⇌ (III)] thus parallels the stereoselectivity of enol–ketone tautomerism previously demonstrated in six-membered-ring ketones.[3] The preferred direction of proton attack on C-3 is probably *trans* to the phenyl group at C-4.

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[1] C. H. Jarboe, "The Chemistry of Heterocyclic Compounds", Interscience, London, Part 2, p. 179.
[2] M. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.
[3] E. J Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, 1958, **80**, 4981 and references therein.