Stereoselectivity Due to Electrostatic Repulsion in Polar Cycloaddition[1]

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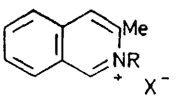
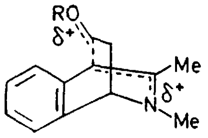
Summary The cycloaddition of 2-alkyl-3-methylisoquinolinium salts occurs stereospecifically in a manner predictable from the repulsive forces which would be expected during the reaction.

It has been shown[2] that the 2,3-dimethylisoquinolinium cation (**1**) reacts regio- and stereo-specifically with vinyl ethers yielding that racemate which would be expected to afford the maximum separation of like charges in the transition state (**3**).[2] The cyclopentadiene adduct (**4**) even in the crude state gave clear n.m.r. evidence of being a single racemate, m.p. 165—170° (decomp.) To permit unambiguous identification of the quaternary nitrogen atom position, the 2-ethyl analogue (**5**), m.p. 167–169° (decomp.) was prepared and subjected to single-crystal *X*-ray analysis.

Crystals of (**5**) from acetonitrile are monoclinic, space group $P2_1/c$, with $a = 8{\cdot}48(1)$, $b = 16{\cdot}46(2)$, $c = 12{\cdot}64(2)$ Å, $\beta = 109{\cdot}87(15)°$, $U = 1673$ Å,[3] D_m (flotation in aqueous zinc chloride) $= 1{\cdot}33$, $Z = 4$, $D_c = 1{\cdot}341$. Three-dimensional *X*-ray intensity data were recorded photographically by the equi-inclination multiple-film Weissenberg technique and estimated visually. The structure was solved by the heavy-atom method, and atomic positional and anisotropic thermal parameters for the non-hydrogen atoms were refined to $R = 0{\cdot}134$ over 2345 independent observed reflections.



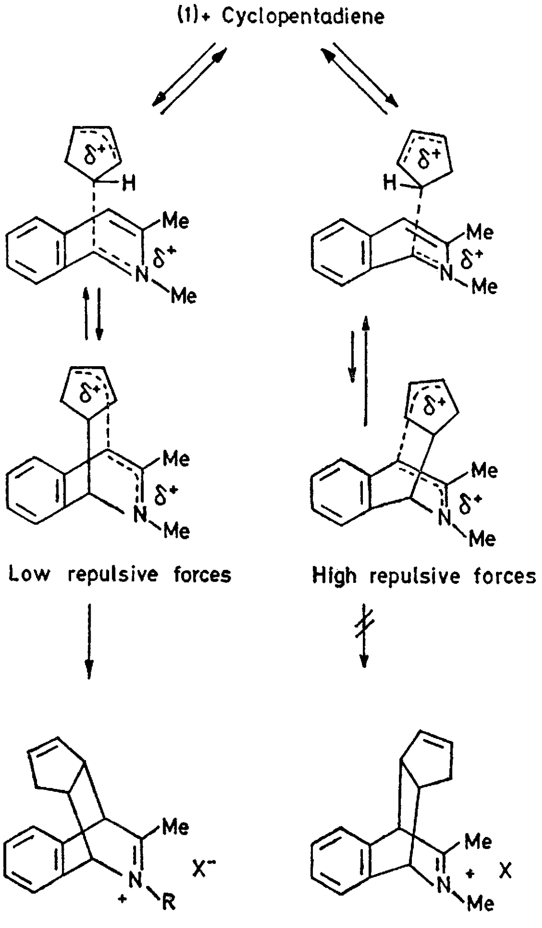
(1) R = Me, X = I
(2) R = Et, X = ClO_4



(3)

The double bond in the cyclopentene ring at 1·386(14) Å is significantly shorter than the other C–C lengths which range from 1·480(14)—1·559(11) Å in this ring. That both of the adducts [(**4**) and (**5**)] had the same stereochemistry is evident from similarities in the n.m.r. spectra.

As would be expected if kinetic control were operative, continuous n.m.r. observation of the cyclopentadiene



(4) (5) R=Me, X=I (6)
(5) R=Et, X=ClO$_4$ (7)

Scheme

addition revealed only a single stereoisomer [(**4**) or (**5**)] and a slight revision of our earlier mechanism[3] can be used to explain the observed stereochemistry (Scheme). The absence of adducts such as (**6**) and (**7**) can be rationalized on the basis of repulsive forces that would be encountered in the transition state leading to the establishment of the second new σ-bond. A concerted but non-synchronous reaction mechanism is not only useful in explaining the regio- and stereo-chemistry of the products, but also is consonant with the charge distribution among the canonical forms contributing to the resonance hybrid of isoquinolinium salts. Whereas one such canonical form bears a positive charge at position 1 the favoured site for the attack of nucleophiles,[4] no canonical form bears a positive charge at position 4.

These instances of high stereoselectivity, combined with others as yet unreported, permit the following generalization. If two geometical isomers are possible in a polar cycloaddition, and if the transition states leading to the establishment of the second new σ-bond in these two isomers differ in the distance between the centres of receding and developing positive charge, then the geometrical isomer formed in the larger amount will be that with the greater distance between charge centres in the transition state.

This rule also explains the almost exclusive (40:1) preference for *endo* cycloaddition of the tropylium ion with cyclopentadiene which Itô and Itoh[5] observed, but were unable to rationalize by calculation of the perturbation energies of the alternative transition states.

Since the stereoselectivity rule has as a premise that polar cycloaddition occurs in two stages, it follows that examples of this new type of stereoselectivity provide evidence for the non-synchronous nature of polar cycloaddition.

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[1] The term polar cycloaddition was originated by R. R. Schmidt, *Tetrahedron Letters*, 1968, 3443.

[2] (a) C. K. Bradsher and F. H. Day, *Tetrahedron Letters*, 1971, 409; (b) C. K. Bradsher, F. H. Day, A. T. McPhail, and Pui-Suen Wong, *ibid.*, p. 4205.

[3] C. K. Bradsher and J. A. Stone, *J. Org. Chem.*, 1969, **34**, 1700.

[4] *E.g.*, W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 1954, 2770; N. J. Leonard and G. W. Leubner, *J. Amer. Chem. Soc.*, 1949, **71**, 3405.

[5] S. Itô and I. Itoh, *Tetrahedron Letters*, 1971, 2969.