

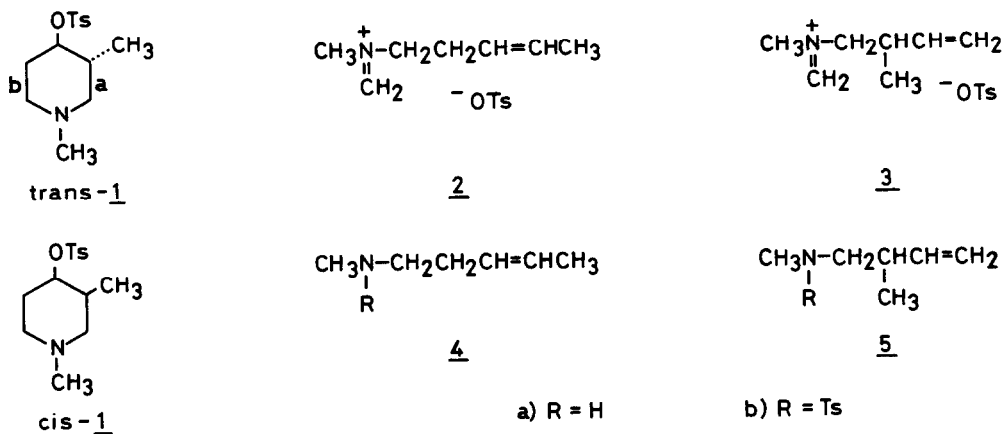
REGIOSELECTIVE SOLVOLYTIC FRAGMENTATION OF UNSYMMETRICAL 4-PIPERIDINOLS

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(Received in UK 23 May 1975; accepted for publication 9 June 1975)

The p-toluenesulfonates (tosylates) of unsymmetrical 4-piperidinols, which can undergo solvolytic fragmentation<sup>1</sup> by more than one pathway, yield the more highly substituted olefin preferentially<sup>2</sup>. This regioselectivity is observed even when the thermodynamically less stable product is thereby formed.

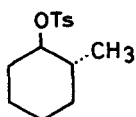
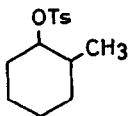
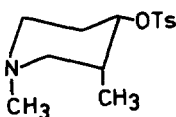
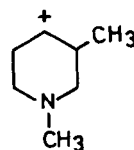
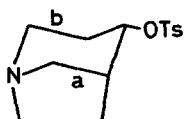
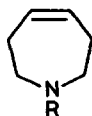
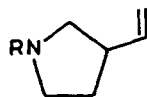
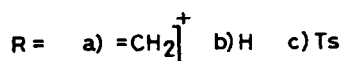


Thus, reaction of trans-1,3-dimethyl-4-piperidinyl tosylate (1) in 80 % aqueous ethanol leads to 98 % of the immonium salt 2 by cleavage of bond a beside 2 % of the salt 3 by cleavage of bond b. This follows from the quantitative formation of formaldehyde<sup>3</sup> along with the trans amino olefin 4a and the terminal amino olefin 5a, which were isolated as N-tosyl amides 4b and 5b, respectively,<sup>4</sup> in the ratio 98:2<sup>5</sup>. trans-1 reacts approx. 700 times faster than trans-2-methylcyclohexyl tosylate 6 (Table) and therefore fragments by the concerted mechanism, in accordance with previously established stereoelectronic rules<sup>6</sup>.

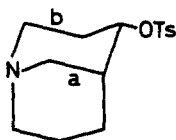
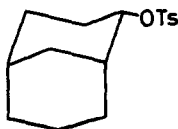
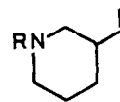
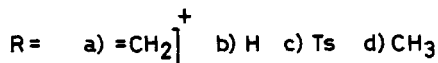
Table. First order rate constants in 80 vol.% ethanol,  $c = 10^{-3}$  m,  $2.0 \times 10^{-3}$  m in triethylamine.

	temp. °C	$k(s^{-1})$	$E^\ddagger$ (kcal/mole)
trans- <u>1</u>	80.00	$7.48 \times 10^{-2}$	23.80
trans- <u>6</u>	80.00	$1.09 \times 10^{-4}$	
cis- <u>1</u>	50.00	$3.81 \times 10^{-5}$	27.27
cis- <u>6</u>	50.00	$3.35 \times 10^{-4}$	
endo- <u>9</u>	45.00	$1.86 \times 10^{-2}$	21.0
endo- <u>12</u>	45.00	$1.21 \times 10^{-5}$	25.3
endo- <u>13</u>	65.00	$5.64 \times 10^{-1}$	21.7
endo- <u>14</u>	65.00	$3.84 \times 10^{-5}$	23.6

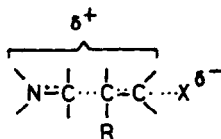
By contrast, cis-1 reacts by the two-step mechanism <sup>6</sup>, i.e. via the carbonium ion 8. In this case conformation 7, which would lead to concerted fragmentation, is highly unfavorable due to repulsion of the syn axial methyl groups <sup>7</sup>. This follows from the reaction rate, which is only 0.11 times that of cis-6 (Table) and from the formation of 37 % of elimination and substitution products together with 63 % of fragmentation products, namely the cis and trans isomers of the amino olefin 4a in the ratio 3 : 2 <sup>5</sup>. Again, the more substituted olefin is formed preferentially.

trans-6cis-6789101112

In 80 % ethanol 1-azabicyclo[3.2.1]octyl-4-endo-tosylate (9) reacts  $1.5 \times 10^3$  times as fast as the homomorphous endo-bicyclo[3.2.1]octyl-2-tosylate (12)<sup>8</sup> (Table) and therefore fragments by the concerted mechanism<sup>6</sup>. In water the tosylate 9 produces a quantitative yield of formaldehyde<sup>3</sup> and both amino olefins 10b and 11b in the ratio 91:9, as shown by the isolation of the corresponding N-tosyl derivatives 10c and 11c, respectively. The latter amino olefin 11b appears to arise through cleavage of bond b. Actually, only bond a is cleaved in the fragmentation step since the N-tosyl derivative of azacyclohept-4-ene (10c) is the sole product when 9 is reacted in aqueous sodium hydroxide and in the presence of an excess of tosyl chloride. The minor amounts (9 %) of 3-vinyl pyrrolidine (11b) therefore result from a sigmatropic [3,3] rearrangement<sup>9</sup> of the first formed immonium salt 10a to its isomer 11a, a reaction which competes with hydrolysis.

13141516

Finally, in 80 % ethanol 1-azabicyclo[3.3.1]nonyl-4-endo tosylate (13) reacts  $1.47 \times 10^4$  times as fast as its homomorph 14 (Table) producing a quantitative yield of formaldehyde<sup>3</sup> beside the amines 15b and 16b, which were isolated as their N-tosyl derivatives 15c and 16c in the ratio 12:88. This result suggests that cleavage of bond b occurs preferentially. However, when the intermediate immonium salts are reduced in situ with sodium borohydride N-methyl azacyclooct-4-ene (15d) and N-methyl-3-vinyl piperidine (16d) are formed in the ratio 94:6. Again, fragmentation leads to the more highly substituted olefin. In this case, however, sigmatropic rearrangement of the thermodynamically less stable immonium salt 15a to its isomer 16a competes more effectively with hydrolysis.



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The observed regioselectivity of concerted fragmentation is explicable if it is assumed that in the transition state 17 the cleavage of the C(3)-X bond is more advanced than that of the C(1)-C(2) bond. On this basis alkyl or cycloalkyl groups at C(2) would be expected to stabilize the resultant partial positive charge as well as the developing double bond <sup>10</sup>.

#### REFERENCES

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- 2) For earlier observations see: M. Geisel, C.A. Grob & R.A. Wohl, *Helv. Chim. Acta*, 52, 2206 (1969); J.A. Marshall & J.H. Babler, *J. Org. Chem.*, 34, 4186 (1969).
- 3) Formaldehyde was isolated as the dimedone derivative.
- 4) The structures of all new compounds are supported by elemental and spectroscopic analyses.
- 5) Determined by g.l. chromatography.
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- 10) This is essentially the same explanation as that proposed for Saytzeff orientation in olefin-forming elimination by J.F. Bunnett, *Angew. Chem., Internat. Edit.*, 1, 225 (1962).