Tetrahedron Letters No. 22, pp. 1493-1497, 1963. Pergamon Press Ltd.
Printed in Great Britain.

ENERGY RELATIONS BETWEEN EPIMERIC TRANSITION STATES FOR SOME REACTIONS INVOLVING CHANGES BETWEEN 3- AND 4-CO-ORDINATE RING NITROGEN AND CARBON ATOMS

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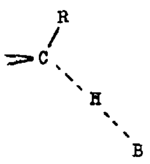
(Received 9 July 1963)

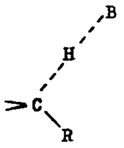
REDUCTION of the previously described (1) epimeric N-methyl-N-ethyl quaternary salts derived from camphidine and tropane with lithium aluminium hydride in tetrahydrofuran (2) shows that a much greater proportion of hydride attack at N-ethyl takes place with each N-methyl base ethiodide than with the corresponding N-ethyl base methiodide (for nomenclature, see ref.1), the proportions of N-methyl base in the total reduction products being of the order of 20 % for the former salts and 3 % for the latter. This result, considered along with the similar contrast previously reported (1) for thiophenate attack on the epimeric salts, suggests that in the two systems studied nucleophilic attack removes an N-alkyl group more readily when this is in the orientation preferentially adopted during its introduction by quaternisation of tertiary base [i.e. equatorial with tropanes and axial with camphidines and several other base systems (1)]. To prove this hypothesis conclusively for any one base system, additional information about relative decomposition rates of epimeric quaternary salts is required. This is more easily provided for the thiophenate- than for the hydride replacement, and we find that with the epimeric N-methyl-N-ethyl camphidinium iodides in diethylene glycol at <u>ca</u>. 180° an "axial" N-alkyl group is removed about one and a half times as rapidly as is the same group from the "equatorial" position in the epimeric salt [the inverted commas signify that in camphidine quaternary salts the 6-ring will undoubtedly be rather distorted (1)]. For each orientation, methyl is removed about five times as rapidly as ethyl.

Since reduced cyclic N-alkyl bases will generally be expected (1,3) to undergo configurational inversion at nitrogen very much faster than quaternisation (except perhaps for particularly rapid quaternisations with more conformationally rigid (4) bases like certain ethyleneimine derivatives) the principle sometimes associated with the names of Curtin and Hammett (5) will apply, and the ratio of quaternisation products will be determined by the free energy difference between the relevant transition states. In our formulations (I - VII; charges are omitted for clarity) of transition states for quaternisations and other reactions at ring atoms, we assume greater steric compression from other parts (not represented) of the molecules at the uppermost of the two groups attached to ring nitrogen or carbon.

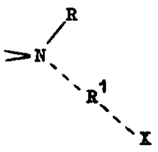
In protonation of carbanions (6), analogous to quaternisation of tertiary bases, the much smaller effective bulk of incoming hydrogen in comparison with that of the other group R in formulae (I) and (II) will ensure that the preferred configuration of product, formed *via* transition state (II), corresponds to the preferred conformation of the carbanion even if (as one may suppose) configurational inversion of the carbanion is faster than protonation. In the quaternisations, however, the effective bulks of the group R and the partly attached R^1 (formulae III and IV) are more comparable. For primary alkyl groups at any rate the most important relevant consideration is not the difference (small) between the inherent effective bulks of the alkyl groups when fully attached to nitrogen (as e.g. in the actual quaternary salts) but the difference between fully bonded R and partly bonded R^1; the latter contains 5-co-ordinate carbon and is more highly solvated, but it is less rigidly attached to nitrogen. The balance of these factors is such that in many cases where the ring itself in the



(I)



(II)



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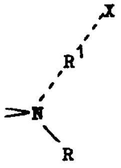
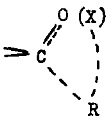
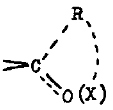


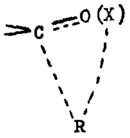
(IV)



(V)



(VI)



(VII)

vicinity of the nitrogen atom is not too rigid, transition state (IV), corresponding to attack in the more hindered of the two relevant space segments around nitrogen, has a lower free energy than (III).

In tropanes, however, where the heterocyclic ring is more rigid in the area of the nitrogen atom, the opposite result is obtained. When R^1 has less inherent effective bulk than R, higher stereoselectivity has been observed (1) for several quaternisations of the type where transition state (IV) is preferred, and indeed such a result has been (cautiously) used for providing empirical support for a decision about the preferred direction of attack in the quaternisations - but evidently the same result could in principle also be obtained for a quaternisation where transition state (III) is preferred.

Transition states (III and IV; R = Me; R^1 = Et), and the corresponding pair (not represented) with R and R^1 reversed, also serve to illustrate the nucleophilic displacements with hydride and thiophenate discussed above. The observed results are intelligible on the reasonable assumption that the free-energy difference between epimeric reactants is smaller than that between corresponding epimeric transition states.

We illustrate also transition states for nucleophilic additions to (a) moderately (or slightly) (epimers V and VI) and (b) strongly (VII) hindered cyclic ketones, partly to indicate the stereochemical analogy between additions of the former category and the quaternisations (in spite of considerable mechanistic differences) and partly because it is difficult to find a clear statement of the fundamental relevant principles in the literature. In formulae (V - VII), X represents a possible co-ordinating group which may be present in the transition states for e.g. Grignard additions or reduction with complex metal hydrides, and the dotted line between R and X represents a possible union which does not, however, affect the argument. Neither is this affected by consideration of whether the important transition states in certain reactions of hindered ketones are those leading to intermediate adducts or to the final products; usually, one may suppose, the latter will be the case, but there is little conclusive information about the detailed mechanisms of many common ketone addition reactions. The important point is that in highly hindered ketones the critical transition state will preferably be of type (VII) for most nucleophilic additions: the ring carbon atom of the carbonyl group will have its three fully bonded groups in nearly the same trigonal disposition as in the reactant ketone, with the incoming nucleophile more remotely attached on the less hindered flank. Both oxygen and nucleophile thus avoid the highly hindered segment (topside of formula VII). In less strongly hindered ketones a more tetrahedral arrangement of groups around the carbonyl carbon is possible in the transition states (V) or (VI), the stereochemical outcome of the addition being determined by the relative effective bulks of O(X) and partly attached R. The theoretical analogy with factors controlling the stereochemistry of the quaternisations discussed above is evident.

We thank the Department of Scientific and Industrial Research for a Maintenance Grant (to J.W.).

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