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ASYMMETRIC INDUCTION IN PHASE TRANSFER CATALYZED REACTIONS: A COMMENT ON A STRUCTURAL FEATURE OF THE CATALYST

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Recently, several groups have expressed interest in employing chiral catalysts in phase-transfer reactions in order to achieve absolute asymmetric syntheses.[1] The attractiveness of this "pseudo-enzymic" process is obvious. The purpose of this communication is to point out one factor which does not seem to have been specifically recognized and which bears on the question of catalyst structure.

The nature of phase-transfer catalysts and their function is well-established. Typically, the anion of a quaternary ammonium salt which possesses some lipophilic character reacts in the organic phase with an organic substrate in an acid-base or nucleophile-electrophile sense. When asymmetric reactions are considered, three distinct approaches can be envisioned: viz. the use of a chiral salt where a) the chirality is contained in the carbon skeleton of the salt, b) the nitrogen atom of the salt is itself chiral, or c) a combination of a) and b). The majority of the published work has centred on a) due largely to the ready availability of suitable chiral salts derived from ephedrine, etc.[1] Approach c) has been most successfully employed by Wynberg and co-workers[2] in their use of salts derived from quinine and related alkaloids. To my knowledge, no examples of method b) have been reported, but it has been pointed out that the greatest effect may well be expected when the existing chirality in the salt is centred on nitrogen.[1] When questions concerning the nature of diastereomeric transition states must be answered, reactions catalyzed by salts containing only chiral quaternary nitrogen atoms must be investigated. In the following, I will show that simple chiral tetraalkylammonium salts must be incapable of producing a significant amount of asymmetric induction.

The reason for this lies in the basic difference between the reaction of a nucleophile (base) X^- which is incorporated into a tight ion-pair with a chiral ion A^+, and that of a nucleophile (base) Y^- which is bonded to the chiral centre. In the latter case, the nucleophilic centre exists on the apex of a tetrahedron and the spatial arrangement of the atoms is invariant. The chiral centre is thus fully described by the R,S method.[3] In the former case, X^- must be associated with one of the four faces of the tetrahedron and is free to change its associated face in solution. Therefore, although a resolved ammonium cation may be described by the R,S method, in the reacting system, the asymmetric effect of that cation on the developing asymmetry in the substrate must depend upon the face of the tetrahedron with which X^- is associated (assuming the four ion-pairs react at approximately equal rates). This is illustrated in Fig.1 for a nucleophilic addition reaction.

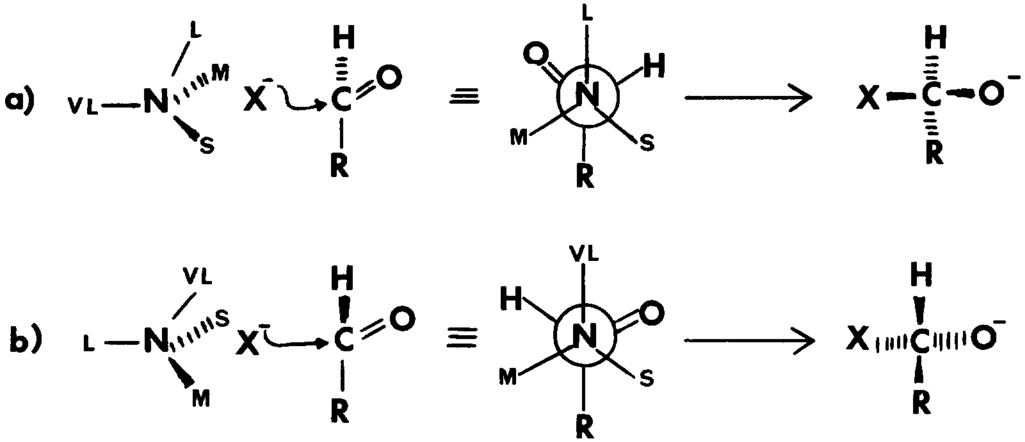

Figure 1

In Fig.1, an asymmetric ammonium cation possessing the S-configuration (for priorities VL>L>M>S) is shown. The three substituents on the salt, which are presented to the reacting substrate, may describe either an R sequence (eq.a) or an S sequence (eq.b). In view of the expected mobility of the anion X^-, significant induction can only be expected when very tight ion pairs are involved (to maximize the interaction of substrate and cation) and using cations whose structures preclude association of X^- with more than one face of the tetrahedron. Ammonium salts meeting this requirement are not common. For example, inspection of models shows that quincludine type bases have one tetrahedral face completely blocked, but the other three are relatively free and open. We are currently investigating the synthesis of salts which fulfill these requirements and hope to report our results in the near future.[4]

References:

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