Efficient Catalytic Asymmetric Alkylations. 1. Enantioselective Synthesis of (+)-Indacrinone via Chiral Phase-Transfer Catalysis

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Received September 26, 1983

Efficient asymmetric alkylation reactions have been a long-sought goal in organic synthesis. The recent literature[1] reports elegant three-step sequences to achieve high enantiomeric excesses (ee's); however, these procedures are complex and require the use of stoichiometric quantities of chiral auxiliaries. Chiral phase-transfer-mediated alkylations offer a potentially simple, one-step solution to this problem. The first reports[2] of such using cyclic β-keto esters as substrates and ephedrinium halides as catalysts claimed ee's of only 15%. These results have subsequently been disputed.[3]

We wish to report the first efficient, catalytic, enantioselective alkylation in the asymmetric synthesis of the new uricosuric (+)-indacrinone (**5**) (MK-0197)[4] via chiral phase-transfer catalysis. Methylation of 0.61 g of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (**1**)[4a] with 0.7 g of CH_3Cl in toluene/50% aqueous NaOH (25 mL/5mL) using 0.11 g of *N*-(*p*-(trifluoromethyl)benzyl)cinchoninium bromide as phase-transfer catalyst at 20 °C for 18 h produced (*S*)-(+)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (**2**) in up to 92% ee in 95% yield.[5] Subsequent O-demethylation ($AlCl_3$, toluene, 45 °C), giving **3**, followed by O-alkylation with ethyl chloroacetate (K_2CO_3, NaI, toluene, reflux), giving **4**, hydrolysis (toluene, NaOH, reflux), acidification (HCl), and crystallization (CH_2Cl_2) afforded the S-(+)-enantiomer[4d] of **5** in 63% isolated yield (overall from **1**), identical in all respects with resolved material[4a,d] (Scheme I).

Preliminary work with *N*-alkyl derivatives of the various cinchona alkaloids[6] readily established *N*-benzylcinchoninium chloride (BCNC) as potentially one of the most effective catalysts, although ee's were in the modest range (20–30%). Subsequent development of the reaction with respect to each of the reaction variables proved critical to the success of the chiral phase-transfer approach.

In general, nonpolar solvents such as toluene or benzene produced higher ee's than polar solvents such as methylene chloride or methyl *tert*-butyl ether.[7] Higher dilution favored higher ee's. Increasing NaOH concentrations also improved the selectivity with

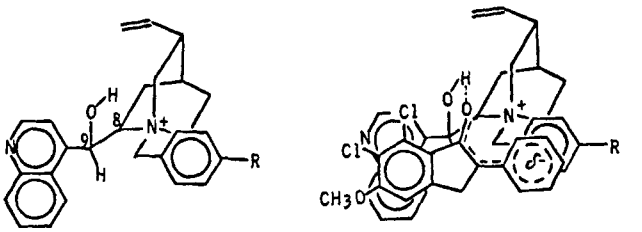
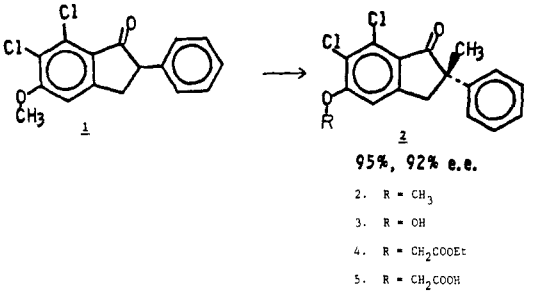


Figure 1. Ion pairing between indanone anion and benzyl cinchoninium cation.

Scheme I



50% aqueous NaOH giving the best results. Excellent agitation was crucial. The catalyst concentration (10–50 mol % range) controlled the rate of reaction but had little effect on the ee. As catalyst counterion, chloride and bromide produced similar results, whereas iodide decreased the ee substantially. As alkylating agent CH_3Cl gave by far the best selectivity relative to CH_3Br or CH_3I. The concentration of CH_3Cl and the reaction temperature had a profound effect on the asymmetric induction. A decrease of the temperature from 25 to 15 to 5 °C at constant CH_3Cl concentration (14 mol/mol of **1**) increased the ee from 78% to 84% to 90%, respectively. However, at the lower temperature the rate of reaction decreased substantially. A decrease of the CH_3Cl concentration from 14 to 7 mol/mol of **1** at 15 °C improved the ee from 84% to 96%.[5b]

CPK molecular models, the single-crystal X-ray structure, and molecular modeling studies of benzylcinchoninium ion suggest that a preferred conformation may be that in which the quinoline ring, the C_9–O bond, and the *N*-benzyl group all lie in one plane (plane of the paper, Figure 1). The quinuclidine ring lies behind the plane. The anion of **1** also has an almost planar structure with the negative charge delocalized into the 2-phenyl ring. Both molecules in their nearly planar conformations fit naturally on top of each other providing π-interaction between the benzyl group of the catalyst and the 2-phenyl group of **1** on the one side and between the quinoline and 3-methoxydichlorobenzene moieties on the other. The C_9-hydroxyl provides a directional handle for the ionic attraction via hydrogen bonding to the indanone anion. The CH_3Cl can only alkylate from the front side and form the (*S*)-(+)-2-methylindanone.

If ion pairing such as depicted in Figure 1 is important, then the asymmetric induction should be sensitive to the electronic effects of substituents on the *N*-benzyl group. Indeed, we have found that other groups (CH_3O, CH_3, F, Cl) give ee's in the range of 60–80%. A Hammett plot of log ee/ee$_o$ vs. the substituent constant σ of the para *N*-benzyl substituted catalysts[6] gave a reaction constant of $\rho = 0.21 \pm 0.02$ demonstrating that substituents with increasing electron-withdrawing power improve the catalyst selectivity.

In summary, we have demonstrated the first truly catalytic and efficient enantioselective alkylation mediated by a chiral phase-transfer catalyst. In addition to catalyst design, fine tuning of all of the reaction variables has proven crucial to the success of the system. The scope and mechanism of this reaction are under intense investigation and will be presented in detail at a later date.

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(5) (a) Authentic **2** was prepared from **3** (ref 4b) by methylation with CH_3I/K_2CO_3 in refluxing acetone; mp 123–124 °C, $[\alpha]^{25}_D$ +76.4° (c 1, acetone). (b) The highest ee of 96% was observed at a conversion of 40%. (c) Determination of ee by NMR, $CDCl_3$, tris[3-((heptafluoropropyl)-hydroxymethylene)-*d*-camphorato]europium(III). (d) The absolute configuration of **5** was determined by single-crystal X-ray structure analysis. The data will be published in combination with a forthcoming full paper.

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0002-7863/84/1506-0446$01.50/0

Acknowledgment. We thank Dr. Peter Gund and Dr. Graham Smith for helpful discussions and molecular modeling studies on the indanone and benzylcinchoninium chloride catalyst. We also thank Dr. James Springer for the X-ray analyses of BCNC and **5**.

Is Tetramethylene an Intermediate?

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Received April 25, 1983

We present computational evidence that singlet tetramethylene is an entropically bound intermediate. Our calculations suggest that it exists in an entropy-dominated free energy minimum *even though it lacks a potential energy minimum.*

Gas-phase pyrolysis results[1-6] indicate that tetramethylene derivatives are short-lived intermediates shared in common among several modes of generation (via diazenes,[3-5] cyclobutanes,[2] and olefin dimerizations[6]) and which undergo competitive cyclization, fragmentation to olefins, and loss of stereochemistry at the radical centers. This picture is largely supported by the seminal ab initio calculations of Segal.[7] Using a 15-configuration wave function and the STO-3G basis set,[8] he found that the gauche (**1**) and anti (**2**) conformers are both local minima on the singlet tetramethylene potential energy surface.[7] We have recently found[9] that the gauche minimum is an artifact of the STO-3G basis set. With a split-valence 3-21G basis set[10] and a two-configuration MCSCF wave function, only **2** survives as a local minimum.[9]

As Segal[7] has indicated, however, a two-configuration wave function gives a poor description of the fragmentation to two ethylenes. This is because of the additional unpairing of the electrons in the central C–C bond. We have thus reexamined the tetramethylene surface using 3-21G and a four-electron four-active-orbital CASSCF[11] wave function. This MCSCF wave function contains the 20 configurations corresponding to full CI with four electrons and four orbitals.

We find that **1** cyclizes and **2** fragments with no potential energy barrier. Extensive searches in other regions of our surface indicate that there are *no minima* in the biradical region of singlet tetramethylene. Two saddle points were located and characterized by force constant calculations, one for the cis–trans isomerization of cyclobutane and the other, 1.3 kcal/mol lower, for fragmentation to ethylenes.[12] Relative to cyclobutane as the zero of energy, the respective potential energies of two ethylenes and the fragmentation saddle point are 2.3 and 52.8 kcal/mol. Experimental $\Delta\Delta H_f°$ values[13] relative to cyclobutane are 18.8 and 61.8 kcal/mol, respectively. Our predicted absence of a biradical minimum is consistent with Doering's[13] recent thermochemical estimate of the depth of the tetramethylene enthalpy well of 2.0 ± 1.5 kcal/mol.

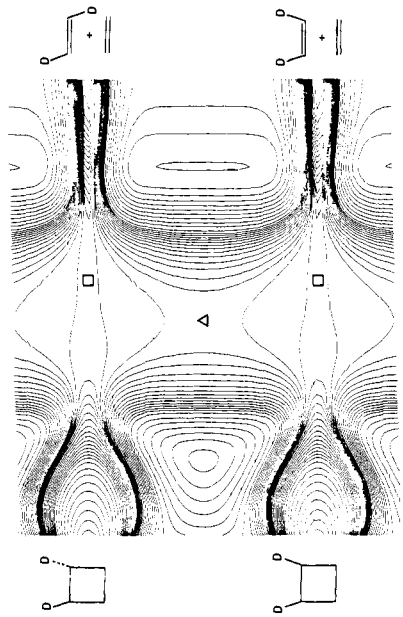

Figure 1. Contour plot of a projection of the full 30-D surface onto a 2-D subspace consisting of a CH_2 twist angle (vertical axis) and a distance parameter (horizontal axis). Squares and triangles mark the saddle points for fragmentation and cis–trans isomerization, respectively.

Our results (details to be reported later) yield a picture of tetramethylene as a broad, flat plateau region of the C_4H_8 potential surface. This is remarkably similar to Hoffmann's[14] extended Huckel results, which led to his twixtyl model. However, our results also show an additional feature that is crucial to a twixtyl-type model of a common intermediate. Along a reaction path proceeding from either saddle point toward a product, two effects occur: the potential energy is lowered and the loose modes (especially the internal rotations and terminal methylene wagging) become tighter. The tightening implies a decrease in entropy as the product starts to form. If the decrease in potential energy is not too great, the entropy reduction can give rise to a free energy barrier to product formation. In the language of canonical variational transition-state theory,[15] the transition state connecting tetramethylene with either product is shifted away from the saddle point to the point where the free energy is maximized along the reaction path. In this model tetramethylene exists as an entropy-locked species.

As a first step toward a rigorous examination of this hypothesis we have calculated an additional force constant matrix at a geometry (**3**) corresponding to incipient cyclization—a gauche conformation with the p orbitals pointing toward one another and a C_2 symmetry axis through the central C–C bond. The potential energy of **3** is 1.0 kcal/mol below the cis–trans saddle point. Nevertheless the free energy of **3**[16] is higher than the free energy at either saddle point. As expected, this is due to tightening the loose modes. Compared to the cis–trans saddle point, the free energy of **3** is higher by 4.1, 2.9, and 2.3 kcal/mol at 700, 500, and 300 K, respectively. This clearly supports the hypothesis of an entropy-dominated free energy minimum. However, these are preliminary conclusions and are by no means proven. We also point out that although the four-electron four-orbital CASSCF wave function is capable of an evenhanded description of the entire

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