

# Stereospecific 1,3-H Transfer of Indenols Proceeds via Persistent Ion-Pairs Anchored By $\text{NH}\cdots\pi$ Interactions

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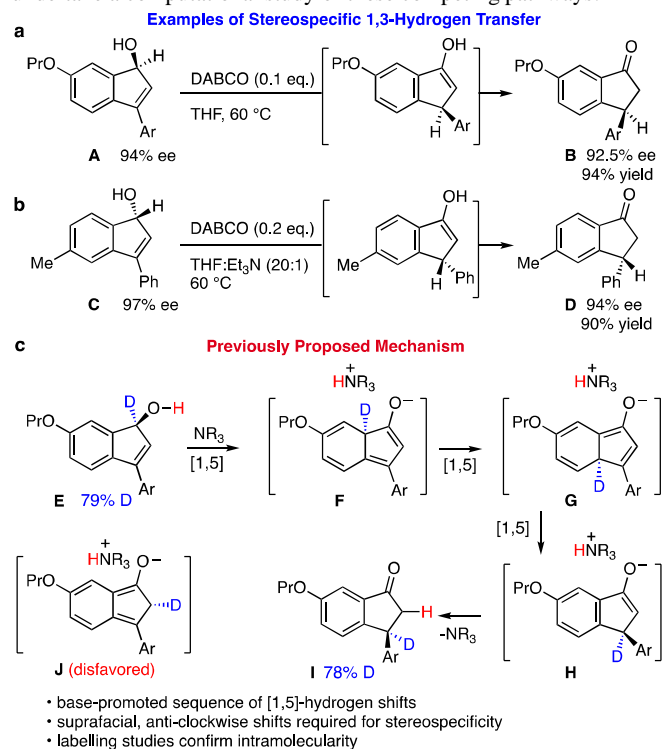
**Abstract:** The base-catalyzed rearrangement of arylindenols is a rare example of a suprafacial [1,3]-hydrogen atom transfer. The mechanism has been proposed to proceed via sequential [1,5]-sigmatropic shifts, which occur in a selective sense and avoid an achiral intermediate. A computational analysis using quantum chemistry casts serious doubt on these suggestions: these pathways have enormous activation barriers and in contrast to what is observed experimentally, they overwhelmingly favor a racemic product. Instead we propose that a suprafacial [1,3]-prototopic shift occurs in a two-step deprotonation/reprotonation sequence. This mechanism is favored by 15 kcal mol<sup>-1</sup> over that previously proposed. Most importantly, this is also consistent with stereospecificity since reprotonation occurs rapidly on the same  $\pi$ -face. We have used explicitly-solvated molecular dynamics studies to study the persistence and condensed-phase dynamics of the intermediate ion-pair formed in this reaction. Chirality transfer is the result of a particularly resilient contact ion-pair, held together by electrostatic attraction and a critical  $\text{NH}\cdots\pi$  interaction which ensures that this species has an appreciable lifetime even in polar solvents such as DMSO and MeOH.

**Introduction:** Thermally activated, concerted suprafacial [1,3]-hydrogen atom transfers, while geometrically plausible, are forbidden by orbital symmetry.<sup>1</sup> Chemists' attention has therefore turned to the catalysis of formal [1,3]-allylic rearrangements in a stepwise fashion.<sup>2</sup> Given their stepwise nature, such reactions need not be stereospecific. Chiral catalysts can be used to control product stereoselectivity and asymmetric examples of olefin isomerization have been reported.<sup>3</sup> However, examples of stereospecific [1,3]-allylic rearrangements showing complete suprafacial transfer of reactant chirality to product are rare.<sup>4,5</sup>

Working toward the synthesis of endothelin receptor antagonists based on an indane scaffold, researchers at SmithKline Beecham discovered the stereospecific [1,3]-allylic rearrangement of chiral 3-aryindenols in 1998 (**Figure 1a**, transformation **A** to **B**).<sup>6</sup> Formally a suprafacial [1,3]-hydrogen atom transfer, this rearrangement is catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) with almost complete retention of chirality. Andersson applied this method in the asymmetric total synthesis of (*R*)-Tolterodine, treating indenol **C** with DABCO in THF at reflux to form the indanone **D**, again with almost complete chirality transfer (**Figure 1b**).<sup>7</sup> These transformations are highly stereoselective, as well as stereospecific, since the product absolute configuration results from the reactant's stereochemistry. They with stereospecific Aryl-indenol substrate (**E**) <sup>2</sup>H-labelled at C1 reacts under the same conditions with complete deuterium transfer to the C3 position (**I**), confirming the intramolecular nature of this rearrangement. The same outcome is obtained in the absence of light, ruling out a photochemical transformation. On the basis of these results the reaction mechanism has been proposed<sup>6</sup> to proceed via a sequence of three thermally-allowed suprafacial [1,5]-H shifts (**Figure 1c**), each of which are accelerated by alcohol deprotonation by the amine base. To account for the stereospecificity and complete deuterium transfer to C3, these [1,5]-shifts must occur selectively in the (anti-clockwise as drawn) direction shown, via intermediates **G** and **H**. This is a necessary requirement, since a [1,5]-sigmatropic shift in the opposite (clockwise from the viewpoint of Figure 1) sense would result in intermediate **J**, which would lead to incomplete [1,3]-deuterium transfer since a [1,5]-H atom shift will also occur. A primary kinetic isotope effect would further reduce the likelihood of the [1,5]-deuterium shift required to form **I**. Furthermore, for unlabeled substrates **A** and **C**, the clockwise pathway (**E**→**J**) results in an achiral intermediate, inconsistent with the observed stereospecificity.

The proposed mechanism for the tertiary amine base-catalyzed [1,3]-rearrangement of arylindenols requires sigmatropic shifts to

occur selectively in anti-clockwise (as depicted in **Figure 1c**) sense, avoiding intermediate **J**. However, the preferred pathway involves a disruption of benzene's 6 $\pi$ -aromaticity (i.e., in intermediates **F** and **G**) and there appeared (at least to us) no obvious reason why anti-clockwise rotation should be strongly favored. This prompted us to undertake a computational study of these competing pathways.



**Figure 1** | The stereospecific [1,3]-allylic rearrangement of 3-aryindenols (a) reported by SmithKline Beecham;<sup>6</sup> (b) by Andersson;<sup>7</sup> (c) results of <sup>2</sup>H-labelling studies and mechanism proposed in the literature.

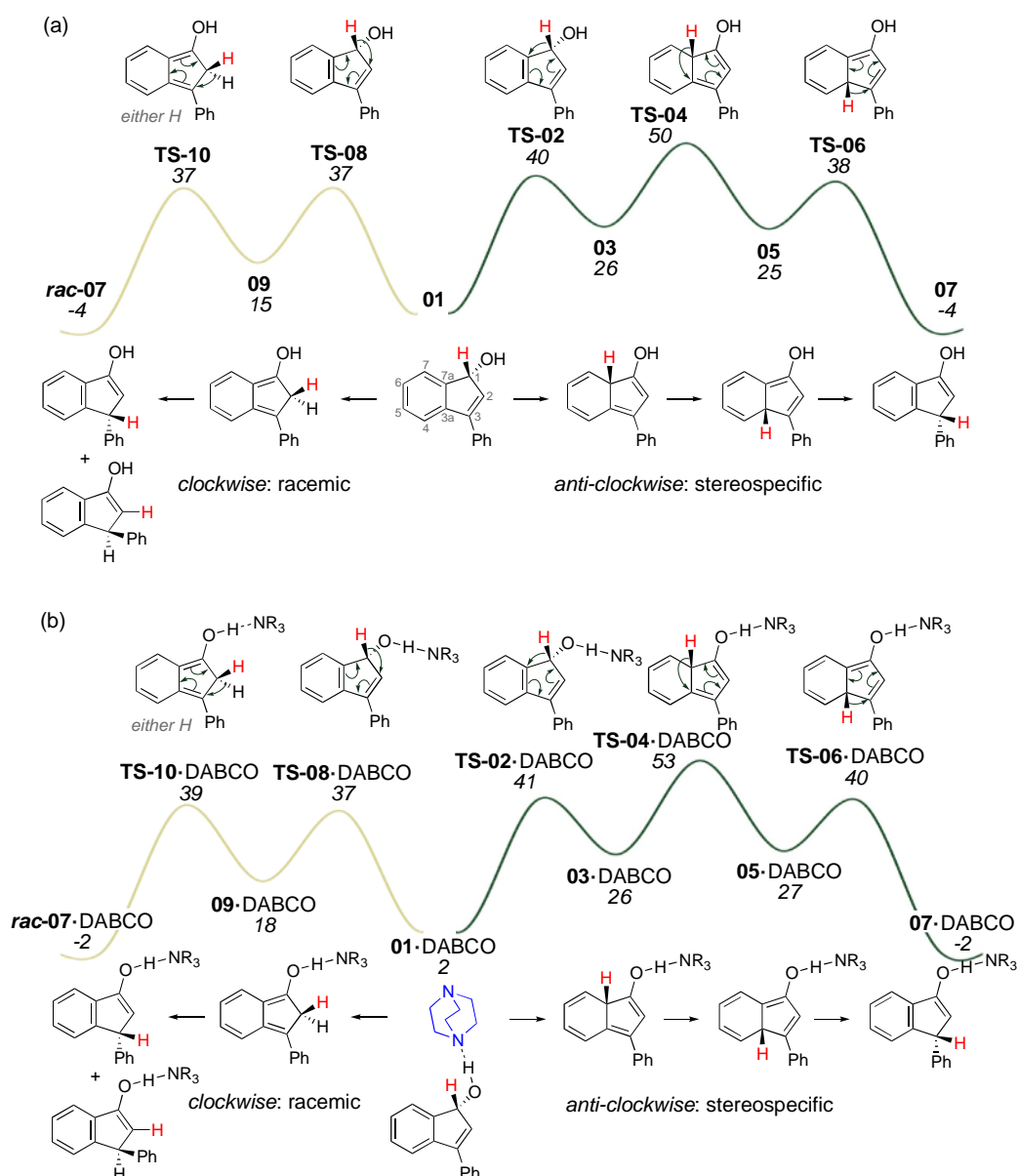
Using both quantum chemical (QM) calculations and classical molecular dynamics (MD) simulations we demonstrate that the proposed pericyclic mechanism for the [1,3]-allylic rearrangement of chiral 3-aryindenols is unfeasible and occurs in a sense which is inconsistent with stereospecificity. We find an alternative mechanism which is contrary to previous proposals: a deprotonation/reprotonation pathway which is kinetically viable, consistent with labelling studies, and

accounts for the stereochemical outcome. Chirality transfer requires the formation of a contact ion-pair between substrate and base; the persistence of which we have studied by explicitly solvated molecular dynamics simulations. An  $\text{NH}\cdots\pi$  noncovalent interaction between aromatic carbanion and ammonium counterion results in a persistent ion-pair in solvents across a range of polarities, preserving chiral information.

**Results and Discussion:** We began our study by exploring the thermally-allowed suprafacial [1,5]-H shifts mechanism (**Figure 1c**) proposed in the literature,<sup>6</sup> using quantum chemical calculations. We optimized structures at the M06-2X/6-311++G(d,p) level of theory for which single point energies were obtained with domain-based local pair-natural orbital coupled-cluster theory, at the DLPNO-CCSD(T)/ma-def2-TZVP level including an implicit (SMD) description of THF solvent.<sup>8</sup> Gibbs energies are reported at 60 °C relative to a standard state of 1M using a quasi-RRHO treatment,<sup>9</sup> without any *ad hoc* corrections to the translational entropies.<sup>10</sup> We have assumed that the final enol-keto tautomerization step is relatively facile and have not explicitly calculated mechanisms for this final step. In gen-

eral, the comparison of computed mechanisms should be done with some caution, particularly where charged species are concerned. For example, errors up to 5 kcal mol<sup>-1</sup> with respect to experiment have been suggested for a similar methodology to that employed here.<sup>11</sup> As we describe below, our conclusions are based on Gibbs energy differences between competing mechanisms of 15 kcal mol<sup>-1</sup> and larger, while the previously proposed mechanism also predicts the wrong stereochemical outcome by more than 13 kcal mol<sup>-1</sup>. We consider these differences to be significant enough on which to base firm conclusions.

The computed pericyclic mechanisms of arylindenol **01** in the absence of DABCO confirmed our suspicions that the postulated [1,5]-sigmatropic shifts are very unlikely indeed (**Figure 2a** and **Figure S1**). The highest barrier is 50 kcal mol<sup>-1</sup> in an anti-clockwise sense (**TS 04**) and 37 kcal mol<sup>-1</sup> in a clockwise sense (**TS 08**). These barriers are extremely high. More importantly, the racemic pathway is favored overwhelmingly, by 13 kcal mol<sup>-1</sup>. The tertiary amine catalyst would need to overturn this substantial innate selectivity in order to promote a stereospecific transformation, as occurs experimentally.



**Figure 2** | SMD(THF)-DLPNO-CCSD(T)/ma-def2-TZVP/M06-2X/6-311++G(d,p) Gibbs energy (kcal mol<sup>-1</sup>) profiles at 60 °C and a standard state of 1 mol l<sup>-1</sup>, comparing sequential [1,5] H-shifts in an anti-clockwise, stereospecific manner (in green) and clockwise, unselective manner (in gold) for (a) uncatalyzed and (b) DABCO-promoted pathways.