TS-torquoselectivity from global conformational profile

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Abstract: From the global conformational profile and differential activation free energies of conrotatory outward and inward ring openings of all the conformers, it is shown that (a) 3-OMe-cyclobutene must open exclusively outward and (b) conformers exist for 3-CHO- and 3-COMe-cyclobutenes that will open outwards as well. All the conformers of 3-OMe-, 3-CHO- and 3-COMe-cyclobutenes are, respectively, within 5.6, 3.2 and 4.0 kcal/mol and, hence, abundantly available under the reaction conditions. 3-OMe-cyclobutene is experimentally known to open exclusively outward. 3-CHO-cyclobutene opens > 98% inward and < 2% outward. In contrast with 3-CHO-cyclobutene, 3-COMe-cyclobutene furnishes a 3:2 mixture of the outward and inward products, respectively.

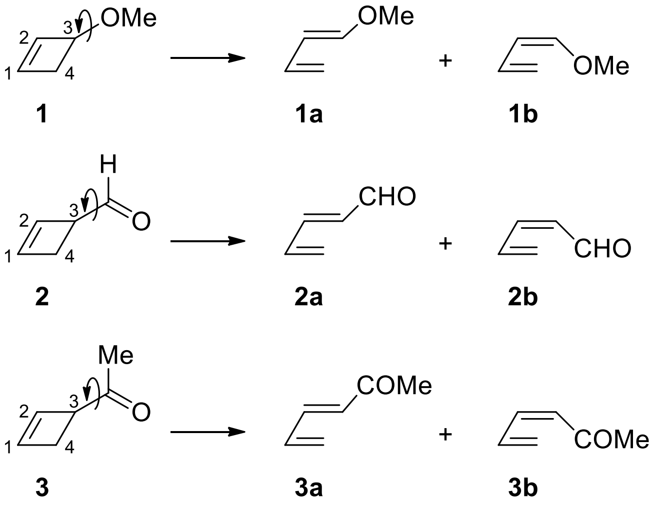
KEYWORDS: torquoselectivity, global conformational profile, global activation energy profile

Introduction. It is not necessary that only the most stable conformer of a reactant be considered to understand the stereochemical outcome as it is usually done in most computational studies. This is so because chemical reactions are controlled by orbital interactions in the transition state (TS) structures and the best orbital interactions arise from antiperiplanar bonds of complementary nature.[1] The interaction is of Lewis acid and Lewis base type, *i.e.*, one of the two interacting bonds is electron-rich and the other electron-poor. Under thermal conditions, a molecule can adopt many rapidly equilibrating conformations and some or several higher lying conformers may even react better than the most stable conformer for being energetically closer to the TS structure for having better bond alignments.

For an effective $\sigma \rightarrow \sigma^*$ interaction, the two σ bonds must be antiperiplanar to each other. Likewise, for the $\sigma \rightarrow \pi^*$ interaction, the σ bond is required to be parallel to the *p* orbitals of the π bond. In the category of $n \rightarrow \sigma^*$ interaction, the axis of the lone pair orbital *n* and the σ bond need to be antiperiplanar. This notion has been extremely well demonstrated by the pioneering work of Berson: reactions predominantly took one of the two symmetry-allowed pathways, which though suffered from high steric interactions but benefitted from superior orbital overlap.[2]

3-Substituted cyclobutenes open in conrotatory manner under thermal conditions to form 1,3-dienes with the substituent located on an either *trans*- or *cis*-double bond depending on its electronic character.[3] The selectivity of such a ring-opening, termed *torquoselectivity*, has been predicted by Houk based on the relative TS barriers for outward and inward openings of the most stable conformer.[4] While all the electron-rich and electron-releasing substituents are favored to rotate outwards in agreement with the experiments, such a clear-cut pattern for inward rotation of the electron-deficient and electron-attracting substituents is absent. For instance, the electron-deficient groups such as acetyl (COMe), carbomethoxy (CO_2Me), nitro (NO_2) and trifluoromethyl (CF_3) are predicted for outward rotation against the inward rotations of the formyl (CHO) and nitroso (NO) groups.

An alternate rationale based on Natural Bond Orbital (NBO) interactions in the TS structure has been advanced.[5] The NBO interaction approach predicts all electron-rich and electron-releasing substituents to rotate outwards and electron-deficient and electron-withdrawing substituents inwards. Deviation, if any, from the experimental selectivity was ascribed to reaction equilibration and relative thermodynamic stability of one product over the other.[5i]



We chose to study the effect of global conformational changes in the substituent with respect to the cleaving ring bond as the same has hitherto not been studied. We chose 3-OMe-cyclobutene **1**, 3-CHO-cyclobutene **2** and 3-COMe-cyclobutene **3** for the study. 3-OMe-cyclobutene is experimentally known to exclusively open outward.[4b] 3-CHO-cyclobutene opens > 98% inward and < 2% outward at 25−70 °C.[4d] In explicit contrast to 3-CHO-cyclobutene, 3-COMe-cyclobutene opens both ways and furnishes a 3:2 mixture of the outward and inward opened products, respectively, at the reflux temperature of C_6D_6.[4e,g] While OMe is electron-rich for the presence of lone pairs of electrons, both CHO and COMe are electron-deficient, CHO more than COMe for its better resonance-acceptor strength.[6]

Computational Methods. All the structures, geometry optimizations and TS structure searches were carried out using the global hybrid meta-GGA M06-2X density functional and 6-31G(d) basis set at 298.15 K and 1 atm pressure.[7] The optimized structures were verified as minima or first order saddle points on their potential energy surfaces by harmonic vibrational frequency analysis. All the calculations were carried out using Gaussian 09 suite of programs.[8]

Results and Discussion. The torsion angles of $\sigma_{\text{O-Me}}$ in 3-OMe-cyclobutene and C=O in 3-CHO- and 3-COMe-cyclobutenes with $\sigma_{\text{C3-C4}}$ bond, as shown in structures **1**−**3**, were altered, 10° at a time, beginning with the most stable ground state conformer of each and the resultant optimized for the geometry. This was followed by locating the TSs for inward and outward openings of each conformer in each instance. The results for the three substrates are graphically presented in the Figure.

All the conformers of 3-OMe-, 3-CHO- and 3-COMe-cyclobutenes are, respectively, within 5.6, 3.2 and 4.0 kcal/mol and, hence, abundantly available at room temperature. The concentration of the higher lying conformers will rise on raise in the temperature and, thus, they may exceedingly take part in the reaction. The higher lying conformers may also react faster than low lying conformers for being closer to the TS structure. The cumulative contribution of the higher lying conformers to the overall outcome of the reaction, torquoselectivity in the present instance, is therefore likely to be significant.

From absolutely no cross-over of the activation energy profiles and substantial difference between the outward and inward cleavage reactions, minimum 12 kcal/mol, of 3-OMe-cyclobutene, its overwhelming outward cleavage to *trans*-1-methoxy-1,3-butadiene is guaranteed. This is in accord with the experiments.

Except for a very tiny region on the far left and a reasonably significant region on the right of the activation energy profiles for the reaction of 3-CHO-cyclobutene, the reaction is geared for inward opening for huge margins in the activation energies. The reaction may basically funnel through the conformers in the region, allowing very little chance to the conformers outside to participate. No doubt, the outward opened product is formed < 2% only.

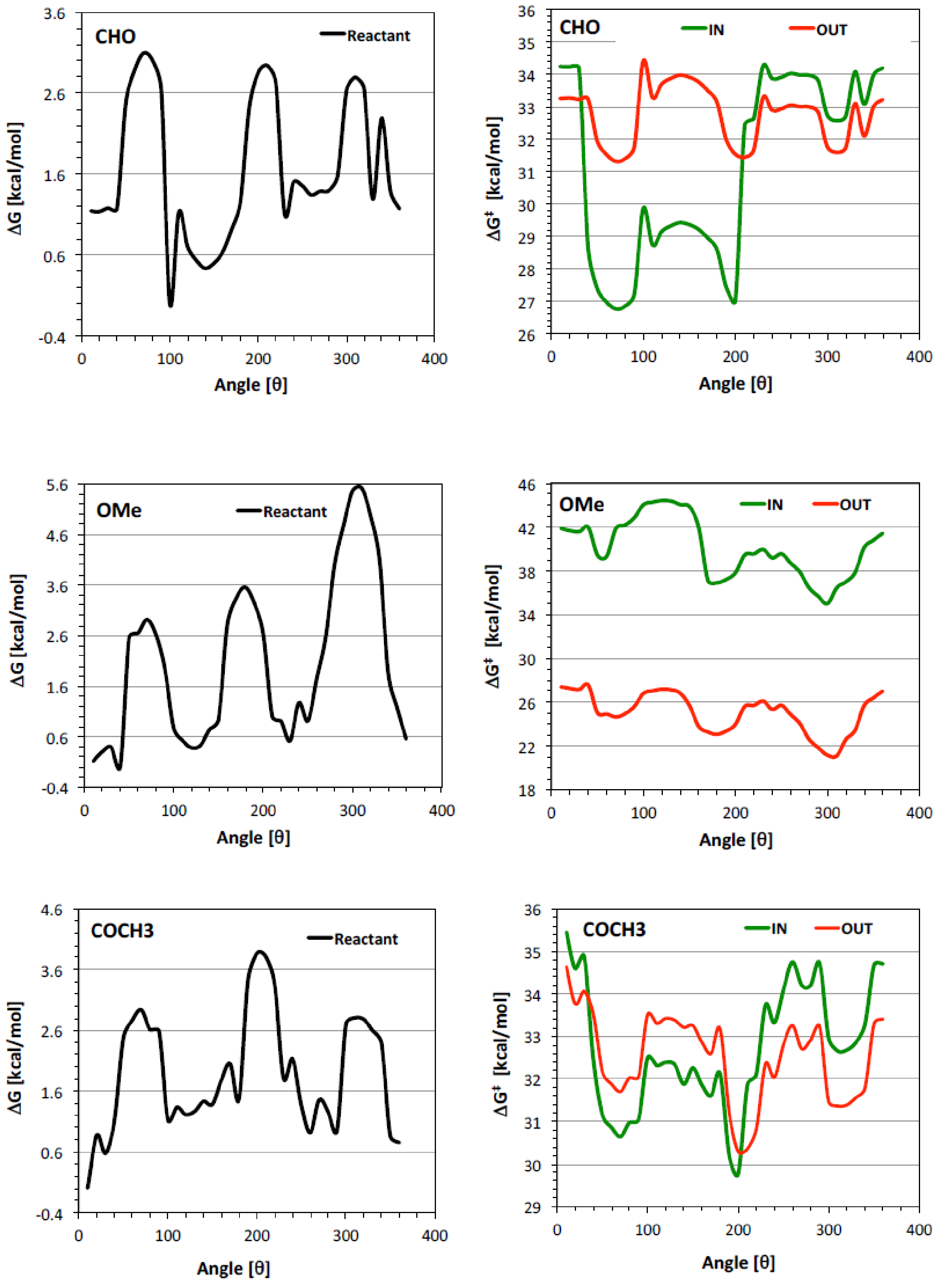


Figure. The global conformational surfaces of 3-CHO-, 3-OMe- and 3-COMe-cyclobutenes (left column) and also the inward and outward opening activation energy profiles (right column)

A good cross over and also significant activation energy differences indicate both inward and outward openings of 3-COMe-cyclobutene. Almost half the conformers appear to open inwards and the other half outwards. 3-COMe-cyclobutene furnishes a 3:2 mixture of the outward and inward opened products at 79 ^oC in C_6D_6. It will be interesting to investigate the conformational profile of 3-COMe-cyclobutene and the corresponding activation energy profiles for outward and inward openings at 79 ^oC to better understand the product distribution.

It is abundantly clear from a comparison of the ground state conformers profile with those of the activation energy profiles that the higher lying conformers react faster than lower lying conformers for the reduced activation energies. Having taken the most stable conformer alone for investigation, one can only predict exclusive inward opening of 3-CHO-cyclobutene and largely outward opening of 3-COMe-cyclobutene by factoring in the differential activation energies and, hence, the kinetic spread of the products.

Conclusions. The study of the global conformational profile and the corresponding activation energies predict exclusive outward opening of 3-OMe-cyclobutene, almost exclusive inward opening of 3-CHO-cyclobutene with very little outward opening, and competitive outward and inward openings of 3-COMe-cyclobutene at 25 ^oC in the gas phase. All the three predictions are in line with the experiments. We plan to carry out this study at elevated temperatures to possibly find a better fit with the experimentally observed product distributions.

The present approach to the analysis of torquoselectivity is first of the kind. The effect of conformational changes on certain other aspects have lately appeared in the literature.[9,10]

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