TS-torquoselectivity from global conformational profile

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Abstract: From global conformational profile and differential activation 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-, 3-COMe-, and 3-NO-cyclobutenes that will open outwards as well. All the conformers of 3-OMe-, 3-CHO-, 3-COMe-, and 3-NO-cyclobutenes are, respectively, within 5.6, 3.2, 4.0 and 2.6 kcal/mol and, hence, abundantly available at room temperature for reaction.

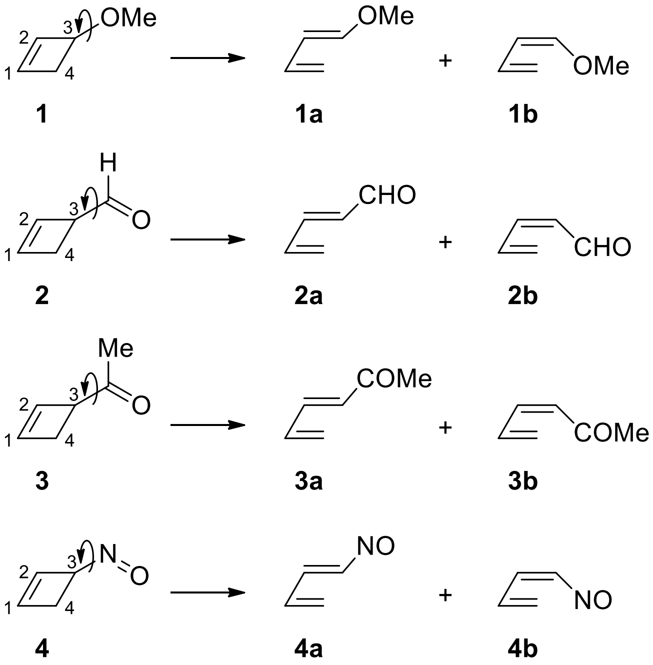
KEYWORDS: torquoselectivity, global conformational profile, global activation energy profile

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 Lewis acid-base type, *i.e.*, one bond is electron-rich and the other electron-poor. A molecule can adopt many rapidly equilibrating conformers and the higher lying conformers may react faster than lower lying, including the most stable, conformers for being energetically closer to TS structure due probably to better bond alignments.

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

3-Substituted cyclobutenes open in conrotatory manner under thermal conditions to form 1,3-dienes with the substituent located on either *trans*- or *cis*-double bond depending upon its electronic etiquette.[3] The selectivity of such a ring-opening, termed torquoselectivity, has been predicted by Houk based on the relative activation barriers for outward and inward openings of a stable ground state conformer.[4] While all the electron-rich and electron-releasing substituents are favored to rotate outwards in excellent agreement with the experiments, such a clear-cut pattern for inward rotation of 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 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 due to reaction equilibration and relative 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 on torquoselectivity as the same has hitherto not been studied. We chose 3-OMe-cyclobutene **1**, 3-CHO-cyclobutene **2**, 3-COMe-cyclobutene **3** and 3-NO-cyclobutene **4** 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] The experimental selectivity of 3-NO-cyclobutene has not been reported. However, it has been predicted by Houk to open inward. 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] Likewise, NO is also electron-deficient.[6]

Computational Methods. All the 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 K and 1.0 atm pressure.[7] The optimized structures were verified as minima or first order saddle points by harmonic vibrational frequency analysis. The energies reported herein are Gibbs Free Energies [Sum of electronic and thermal Free Energies]. All the calculations were carried out using Gaussian 09 suite of programs.[8]

Results and Discussion. The torsion angles of $\sigma_{O\text{-}Me}$ in 3-OMe-cyclobutene, C=O in 3-CHO- and 3-COMe-cyclobutenes and N=O in 3-NO-cyclobutene with $\sigma_{C3\text{-}C4}$ bond, as shown in structures **1**–**4**, were altered, 10° at a time, beginning with a stable ground state conformer of each and the resultant optimized for the geometry. This was followed by locating the TS structures for inward and outward openings of each conformer in each instance. The results for the three substrates are graphically presented in Figure 1.

All the conformers of 3-OMe-, 3-CHO-, 3-COMe- and 3-NO-cyclobutenes are, respectively, within 5.6, 3.2 and 4.0 kcal/mol and, hence, abundantly available at room temperature. The concentrations of higher lying conformers will rise on raise in temperature. Further, a higher lying conformer may react faster than a low lying conformer for being closer to the TS structure. The cumulative contribution of 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 of 3-OMe-cyclobutene, minimum 12 kcal/mol, its overwhelming outward cleavage to *trans*-1-methoxy-1,3-butadiene is guaranteed. This is in excellent agreement with Houk's prediction by considering a lone conformer.

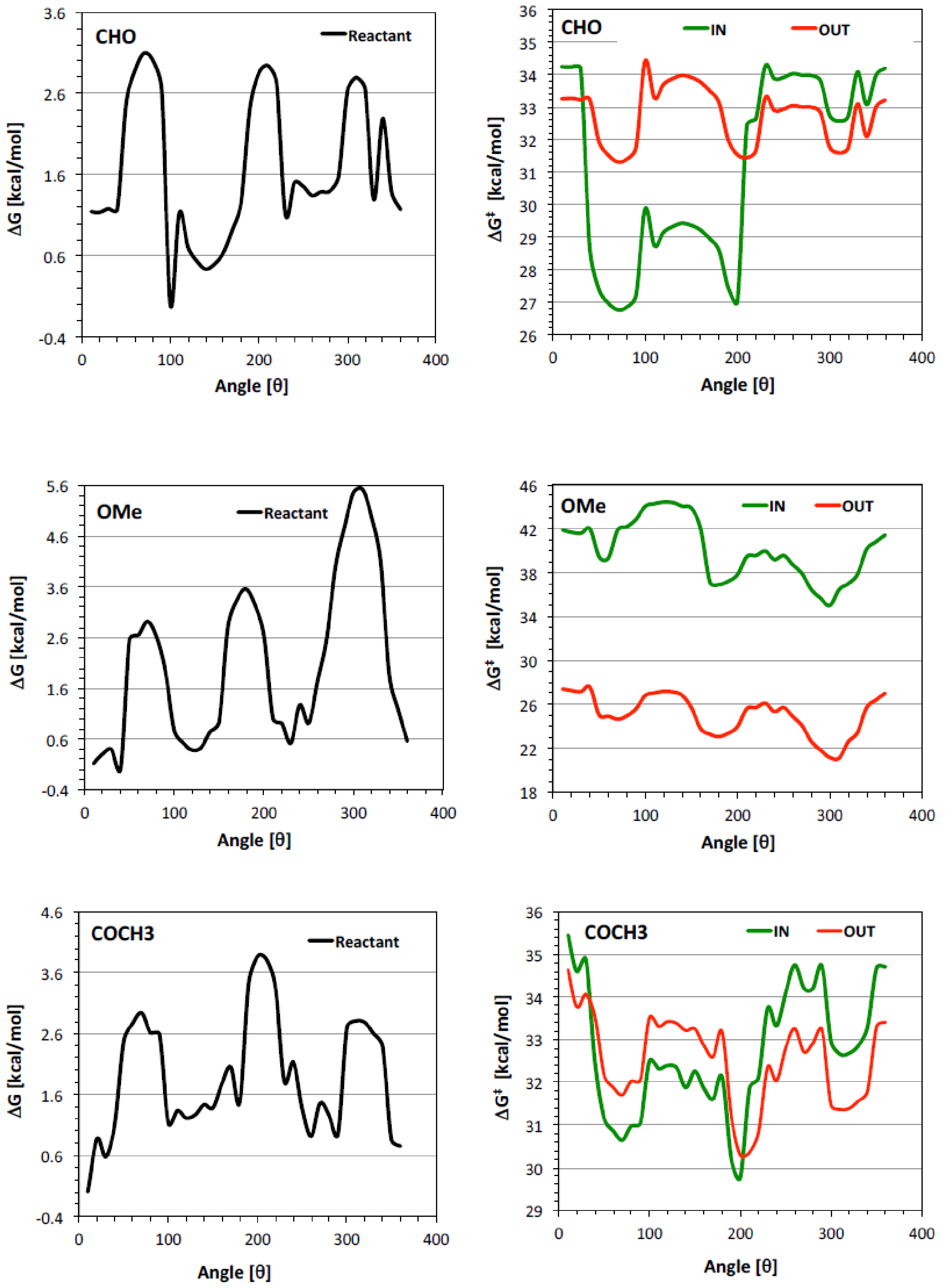


Figure 1. The global conformational surfaces of 3-CHO-, 3-OMe- and 3-COMe-cyclobutenes (left column) and also the inward and outward opening activation energy profiles (right column) at 1 atm and 298 K.

Except for a tiny region on the far left and reasonably significant region on the right end of 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 this region, allowing only a small scope to the conformers outside to participate. No wonder, the outward opened product is formed to the extent of < 2% only.

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 ^{o}C in C_6D_6. It will be interesting to investigate the conformational profile of 3-COMe-cyclobutene and the corresponding activation energy profiles for ring openings at 79 ^{o}C under the solvent effects of C_6D_6 to understand the product distribution.

Houk predicted outward rotation of NO group in the ring opening of 3-NO-cyclobutene. However, from global conformational analysis of the reactant and activation energy profiles given in Figure 2, it is clear that approximately half the conformers are poised for inward rotation. Significantly, all the substrate conformers are within 2.6 kcal/mol and, hence, abundantly available for reaction at room temperature.

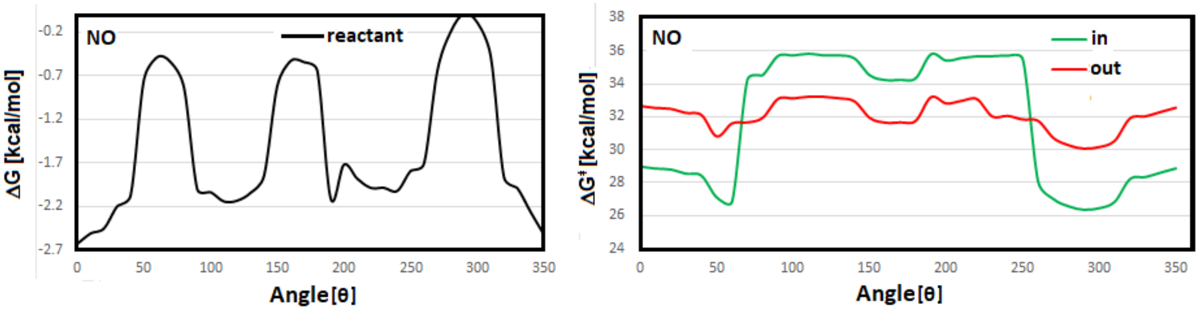


Figure 2. The global conformational surface of 3-NO-cyclobutenes (left column) and the inward and outward opening activation energy profiles (right column) at 1.0 atm and 298 K

A comparison of ground state conformers profile with corresponding activation energy profiles also shows that higher lying conformers react faster than lower lying conformers for reduced activation barriers. Having taken the most stable ground state conformer alone for investigation, one would predict exclusive inward openings of 3-CHO- and 3-NO-cyclobutenes, outward opening of 3-OMe-cyclobutene, and approximately 50:50 opening of 3-COMe-cyclobutene.

Conclusions. The study of global conformational profile and corresponding activation energies predict exclusive outward opening of 3-OMe-cyclobutene, inward opening of 3-CHO-cyclobutene with a small scope for outward opening, and competitive outward and inward openings of 3-COMe- and 3-NO-cyclobutenes at 298 K in the gas phase. The predictions for 3-OMe-, 3-CHO- and 3-COMe-cyclobutenes are in line with the experiments. The experimental selectivity of 3-NO-cyclobutene is not reported. 3-Me-3-NO-cyclobutene has been predicted by Houk for inward rotation of the NO group. The outward rotating influence of the Me group, however, also needs to be taken into account. We wish to carry out this study at elevated temperatures to understand its effects on torquoselectivity.

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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For Table of Contents

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