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Computation Revealed a Case where Kinetic Selectivity is Controlled by Dynamics: Isomerization of Benzylideneanilines

Salai Cheettu Ammal[a] and Hiroshi Yamataka*[a]

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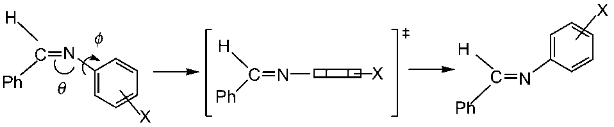
The *cis–trans* isomerization of benzylideneaniline proceeds via a single transition state to afford two conformational isomers on the potential energy surface. Ab initio molecular dynamic simulations revealed that the observed kinetic selectivity of the two conformers for each of the *cis* and *trans* isomers is not governed by the relative stabilities of two independent transition states that would lead to the two conformers, respectively, but by the reaction dynamics.

Introduction

The discovery of a method to perform reactions in a selective manner is among the central issues in organic chemistry in both scientific and technological fields. As a commonly accepted idea, the product selectivity of a reaction is controlled by the relative reactivities of the two independent reaction channels and hence by the relative stabilities of the two transition states (TSs). Thus, development of a reaction of high product selectivity, for example, an enantioselective reaction, has often been based on the design of hypothetical TS structures. However, it is increasingly recognized that chemical reactions are more complex than initially thought.[1–5] For example, recent computational experiments revealed cases where the TS has only limited significance in the determination of the reaction route and the product selectivity.[3] In the present article, our computational simulations demonstrate a case where two reaction products are formed with an unexpectedly high product selectivity by the divergence of the reaction pathway after the TS. Although the results for this particular reaction shown in this article are difficult to test experimentally, similar situations may well occur in other reactions. This requires a new interpretation of organic reactivity.

The reaction considered is the *cis–trans* isomerization of PhCH=NPh [Equation (1)].



(1)

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The ab initio quantum mechanical calculations were reported previously.[6] For the parent compound, the isomerization TS has a C_s symmetry with θ = 179.5° and φ = 90.0°. The contour energy map of the reaction in Figure 1 shows that the TS separates the *trans* and *cis* isomeric regions, and that for each region a pair of conformers is separated by TS2 and TS3, respectively. The conformers in each region are enantiomers with different directions of rotation around the N–Ph bond. When the *cis–trans* isomerization takes place, the reaction that starts from the *cis* isomer is expected to go through the TS to give equal amounts of the pair of *trans* isomers, since the potential energy surface is symmetrical. However, if a substituent is introduced on the *meta* or the *ortho* position of the aniline ring, the two rotational isomers become different, as exemplified in Figure 2, where the reaction scheme for benzylidene-*m*-fluoroaniline is depicted. In this example, the fluorine atom may take the position close to (in-conformer) or away from (out-conformer) the benzylidene moiety. The reaction starting from either the in- or the out-*cis* conformer proceeds through the common TS and then affords the in- and out-*trans* conformers. Under such circumstances, the product selectivity is not governed by the relative stability of the two independent TSs as in the normal case.

Computational Methods

Ab initio calculations at different levels (HF, B3LYP, and MP2 theories with 6-31G*, 6-31+G*, and 6-311+G** basis sets) afforded essentially the same structures for **1** (X = H) and similar isomerization TS structures with a linear C=N–Ph and slightly twisted N–Ph conformation.[6] The activation barrier slightly depends on the computational level; B3LYP calculations tend to give lower barriers than HF and MP2, and the calculated HF/6-31G* barriers ($\Delta H^{\ddagger}$,

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[a] Department of Chemistry, Rikkyo University,
Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan
E-mail: yamataka@rikkyo.ac.jp

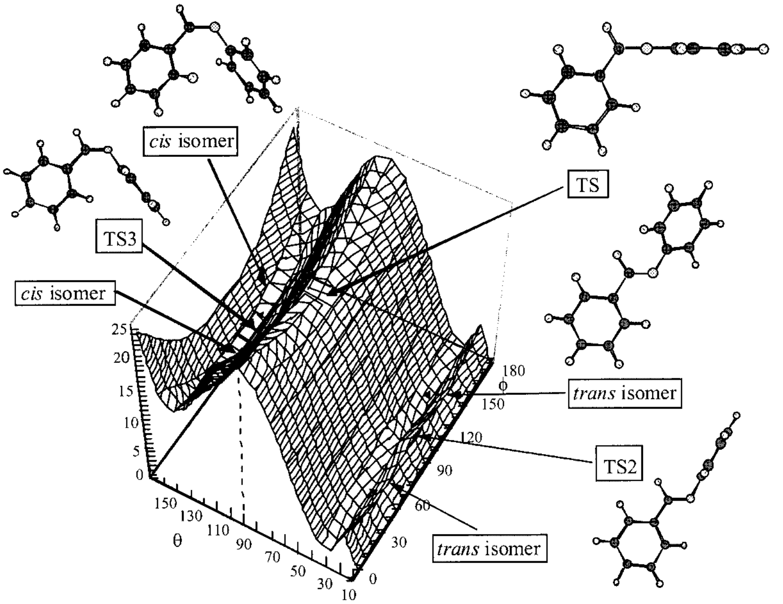

Figure 1. Contour energy map for the *cis–trans* isomerization of PhCH=NPh.

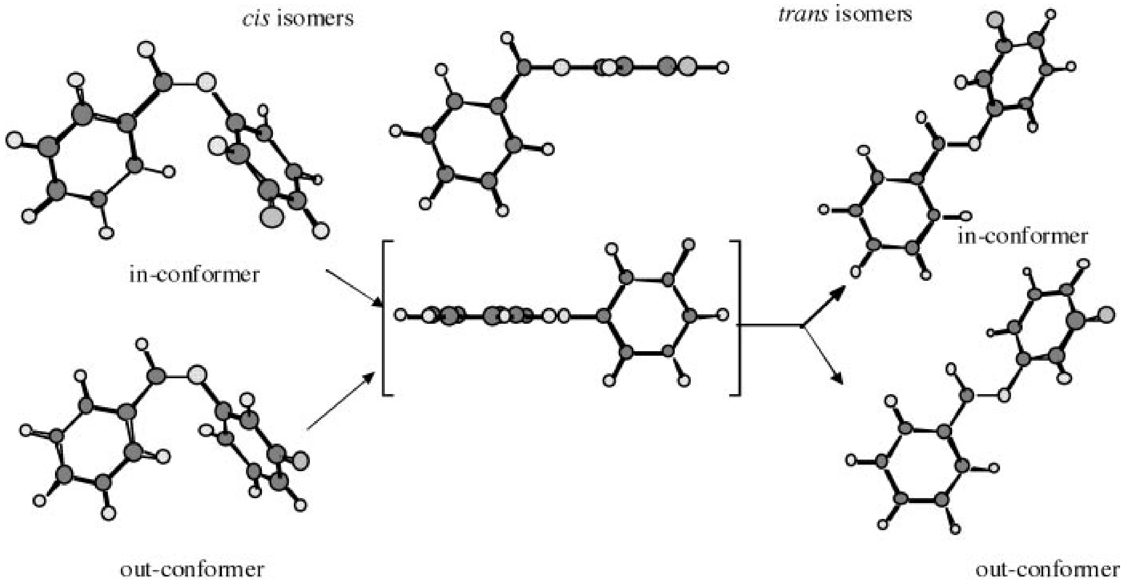

Figure 2. Schematic reaction path for the isomerization of the in- and out-conformers of the *cis* isomer to the in- and out-conformers of the *trans* isomer.

57.8 kJ mol^{-1} and $\Delta G^{\ddagger}$, 60.7 kJ mol^{-1}) are qualitatively similar in magnitude to the experimental $\Delta H^{\ddagger}$(58.6 ± 0.8 kJ mol^{-1}) and $\Delta G^{\ddagger}$ (64.4 ± 0.1 kJ mol^{-1}) values in pyridine at 25 °C.[7] The effect of dynamics on the reaction pathway was examined with direct ab initio molecular dynamic (MD) simulations in a similar manner reported previously.[4] Two hundred trajectories were calculated that started at the isomerization TS with a total Maxwell-Boltzmann equipartitioned thermal kinetic energy of 3.5 kcal mol^{-1}.[8]

Results and Discussion

Twenty representative MD trajectories, with different seeds, which lead to the *trans* isomers are shown in Figure 3, where the ordinate is the θ angle and the abscissa is the difference in the two atomic distances (d^1 and d^2). Although the two *ortho* (or *meta*) positions are undistinguishable experimentally for the unsubstituted compound, it is computationally possible to label the positions and define the in-conformer with the negative sign of d^1 – d^2 and the

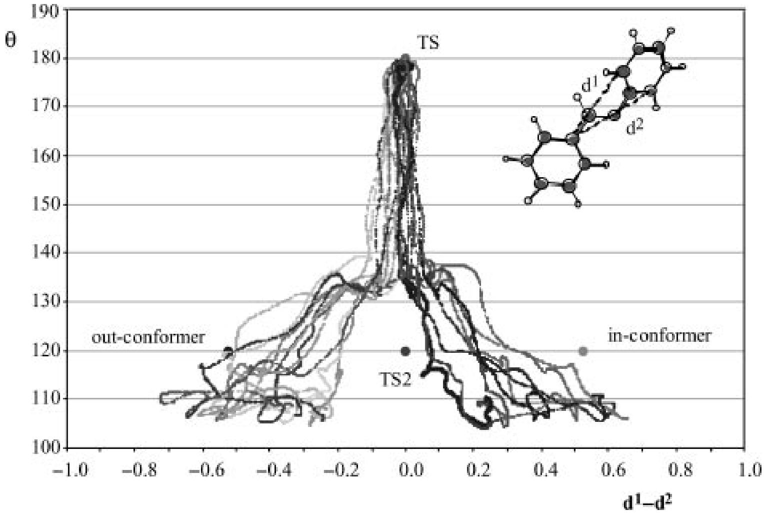

Figure 3. Direct MD trajectories that start at the isomerization TS to the *trans* isomer. The simulations were carried out at the HF/6-31G* level with random initial velocities and with a kinetic energy of 3.5 kcal/mol. Atomic distances, d^1 and d^2, are those between the *ipso*-carbon of the benzylidene moiety and the two *ortho* carbons of the aniline ring. Only 20 trajectories out of 200 are shown in this figure for clarity.

out-conformer with the positive sign. It can be seen in Figure 3 that each trajectory comes down toward the TS2 region, but before it reaches that point it goes to either the in- or the out-conformer region. Similar results were obtained for trajectories that lead to the *cis* products.

Out of the 200 trajectories calculated for the parent compound, 100 gave the *trans* isomers and 100 led to the *cis* isomers. Among the 100 trajectories that resulted in the *trans* isomers, 48 led to the in-conformer region and 52 to the out-conformer region, while the in/out ratio of the *cis* isomers was found to be 45:55. Theoretically, these numbers should be 50:50 because the pairs of the conformers have identical energies. The nonequality of the calculated ratio is probably due to the limited number of the trajectories, and the ±5% deviation from the equality is taken to represent the precision in the computational experiment.

Analogous trajectory calculations were carried out for the *meta*-F substituted substrate, for which the in- and out-conformers have slightly different energies; the out-conformer is ca. 0.1 kcal mol^{-1} more stable than the in-conformer for both the *cis* and *trans* products. Out of the 200 trajectories calculated for the *meta*-F substituted substrate, 103 gave the *trans* isomers and 97 led to the *cis* isomers after 300 fs. Among the 103 trajectories that resulted in the *trans* isomers, 27 led to the in-conformer region and 76 to the out-conformer region, while the in/out ratio for trajectories that afforded the *cis* isomers was found to be 17:80. Thus, for the *meta*-F substituted substrate, the out-conformers were preferably obtained over the in-conformers by the ratios of 2.8:1 (for *trans*) and 4.7:1 (for *cis*), which are clearly beyond the limits of computational uncertainty. The ratios are unexpectedly large compared to the extremely small stability differences that are observed for both the *cis* and the *trans* products. It should be noted that continuation of the trajectory calculations resulted in isomerization of the out-conformers to the in-conformers, and the in/out ratio then became 45:58 for the *trans* isomers and 44:53 for the *cis* isomers at 500 fs. Thus, the kinetic selectivities for the in/out conformers are large, while the thermodynamic selectivities are much smaller, which is consistent with the similar stabilities for each pair of conformers.

Intrinsic Reaction Coordinate (IRC)[9] calculations revealed that the IRC path on the potential energy surface from the isomerization TS to the *trans* isomer reaches TS2, where TS2 is the point at which separation of the two rotational isomers occurs. On the other hand, most of the MD trajectories determine their directions to either the in- or the out-conformer before TS2 is reached at a θ angle of about 225° for both the parent and the *m*-F substituted substrates. Thus, the path that leads to either the in- or the out-conformer is determined somewhere on the way down to TS2.

The reason for the high kinetic selectivities is not clear at present, but the 3D energy surface of the *trans*-isomer region of PhCH=NC$_6$H$_4$-*m*-F shown in Figure 4 may help to understand the results. The reaction trajectories that

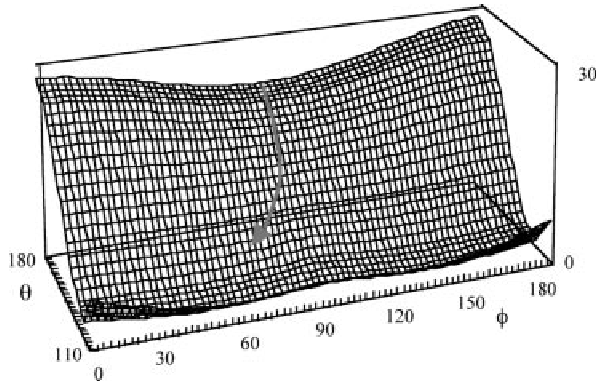

Figure 4. Potential energy surface of the *trans* region for the isomerization of PhCH=NC$_6$H$_4$-*m*-F.

come down from the TS reach the ridge that separates the in- and out-regions and then move toward either of the two conformer sides. Because of the F substituent, the in-conformer and out-conformer sides are not identical in energy, and at the region where $\theta \approx 225°$, the out-conformer side is slightly more stable than the in-conformer side. Since the edge of the ridge is located in the less stabilized side (in-conformer side) of the surface, the trajectories are likely to move more favorably toward the out-conformer side.

Conclusions

In summary, we present in this article a case where two products form via a single TS and the product selectivity is extremely large as judged from the relative product stability. The observed kinetic selectivity of the in/out conformers for each of the *cis* and *trans* isomers is not governed by the relative stabilities of two independent TSs that would lead to the two conformers, respectively, since there are no such competing reaction pathways. Thus, the TS has only limited significance with respect to the actual mechanism. Care should be taken in the design of a product-selective reaction that is modeled after the structures and the stabilities of the TSs.

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[8] We used a simple trajectory scheme and started at the optimized TS structure with a constant thermal energy rather than a random Boltzann sampling. This was done because the purpose of the study was not to obtain statistically precise numbers comparable to experimental observations, but to observe, with a limited number of trajectories, any effect of dynamics that may lead to conclusions different from those based on potential energy surface considerations.

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