Molecular Dynamics

Methyl Group Rotation Driven by Proton Transfer through a Long-Range Chemical Interaction**

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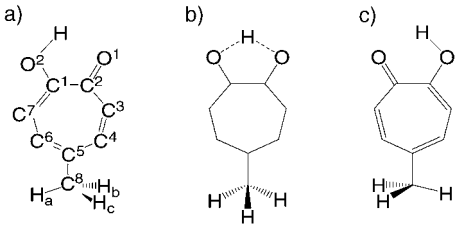
Proton transfer takes place ubiquitously in water, many organic compounds, proteins, DNA, and so on, and therefore it is a very fundamental chemical reaction that plays a vital role in biological processes and material sciences.[1–3] Likewise, the internal rotation of the methyl group and its derivatives constitute a fundamental notion in the study of molecular structure and dynamics.[4] Herein, we discuss an almost unidirectional interaction between these two dynamical elements, by which proton transfer can induce the internal rotation of a methyl group in a mutually remote site. Such an interaction can be typically found in the ground state of 5-methyltropolone (5MTR, Scheme 1). Reciprocating motion



Scheme 1. a) Stable structure of 5-methyltropolone (5MTR), b) the transition state, and c) the mirror image of a). The torsional angle θ of the methyl group is defined as the dihedral angle between the planes of C4-C5-C8 and C5-C8-H_a. $\theta = \pi$ and 0 for the structures a) and c), respectively. The irrelevant hydrogen atoms are omitted for clarity.

of the proton is mechanically transformed to rotational motion of the methyl group. This phenomenon is not only chemically surprising but interesting for the study of molecular machines.[6–9] Also, this dynamic coupling interaction suggests that a large conformational change in a molecule can be triggered by relevant proton transfer processes.[4] We have found that the mechanism of this long-range interaction is quite generic and can be explained by quantum-mechanical interactions between the hyperconjugation of the methyl group and the tautomerization resulting from proton transfer.

Recently, in the fluorescence excitation and hole-burning spectra in the S_1–S_0 region of 5MTR, Nishi et al. found that the excitation of the internal rotational levels of the methyl group promotes proton tunneling.[10,11] This finding suggests the existence of a very long-range interaction between proton tunneling and methyl internal rotation in the *excited state.* Inspired by this remarkable discovery, we studied the proton transfer dynamics in the *ground state* potential surface of 5MTR and other relevant molecules by different theoretical methods. We were looking for a long-range mechanical interaction and found an interesting interaction that is fundamentally essential to many aspects of molecular science.

The basic energetics of 5MTR are: The density functional theory (DFT) with the B3LYP functional using 6-31G** gives 0.219 eV for the transition state (the energy barrier from a) to c) via b) in Scheme 1), whereas for tropolone, that is, without the methyl group, it is 0.193 eV. On the other hand, the rotational barrier of the methyl group in the torsional angle, freezing all the other molecular geometries at the potential minimum, is 0.034 eV.[12] Therefore the difference between the barrier heights of 5MTR and tropolone in their transition states comes from the rotational barrier of the methyl group. These values depend on the computational methods used, and DFT tends to give smaller values. However, the overall features estimated by other methods are all qualitatively common. We applied the restricted Hartree–Fock (RHF), Møller–Plesset perturbation theory (MP2), and configuration interaction with single and double excitations (CISD). The basic nature of the electronic structure is reflected in the bond lengths. The single bonds (C2−C3, C4−C5, and C6−C7) are about 1.42 Å, whereas the double bonds (C3=C4, C5=C6, and C7=C1) are shorter (1.37 Å). Bond alternation follows proton transfer, switching the sites of the single and double bonds; that is, tautomerization (Scheme 1). In other words, proton transfer has to surmount the potential barrier to perform such a tautomerization and large geometrical deformation.[13] The bond C1−C2 is exceptional since it remains single and long during proton transfer.

To study the relevant dynamics, we carried out the full dimensional ab initio molecular dynamics at the RHF level of approximation.[14,15] In our ab initio simulation, energies and potential derivatives were calculated with the RHF method of the 6-31G basis set. Even with the RHF method, full-dimensional dynamics are very time-consuming. We first sampled the position of each atom $\boldsymbol{R}_{\mathrm{init}}$ randomly around the optimized stable structure $\boldsymbol{R}_{\mathrm{opt}}$ within the range of $|\boldsymbol{R}_{\mathrm{init}} - \boldsymbol{R}_{\mathrm{opt}}| < 0.2$ Å. Each trajectory was integrated with zero initial momenta in terms of the locally analytic integrator.[16] After the trajectories had been run for 10 fs, all the momenta were scaled to attain an aimed total amount of energy. We studied three cases having a total energy of $1.25\,E_0$, $2.75\,E_0$, and $4.25\,E_0$, where E_0 is the vibrational zero point energy (4.205 eV) of 5MTR. Fifty trajectories were sampled for each energy. Although these energies are seemingly much higher than the transition state energy, proton transfer does not take

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place readily, since the energy is distributed over all the possible modes. Only 4 (for $1.25\,E_0$), 13 (for $2.75\,E_0$), and 20 (for $4.25\,E_0$) trajectories out of the individual fifty samples realized proton transfer within 1 ps. Except for the clear difference in the frequencies of proton transfer, not much dependence on energy was observed. In particular, all proton transfers were always followed by methyl group rotation.

Herein, we define the moment of proton transfer as the instant when the relevant proton comes to the middle position between the two oxygen atoms. At this moment, bond alternation is not usually observed yet; however, 10–15 fs after this, the reorganization of the electronic structure follows. Thus, the proton undergoes transfer prior to tautomerization, and moreover, if the bond alternation does not follow successfully, the proton returns to the original site.[13] On the other hand, it has been numerically confirmed that the electron density on the seven-membered ring is virtually unchanged before and after rotation of the methyl group. Thus, virtually no mechanical path exists through which internal rotation of the methyl group can transmit energy to the proton transfer site.

Figure 1 shows the change in the torsional angle of the methyl group after proton transfer, which has been averaged over the sampled trajectories of $2.75\,E_0$. Around 30–40 fs

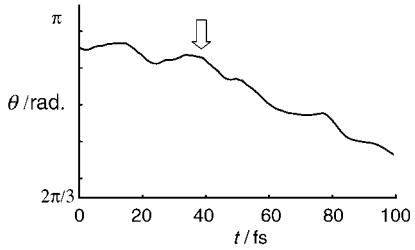

Figure 1. Time dependence of the torsional angle θ of the methyl group after proton transfers (see Scheme 1). The angles are statistically averaged over the different occasions of proton transfer observed in the trajectories of $2.75\,E_0$. θ larger than π has been transformed to $2\pi-\theta$.

(marked with an arrow) after proton transfer, the methyl group begins to rotate, which changes the angle by 60° over approximately 100 fs. (For a more direct inspection a movie can be seen in the Supporting Information.) The rotation often continues and exceeds 60° because of inertia and slow intramolecular energy relaxation, although sometimes it stops at approximately this angle. If proton transfer does not occur, the torsional angle most frequently remains constant in this time scale. Since the tautomerization takes place 10–15 fs after the proton transfer, the methyl group begins to rotate after the tautomerization is finished. Although these estimated values are dependent on the quality of the adopted approximation, it is thus confirmed that methyl group rotation follows proton transfer. Therefore it is established that a quantum-mechanical mechanism is involved in the conformational change of this molecule, by which the in-plane reciprocating motion of the proton is unidirectionally transmitted to the rotational motion of the methyl group at a remote site.

We analyzed the mechanism of these correlated dynamics in terms of hyperconjugation within the molecule coupled with the tautomerization. Hyperconjugation is a classic concept in organic chemistry established by Dewar many years ago[17,18] (refs. [5,19] give a more sophisticated treatment of hyperconjugation): A minus linear combination of the 1s atomic orbitals of two hydrogen atoms in a methyl group can behave somewhat like a 2p orbital and thereby can participate in a nearby π conjugation at an appropriate orientation. Therefore it is quite natural to consider that the hyperconjugation can couple with the π system of the seven-membered ring of tropolone and this interaction should be (positively or negatively) greatest when a pair of hydrogen atoms is positioned vertically to the tropolone plane. We shall call this pair in the upright position the vertical pair (VP).

Since the methyl group is regarded as an electron-donating functional group, the primary interaction between the methyl and π system should arise from the HOMO of the methyl group and the LUMO of tropolone. In practice, the methyl group is represented as methane in terms of its size and orientation in this study. As for another HOMO–LUMO interaction, the LUMO of methane is symmetric with respect to the molecular plane, whereas the HOMO of tropolone, which is a π orbital, is antisymmetric. Hence, this pairing results in virtually no interaction between these two orbitals.[20] Figure 2 shows such a HOMO–LUMO interaction.

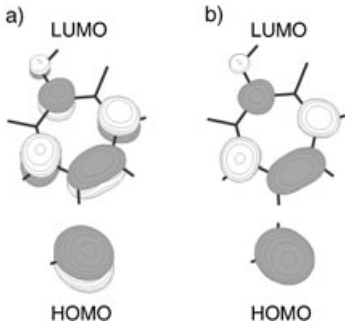

Figure 2. A HOMO (methyl group)–LUMO (tropolone) interaction representing coupling between hyperconjugation and tautomerization. a) A perspective view of 5-methyltropolone (5MTR) of Scheme 1 a from the side of the methyl group. b) Projection of a) onto the molecular plane.

Here, one of the HOMOs of methane, representing the methyl group is primarily composed of two 1s orbitals on two hydrogen atoms, which are perpendicular to the molecular plane, and looks just like a 2p orbital. (The two hydrogen atoms that are seen lie in the molecular plane and have nothing to do with hyperconjugation. One of them is responsible for the C–C bond between tropolone and the methyl group.) As is clearly seen in Figure 2 b, the LUMO of tropolone has a large amplitude on the C4–C5 bond and has the right phase thus allowing a good overlap with the HOMO of the methyl group. On the other hand, the LUMO has a node inbetween C5 and C6, which should cancel or weaken the hyperconjugation. Besides, there is a large component of the tropolone's HOMO at C5–C6 (not shown graphically),

which induces an exchange repulsion with the HOMO of the methyl group (HOMO–HOMO interaction). Therefore the VP should be placed at the side of C4–C5, thus letting the methyl group sit comfortably with the tropolone π system. (The rotational barrier is estimated to be 0.034 eV.) Once the proton transfer, which is associated with tautomerization, takes place, the HOMO of the methyl group loses its stability and faces repulsion. (The LUMO of tropolone after proton transfer can be readily obtained as the mirror image of the LUMO in Figure 2.) To avoid this repulsion, the methyl group rotates by 60° to establish a new stable HOMO–LUMO interaction by placing the VP at the site of C5–C6, as in Scheme 1c.

This mechanism is qualitative, general, and robust. For instance, it is likely that the present dynamics will occur even if proton transfer proceeds by quantum-mechanical tunneling, as long as the associated wavepacket state can induce tautomerization. From this mechanism, certain theoretical deductions and predictions may be made. Figure 3 shows the

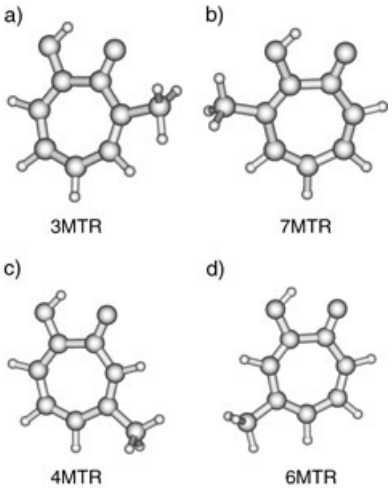

Figure 3. Stable structures of methyltropolones: a) 3-methyltropolone (3MTR) (0.082 eV), b) 7-methyltropolone (7MTR) (0.052 eV), c) 4-methyltropolone (4MTR) (0.038 eV), and d) 6-methyltropolone (6MTR) (0.042 eV). The values in parentheses are the height of their rotational barrier (0.034 eV for 5-methyltropolone).

stable structures of the methyltropolone derivatives: 3-methyltropolone (3MTR), 7-methyltropolone (7MTR), 4-methyltropolone (4MTR), and 6-methyltropolone (6MTR). Noting the orientation of the methyl group, the rotational barriers of the methyl group in these molecules as estimated by DFT are 0.082, 0.052, 0.038, and 0.042 eV, respectively. The primary reason for these orientations is that the VP of 3MTR avoids the node of the LUMO at C3–C4 preferring the simple LUMO at C2–C3. The orientation in 7MTR is interesting in that the VP seems to avoid the node of the LUMO formed inbetween C1 and O2 and prefers the simple LUMO component between C6–C7. It is easy to extend this view to 4MTR and 6MTR.

It can be readily seen that 3MTR and 7MTR are the proton-transfer product counterparts of each other as are 4MTR and 6MTR. This implies that proton transfer in 3MTR should cause methyl rotation leading to the most stable orientation of 7MTR. Likewise, proton transfer in 7MTR should induce methyl rotation. A similar phenomenon should be the case for 4MTR and 6MTR. Thus, internal rotation of the methyl group can be induced at any site from C3 to C7.

Although our study was stimulated by the dynamics of 5MTR, we emphasize that the present phenomenon and its mechanism can be observed in other molecular systems. A simple example is methylmalonaldehyde (larger and more complicated systems, including intermolecular proton transfer, will be reported elsewhere).[21] Figure 4 shows the

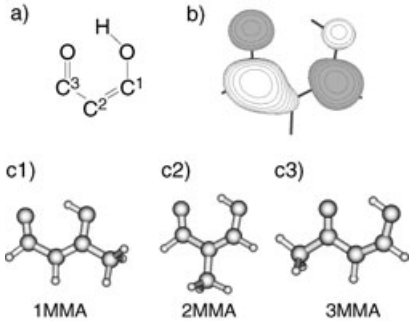

Figure 4. a) Molecular structure of malonaldehyde (MA), b) the LUMO of MA, and c1)–c3) the stable structures of 1-methylmalonaldehyde (1MMA) (0.054 eV), 2-methylmalonaldehyde (2MMA) (0.030 eV), and 3-methylmalonaldehyde (3MMA) (0.023 eV), respectively. The values in parentheses are the height of their rotational barriers.

structure of malonaldehyde, its LUMO, and the stable structures of 1-methylmalonaldehyde (1MMA), 2-methylmalonaldehyde (2MMA), and 3-methylmalonaldehyde (3MMA). The quantum-chemical origins of these orientations are almost completely the same as that of the methyltropolones. From Figure 4, it can be readily seen that the internal rotation of the methyl group at any position is induced by proton transfer, as long as the associated tautomerization can sufficiently couple with the hyperconjugation.

There is a simple rule to predict the orientation of a methyl group in bond alternation systems such as tropolone and linear polyene:[22] The VP of a methyl group tends to be more stable at the site of a single-bond (the other side of the double-bond). Various explanations are possible for this preferred orientation; however, we account for it in terms of the following facts as observed in the above examples, a) the LUMO π orbital tends to have large components in single bonds, b) the LUMO π orbital tends to have a node on the double bonds, and c) at double-bond sites there are large components of the HOMO of the π system. These are just guiding principles to be confirmed with individual molecular orbital calculations. Also, many other secondary effects may exist that violate this "rule". Where this rule holds, proton transfer or other dynamics that alter the position of single and double bonds within a molecule can induce the rotation of methyl groups at the relevant sites.

An important implication of the present finding is that proton transfer can trigger a large conformational change

through methyl group rotation.[4] For example, if one of the hydrogen atoms in the methyl group is substituted with a large alkyl group, a large amplitude conformational change can be driven by a relevant proton transfer.

Protein motors are of interest to many biologists and chemists.[23,24] They are usually assemblies of large molecules that tie molecular dynamics with biological functioning. Yet chemists are interested in far smaller elementary molecules that can potentially work as molecular machines or elements within one.[6–9] The present dynamics, in which a reciprocating motion is transformed into a rotational motion on a molecular level, may be utilized as a molecular rotor or for transmisson. The molecule 5MTR is very well-suited to such an application. Besides, it is interesting to recall that the interaction of the methyl group through tautomerization or bond alternation can be conveyed in principle to a very remote site through, for example, a linear polyene. However, for this mechanism to be applied to a molecular motor, one needs to introduce asymmetry into the methyl group so that it rotates only in one direction.[25] Also, practical ways of continuously injecting energy into the proton transfer should be investigated so that the methyl group can be kept rotating.[26] These studies are underway in our laboratory.

In summary, methyl group rotation can be driven by proton transfer because of coupling between hyperconjugation and tautomerization. This is important not only as a basic long-range interaction in fundamental chemistry but also as a mechanical transformation that can be utilized as an integral part of molecular machinery and stereochemistry.

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