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Quantum Mechanics

Tunneling Governs Intramolecular Proton Transfer in Thiotropolone at Room Temperature**

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The role of quantum mechanical tunneling has been found to be significant in a variety of reactions like oxidative additions and reductive eliminations in organometallic complexes,[1] proton transfer and proton-coupled electron transfer (PCET) processes in molecules and enzymes,[2,3] 1,5-hydride shift reactions in hydrocarbons[4] and free-radical polymerization.[5] Schreiner et al. have recently reported hydrogen tunneling in hydroxymethylene to form formaldehyde. This tunneling reaction has a half-life of only 2 h and tunneling occurs through a large energy barrier.[6] But its congeners, mercaptocarbene and selenocarbene, do not show quantum mechanical hydrogen tunneling.[7] Recent experiments have confirmed computational predictions[8] of heavy atom tunneling in the ring opening of radical clocks.[9] However, experimental detection of tunneling in chemical reactions are confined mostly to low temperatures and hence, examples of tunneling at room temperature are rare.[10,11]

In a recent paper, Yamabe and co-workers reported an extremely fast intramolecular proton transfer between the thione (**1a**) and the enethiol (**1b**) tautomers in thiotropolone (**1**), the sulfur analogue of tropolone in the solid state (see Scheme 1).[12] The crystal structure of **1** showed no signatures of intermolecular hydrogen bonding with the molecules being almost perpendicular to each other. The S···O distance in **1** is (2.804 ± 0.001) Å and therefore much smaller than the sum of their van der Waals radii (3.2 Å). The computed harmonic (anharmonic) IR stretching modes for C=S and C=O in **1a** and **1b** are 1120.4 cm^{-1} (1102.0 cm^{-1}) and 1627.0 cm^{-1} (1594.0 cm^{-1}), respectively, at the B3LYP/6-311G(d) level, while the measured values for C=S and C=O are 1088–1109 cm^{-1} and 1566–1600 cm^{-1}. For a detailed comparison of the important vibrational modes at various levels of theory see the Supporting Information. Anharmonicity is observed to be significant. Based on this observation, it was concluded that **1** exists in the solid state as a monomer with substantial intramolecular O–H···S and S–H···O H-bonding for the tautomers **1a** and **1b**, respectively. Variable-Temperature (VT) NMR studies showed that the proton hops rapidly between the two tautomers with a measured $\Delta G^{\neq} < 6$ kcal mol^{-1} for $\mathbf{1a}\rightleftarrows\mathbf{1b}$ at 238 K. The computed free-energy barrier height at G2(MP2) level was 5.0 kcal mol^{-1}. The energy difference between the minima of **1a** and **1b** is 3.4 kcal mol^{-1} at MP2/TZVP (3.8 kcal mol^{-1} at CCSD(T)/cc-pVTZ level on the MP2/TZVP geometry). The tunneling correction based on the Wigner approximation for an Eckart potential[13] was estimated to be 0.8 kcal mol^{-1} thereby leading to an effective computed free-energy barrier height of 4.2 kcal mol^{-1}. However, the ^{13}C and ^{17}O NMR spectra in **1** showed no temperature dependence at various temperatures of 143, 173, 213, and 298 K. In fact, even in the molten state at 333 K, the ^{13}C NMR signals for **1** are similar to the low-temperature measurements. This we find interesting, since based on a classical over-the-barrier mechanism as predicted by the transition-state theory (TST), the reaction should have a large temperature dependence across a span of 190 K (from 143 K to 333 K).[11] But, for a reaction occurring purely through quantum mechanical tunneling such a behavior is expected since the probability of tunneling is independent of the temperature.[14]

Scheme 1. Proton transfer reaction in thiotropolone and tropolone and their derivatives.

The significance of quantum tunneling in keto–enol tautomerization is well established in the literature.[15] Jhonson et al. have studied the significance of tunneling in the hydrogen atom transfer reaction in 6,9-dimethylbenzosuberone.[15c] To understand and quantify the contribution of quantum mechanical tunneling for this reaction, we performed DFT calculations using the MPW1K hybrid functional.[16] The success of the MPW1K functional has been established in many H-transfer reactions.[17] The 6-31+G-(d,p) basis set was employed.[18] Calculations were also done at MP2[19]/TZVP[20] level for comparison. CCSD(T)[21]/cc-pVTZ[22] calculations at MP2/TZVP reference geometry have

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Supporting information for this article, including cartesian coordinates for the reactants, products, and the transition states, energies, harmonic frequencies, complete Gaussian 03, Gaussrate and POLYRATE references, CVT and CVT + SCT rate constants for temperatures of 77 to 600 K, is available on the WWW under http://dx.doi.org/10.1002/anie.201203355.

also been performed for the energetics of the reaction. The transition-state between **1a** and **2a** were located using canonical variational transition-state theory (CVT).[23] Quantum effects on the reaction dynamics were computed, using the small-curvature tunneling (SCT) approximation.[24] Direct dynamics calculations were carried out with GAUSSRATE[25] as the interface between Gaussian 03[26] and POLYRATE.[27]

Without inclusion of tunneling, the CVT rate constants (k_{CVT}) for proton transfer in **1** at 143, 173, 213, 298, and 333 K are 1.81×10^{4}, 5.55×10^{5}, 1.22×10^{7}, 5.89×10^{8}, and $1.67\times10^{9}\,\mathrm{s}^{-1}$, respectively. Therefore, based on classical over-the-barrier reaction dynamics, the rate constants increases by a factor of about 10^{5} within the experimental temperature range. At 238 K, the CVT value for the activation energy (E_a) is $5.8\,\mathrm{kcal\,mol^{-1}}$ which is in reasonable agreement with the classical free-energy barrier at 298 K at the G2(MP2) level. The energy barrier at 298 K for MP2/TZVP and CCSD(T)/cc-pVTZ levels on the MP2/TZVP geometry are $6.6\,\mathrm{kcal\,mol^{-1}}$ and $7.5\,\mathrm{kcal\,mol^{-1}}$, respectively. The value for the pre-exponential factor (A) is $9.77\times10^{12}\,\mathrm{s}^{-1}$.

However, calculations with the inclusion of small-curvature tunneling were found to give CVT + SCT rate constants ($k_{\mathrm{CVT+SCT}}$) of 3.67×10^{10}, 4.05×10^{10}, 4.53×10^{10}, 5.47×10^{10}, and $5.88\times10^{10}\,\mathrm{s}^{-1}$ at 143, 173, 213, 298, and 333 K, respectively. The rate constant increases only 1.6 times for an increase of 190 K which is clearly a nonclassical behavior. At 238 K, the CVT + SCT value for E_a is $0.3\,\mathrm{kcal\,mol^{-1}}$ suggesting that the reaction occurs entirely through quantum mechanical tunneling. Even in the molten state at 333 K, E_a is $0.5\,\mathrm{kcal\,mol^{-1}}$ and much lower than the classical CVT barrier for the reaction with a $k_{\mathrm{CVT+SCT}}/k_{\mathrm{CVT}}$ ratio of 34.8 with 97.0 % of the reactions occuring through a tunneling pathway. The value for the pre-exponential factor A reduces to $1.35\times10^{11}\,\mathrm{s}^{-1}$.

In Figure 1, an Arrhenius plot is shown for the CVT + SCT rate constants for $\mathbf{1a}\rightleftarrows\mathbf{1b}$. The curvature in the Arrhenius plot becomes quite evident below 400 K. Below 400 K, the Arrhenius plot becomes flat and is hardly affected by further reduction in temperature with a small decrease in the slope of the plot from an E_a of $0.3\,\mathrm{kcal\,mol^{-1}}$ at 238 K to $0.1\,\mathrm{kcal\,mol^{-1}}$ at 125 K and further down to an E_a of $0.06\,\mathrm{kcal\,mol^{-1}}$ at liquid N_2 temperature. Similarly, the pre-exponential factor A exhibits a small decrease from $8.91\times10^{10}\,\mathrm{s}^{-1}$ at 238 K to $5.01\times10^{10}\,\mathrm{s}^{-1}$ at 125 K and $10.61\,\mathrm{s}^{-1}$ at 77 K. The CVT + SCT rate constant increases by only three times for the increases in temperature of 500 K from 100 to 600 K.

For a qualitative understanding of the reasons why the reaction occurs entirely by tunneling even at such high temperatures, we analyze the structures of **1a** and **1b**. The H···S distance in **1a** is 2.06 Å while the H–S distance in **1b** is 1.35 Å. Therefore, the proton effectively moves by only about 0.7 Å from the reactant to the product (see the Supporting Information for details). Considering also the fact that the free-energy barrier height is only $5\,\mathrm{kcal\,mol^{-1}}$, tunneling from the lowest vibrational level[28] is expected to be highly efficient.[29]

Substituting the proton in **1** by its heavier isotope deuterium should slow down the rate of the reaction by simultaneously increasing the barrier height of the reaction[30] as well as rendering the tunneling effects less prominent (because of a pure mass effect) in **2**. The CVT + SCT rate constants for **2** are 3.01×10^{7}, 3.68×10^{7}, 4.50×10^{7}, 6.10×10^{7}, and $6.89\times10^{7}\,\mathrm{s}^{-1}$ at 143, 173, 213, 298, and 333 K, respectively. The increase in the rate constants is 2.3 times within this temperature range and it is 1.4 times more than that for **1**. The primary kinetic isotopic effect (PKIE) are 1.22×10^{3}, 1.11×10^{3}, 1.01×10^{3}, 9.22×10^{2}, and 8.53×10^{2} at 143, 173, 213, 298, and 333 K, respectively. Though in general, a large PKIE is considered as an indication of preferential tunneling by the lighter isotope relative to the heavier isotope in a chemical reaction, we find that the tunneling is also significant in **2**. The CVT + SCT activation energies are only 0.8, 0.4, 0.3, and $0.2\,\mathrm{kcal\,mol^{-1}}$ at 333, 238, 125, and 77 K, respectively. Though the activation energies in **2** are marginally higher than in **1** at the same temperatures, these are much smaller than the barrier height of $6.3\,\mathrm{kcal\,mol^{-1}}$ for **2**. At 333 K, the ratio $k_{\mathrm{CVT+SCT}}/k_{\mathrm{CVT}}$ is 12.2 for **2** with 92.2 % of the reaction occurring through quantum mechanical tunneling. Therefore, even though for both **1** and **2** tunneling from the lowest vibrational level controls the reaction, the higher probability of tunneling of H with respect to D ensures a large PKIE.[31]

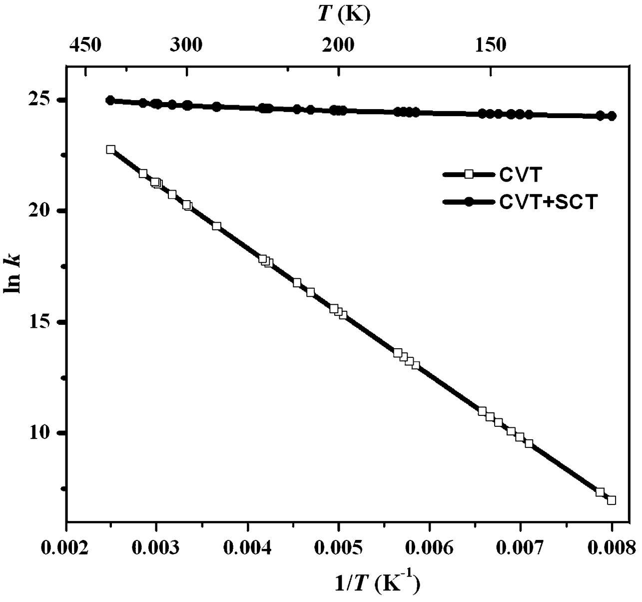

Figure 1. Arrhenius plots of the CVT and CVT + SCT rate constants for intramolecular proton transfer in **1** from 125 to 400 K.

While direct experimental evidence for tunneling of proton is still awaited for thiotropolone (**1**), tunneling in tropolone (**3**) is well-known. Several experimental as well theoretical studies have established tunneling in **3**.[32] The computed barrier height for proton transfer for **3** at MPW1K/6-31 + G(d,p) is $3.1\,\mathrm{kcal\,mol^{-1}}$, which matches well with a previously reported value of $3.6\,\mathrm{kcal\,mol^{-1}}$ at MP2 level using a 6-311G(df,pd) basis set for the atoms of the five-membered COH···O=C ring, and a 6-311G(d,p) basis set for atoms of the $(CH)_5$ loop.[33] The barrier heights at MP2/TZVP level and CCSD(T)/cc-pVTZ level on the MP2/TZVP geometry are $4.7\,\mathrm{kcal\,mol^{-1}}$ and $6.2\,\mathrm{kcal\,mol^{-1}}$, respectively. Interestingly, the barrier height for **3** is $2.5\,\mathrm{kcal\,mol^{-1}}$ lower than for **1**. This arises due to the fact that even though in the ground state O–H···O hydrogen bonding (in **3**) is stronger than O–H···S hydrogen bonding (in **1**), the TS for the symmetric double-well potential for **3** is more stabilized because of a much stronger O···H···O interaction than that for the O···H···S interaction in the unsymmetric double well for **1**. Nevertheless, since an O–H bond is shorter than an S–H, the effective distance covered by the proton in **3** between the reactant and the product is larger (by 0.15 Å) than in **1**. Thus, **3** is different from **1** in having a smaller but wider barrier. The barrier width is a potent factor in tunneling as pointed out by Carpenter.[34] Schreiner et al. have illustrated the significance of the barrier width in competing H tunneling reactions in methylhydroxycarbene.[35] The CVT + SCT rate constants ($k_{\mathrm{CVT+SCT}}$) for **3** are 7.75×10^{9}, 1.31×10^{10}, 2.44×10^{10}, 6.96×10^{10}, and $9.78\times10^{10}\,\mathrm{s}^{-1}$ at 143, 173, 213, 298, and 333 K, respectively. The rate constant increases substantially by 12.6 times for an temperature increase of 190 K suggesting a more classical over-the-barrier mechanism in **3**. The ratio of the CVT + SCT rate constants and the CVT rate constants ($k_{\mathrm{CVT+SCT}}$)/k_{CVT}) are 484.3, 89.7, 22.8, 5.4 and 3.9 for 143, 173, 213, 298, and 333 K, respectively. At 333 K, 74.5 % of the reaction proceeds through the tunneling pathway. The CVT + SCT activation energies show a significant temperature dependence. The activation energies for **3** are 2.0, 1.5, 0.6, and 0.3 kcal mol^{-1} at 333, 238, 125, and 77 K, respectively. Therefore, unlike **1** and **2** tunneling for this reaction occurs through vibrational activation.[36] This is also understood from the Arrhenius plot of **3** as shown in Figure 2.

The curvature in the Arrhenius plot becomes evident only at temperatures below 250 K. Also, the curvature in the Arrhenius plot of **3** is less distinct than in **1** which indicates a less prominent quantum behavior of the proton in **3**. As a manifestation of the temperature dependence of tunneling in **3**, we observe that $k_{\mathrm{CVT+SCT}}$ (**3**) < $k_{\mathrm{CVT+SCT}}$ (**1**) for $T < 240$ K while $k_{\mathrm{CVT+SCT}}$ (**3**) > $k_{\mathrm{CVT+SCT}}$ (**1**) for $T > 240$ K (see the Supporting Information for Arrhenius plots for both **1** and **3**). This can be understood from the fact at $T < 240$ K, tunneling in **3** occurs far below the top of the barrier. Therefore, as discussed earlier, since the effective distance covered by the proton is larger in **3** than in **1**, the probability of tunneling is smaller which reduces the rate of proton transfer. However, at higher temperatures, where tunneling occurs through vibrational assistance, the distance that the proton covers is smaller which, along with the fact that the effective barrier height is smaller at higher temperatures,[31] increases the probability of tunneling.

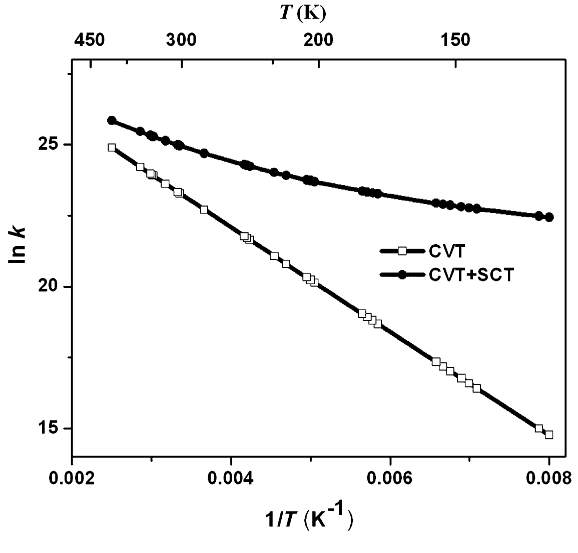

Figure 2. Arrhenius plots of the CVT and CVT + SCT rate constants for intramolecular proton transfer in **3** from 125 to 400 K.

For the deuterium-substituted tropolone (**4**), quantum tunneling is further quenched. The CVT + SCT rate constants for **4** are 3.45×10^{8}, 8.09×10^{8} 2.25×10^{9}, 1.21×10^{10}, and $2.05\times10^{10}\,\mathrm{s}^{-1}$ at 143, 173, 213, 298, and 333 K, respectively. The increase in the rate constants is 59.4 times within this temperature range which is 4.7 times more than for **3**. The PKIEs are 22.5, 16.2, 10.8, 5.8 and 4.8 at 143, 173, 213, 298, and 333 K, respectively. The CVT + SCT activation energies though smaller than the classical barrier height of 5.8 kcal mol^{-1} show substantial variation with temperature. The activation energies for **4** are 3.1, 2.4, 0.9, and 0.3 kcal mol^{-1} at 333, 238, 125, and 77 K, respectively, suggesting a vibrationally activated tunneling process. For **4**, the ratios of $k_{\mathrm{CVT+SCT}}/k_{\mathrm{CVT}}$ are 328.6, 53.2, 13.3, 3.7, and 2.8 for 143, 173, 213, 298, and 333 K, respectively. At 333 K, only 65 % of the reaction proceeds through the tunneling pathway.

In summary, our CVT + SCT calculations suggest that proton tunneling from the lowest vibrational level in **1** across a narrow and small barrier accounts for the temperature independence of the tautomerism reaction across a rise in reaction temperature by 190 K. These calculations also suggest that for reactions like intramolecular proton transfer across an H bond with small and narrow barriers, the tunneling probabilities are more sensitive to even a small change in the barrier width than to a change in the barrier height. As a consequence of this effect, the computed rate of proton transfer is more for **1** compared to **3** at $T < 240$ K and vice versa at higher temperatures.[37] A convenient experimental test for this prediction would be to determine the ratio $k(\mathbf{3})/k(\mathbf{1})$ at temperatures below and above 240 K. A ratio $k(\mathbf{3})/k(\mathbf{1}) < 1.0$ shall prove that tunneling can be more facile even if the barrier height is larger provided that its width is small.

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[28] Tunneling occurs from the lowest vibrational level in **1** and is verified by the fact that the CVT + SCT representative tunneling energy (RTE) is 73.0 kcal mol^{-1}, which remains constant throughout the temperature range of 75 K to 600 K. For the saddle point, V_a^G (adiabatic vibrational ground-state energy), (reaction path, $s=0$) is 78.3 kcal mol^{-1}. Therefore, the most typical tunneling energy is 5.3 kcal mol^{-1} below the barrier top, which is exactly the calculated barrier height of the reaction.

[29] The distance covered by the proton in **1** between the thione and the enethiol forms is in fact, comparable to the hydrogen 1s orbital radius, $\langle r_{1s}\rangle = \frac{4}{a_0^3}\int_0^\infty r^3 \exp(-2r/a_0)dr = \frac{3}{2}a_0$ where a_0 is the Bohr radius (0.52 Å).

[30] At 298 K for CVT calculations, $E_a^D - E_a^H$ is 1.0 kcal mol^{-1} between **2** and **1**, respectively. This is smaller than the zero-point energy (ZPE) difference between the stretching frequencies of an O–D and an O–H bond because the normal mode being lost in this TS for the reaction is a lower-energy C–O–H (D) bending mode ($\nu_{TS}(\mathbf{1}) = 1091.3i$ cm^{-1} and $\nu_{TS}(\mathbf{1}) = 813.6i$ cm^{-1}).

[31] For a parabolic barrier located between two harmonic potential wells (reactant and products), the probability of tunneling, $P \approx \exp\left(\frac{-w\pi^2\sqrt{2mE}}{h}\right)$, decreases with increase in the mass (m) of the particle, increase in the energy difference between the top of the barrier and the energy at which tunneling occurs (E), and increase in the barrier width (w). For D, not only is the mass twice that for H and the barrier height 1 kcal mol^{-1} more but also the barrier width is more because D tunnels from further down of the harmonic well of the reactant which effectively increases the tunneling path.

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[36] For **3**, V_a^G $(s=0) = 78.1$ kcal mol^{-1} and the CVT + SCT representative tunneling energy (RTE) increases from 74.7 kcal mol^{-1} at 77 K to 76.6 kcal mol^{-1} at 298 K to 77.9 kcal mol^{-1} at 600 K. Therefore, at 298 K most typical tunneling occurs 1.5 kcal mol^{-1} below the saddle point which is approximately at half maximum of the barrier height of the reaction.

[37] At all temperatures, $k_{CVT}(\mathbf{3}) > k_{CVT}(\mathbf{1})$ (see the Supporting Information for rate constants) implying that in the absence of tunneling, a smaller barrier height for **3** favors a faster proton transfer.