Kinetics

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Tunneling Assists the 1,2-Hydrogen Shift in N-Heterocyclic Carbenes**

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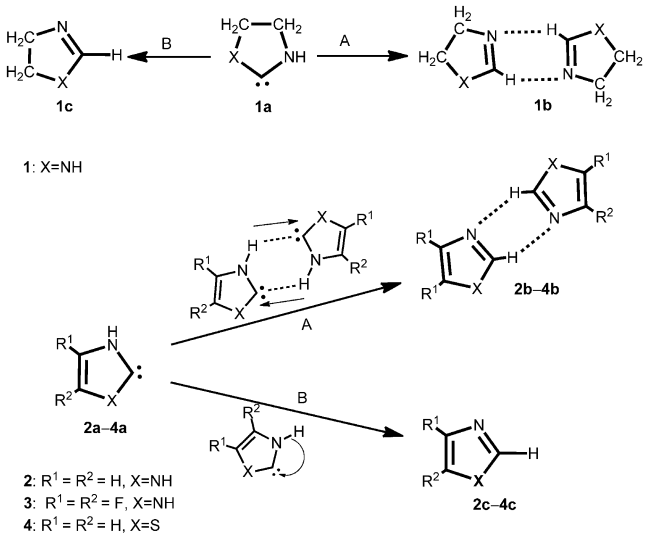
Abstract: *At room temperature, 1,2-hydrogen-transfer reactions of N-heterocyclic carbenes, like the imidazol-2-ylidene to give imidazole is shown to occurr almost entirely (> 90 %) by quantum mechanical tunneling (QMT). At 60 K in an Ar matrix, for the 2, 3-dihydrothiazol-2-ylidene→thiazole transformation, QMT is shown to increase the rate about 10^5 times. Calculations including small-curvature tunneling show that the barrier for intermolecular 1,2-hydrogen-transfer reaction is small, and QMT leads to a reduced rate of the forward reaction because of nonclassical reflections even at room temperature. A small barrier also leads to smaller kinetic isotope effects because of efficient QMT by both H and D. QMT does not always lead to faster reactions or larger KIE values, particularly when the barrier is small.*

Imidazol-2-ylidenes, the first stable carbene[1,2] and its various structural analogues, N-heterocyclic carbenes (NHC), have emerged as one of the most versatile ligands for the synthesis of catalytically relevant organometallic catalysts.[3,4] Nevertheless, NHC molecules are known to dimerize in solution,[5] thereby reducing the effectiveness of the ligand (in its monomeric form) to coordinate with metal centers. Dimerization of NHCs, first proposed by Wanzlick,[6] has been a subject of interest both experimentally and theoretically.[7] A direct approach mechanism of NHC monomers to form a dimer, though highly exothermic, has been found to have prohibitively large activation energy.[8,9] In contrast, in the presence of protons (or electrophiles) the reaction has been shown to be extremely fast.[10] Therefore, there exists an agreement in the literature that dimerization of NHCs is proton catalyzed.[9]

Apart from dimerization, imidazole-2-ylidene and its dihydro analogue can also undergo 1,2-hydrogen-shift reactions to form imidazole and dihydroimidazole, respectively (see Scheme 1), under acid-free conditions.[11] Based on CISD + Q/TZ2P calculations, Heinemann and Thiel has shown that the barriers to intramolecular 1,2-hydrogen shifts in diaminocarbenes are too large (> 45 kcal mol^{-1}) to be feasible under ambient experimental conditions.[12] Nevertheless, Maier et al. have shown that photochemically generated 2,3-dihydrothiazol-2-ylidenes readily rearranged to thiazole in a matrix at 60 K.[13] In line with the estimate of Heinemann and Thiel, they calculated the barrier for an intramolecular 1,2-hydrogen shift to be 42.3 kcal mol^{-1} at the MP4SDTQ(fc)/6-31G(d)//MP2(fc)/6-31G(d) level of theory. Therefore, Maier et al. concluded that the isomerization of 2,3-dihydrothiazol-2-ylidenes to thiazole proceeds through a intermolecular hydrogen shift between two molecules of the reactant. Based on B3LYP/aug-cc-pVTZ calculations, Hu et al. estimated the barrier for an intermolecular hydrogen shift to be $\Delta E^{\ddagger}$(zero-point energy corrected) = 2.3 kcal mol^{-1}.[14] Hence, an intermolecular process is expected to be the dominant pathway for such 1,2-hydrogen shifts. The mechanisms for intermolecular and intramolecular hydrogen-transfer reactions of NHCs are shown in Scheme 1. We show herein that quantum mechanical tunneling (QMT) plays a very important role in the conversion of imidazole-2-ylidenes into imidazole and their various derivatives, both at room and low temperatures.



Scheme 1. Hydrogen transfer in **1**–**4** by intermolecular (Path A) and intramolecular (Path B) mechanisms.

The hybrid M06-2X DFT functional[15] along with the 6-31 + G(d,p) basis set[16] was employed for the calculation of the reaction energies (ΔE) and the energy of activation ($\Delta E^{\ddagger}$) for (intra) intermolecular hydrogen-transfer reactions for **1**–**4**. Table 1 lists the zero-point energy (ZPE) corrected ΔE and $\Delta E^{\ddagger}$ values for both the paths. The structural coordinates of the reactant complexes, product complexes, and transition states (TSs) are shown in the Supporting Information. In the case of the intermolecular hydrogen-transfer reaction, ΔE is

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Table 1: Reaction energy and barrier height (ZPE corrected) at the M06-2X/6-31+G (d,p) level of theory (in kcal mol^{-1}).

	Path	ΔE	$\Delta E^{\neq}$
1a→**1b**	A	−31.3	11.4
1a→**1c**	B	−18.8	44.1
2a→**2b**	A	−40.8	6.6
2a→**2c**	B	−25.1	42.4
3a→**3b**	A	−50.1	1.6
3a→**3c**	B	−30.2	38.6
4a→**4b**	A	−45.0	2.5
4a→**4c**	B	−28.6	42.5

defined as the energy difference between the hydrogen-bonded product complex (imidazole dimer or its derivatives) and the reactant complex (imidazole-2-ylidene dimer or its derivative), and $\Delta E^{\neq}$ is the energy barrier between them. For all cases, the TS corresponds to the first-order saddle point with two non-equivalent N–H···C hydrogen bonds.[17] Our computed reaction energies and barrier heights are in excellent agreement with the previous estimates.[13,14] Clearly, hydrogen-transfer reactions are predicted to be thermodynamically favorable for both the pathways.

The barriers for intramolecular hydrogen transfer in all the reactions are found to be very large. It is important to note that the width of the barrier is actually very small for an intramolecular 1,2-hydrogen-transfer process and should be typically less than 1 Å. Though an accurate estimation of the width of the barrier is difficult, based on the superposition of the profile of the vibrational ground-state adiabatic potential energy (V_a^G) with respect to the mass-scaled reaction coordinate (s) and the representative tunneling energy (RTE) at 298 K, we estimate the width of the barrier to be $\Delta s = 1.9$ amu$^{1/2}$Bohr (reduced mass, $\mu = 1$ amu) for **1a**→**1c**. The calculation is shown in the Supporting Information.[18] Notwithstanding, the small barrier width which would tend to facilitate QMT, the reaction rate, inclusive of QMT (at the CVT+SCT level of theory), is negligible. At 298 K, k(CVT+SCT) = 5.24×10^{-17} s^{-1} for **1a**→**1c**, thereby negating the possibility of such a reaction even with the assistance from tunneling.[19]

The activation energies for the intermolecular hydrogen-transfer reaction are rather small, and when coupled with their high reaction energies, should lead to facile and irreversible NHC→imidazole transformation. The presence of -I/-R groups on the NHC further reduces the activation energy for hydrogen-transfer reactions. For example, $\Delta E^{\neq}$ (ZPE corrected) reduces from 11.4 kcal mol^{-1} in **1** to 1.6 kcal mol^{-1} in **3** upon fluorination. At 298 K, $k_{CVT} = 2.91 \times 10^3$ s^{-1}, 2.00×10^7 s^{-1}, and 4.80×10^{10} for **1a**→**1b**, **2a**→**2b**, and **3a**→**3b** respectively.

With the incorporation of small-curvature tunneling, the rates for hydrogen transfer ($k_{CVT+SCT}$) increase significantly for **1** and **2**. At 298 K, $k_{CVT+SCT} = 3.56 \times 10^4$ s^{-1} and 1.27×10^8 s^{-1} for **1a**→**1b** and **2a**→**2b**, respectively. QMT contributes majorly in comparison to the classical over-the-barrier process since, 92 and 84% of the reaction is found to be occurring by tunneling for **1a**→**1b** and **2a**→**2b**, respectively, at room temperature. Figure 1 shows the Arrhenius plots for **1a**→**1b** and **2a**→**2b** for 100 K to 400 K. The CVT rates are also shown for comparison. The positive contribution of QMT towards the reaction results in smaller activation energy, thereby leading to CVT+SCT rates exceeding the CVT rates. At 298 K, E_a^{CVT}(**1a**→**1b**) = 11.5 kcal mol^{-1}, $E_a^{CVT+SCT}$(**1a**→**1b**) = 9.8 kcal mol^{-1}, and E_a^{CVT}(**2a**→**2b**) = 6.7 kcal mol^{-1}, $E_a^{CVT+SCT}$(**1a**→**1c**) = 4.2 kcal mol^{-1}. Though at low temperatures (~100 K), the Arrhenius plot is unambigiously curved, at room temperature the curvature seems rather modest as a result of thermally activated tunneling. The most probable energy at which tunneling occurs (RTE) for **1a**→**1b** and **2a**→**2b** is found to be 1.7 kcal mol^{-1} and 2.5 kcal mol^{-1}, respectively, below the top of the barrier at 298 K.

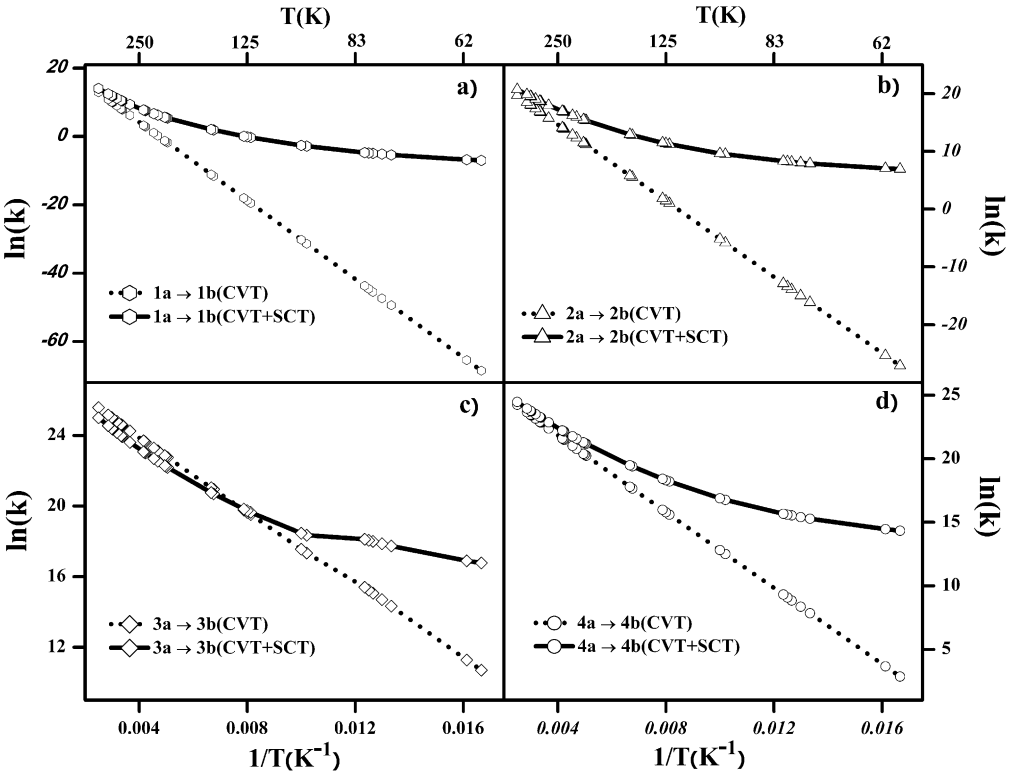

Figure 1. Arrhenius plots of the CVT and CVT+SCT rate constants for a) **1a**→**1b**, b) **2a**→**2b**, c) **3a**→**3b**, and d) **4a**→**4b**. T = 60–400 K.

Counterintuitively, QMT reduces the rate of the reaction for **3a**→**3b** at room temperature. At 298 K, $k_{CVT+SCT} = 2.55 \times 10^{10}\ s^{-1}$. Though at cryogenic temperatures $k_{CVT+SCT} > k_{CVT}$, for temperatures above 150 K, tunneling is found to decrease the rate of the reaction with respect to the classical CVT rates. The barrier for this reaction is very low and hence, even at room temperature most of the reacting molecules are vibrationally excited to levels with energy exceeding the barrier ($E_{thermal} > E^{\pm}$). For such cases, nonclassical reflection reduces the overall probability of forward product formation.[20]

For $T > 150$ K, nonclassical reflections make the CVT + SCT rate constants about a factor of two lower than the CVT rate constants. One can physically view this as an outcome of the uncertainty principle. It is well known that in quantum mechanics a particle with energy below a barrier height can have a nonzero probability of transmission, and also that a particle with an energy greater than a barrier height can have a probability of transmission less than unity. Usually the former dominates because of the larger Boltzmann factors at lower energy, and this makes the thermally averaged transmission coefficient greater than one. However, in the present case the latter dominates, and the thermally averaged transmission coefficient is less than one. Nevertheless, at cryogenic temperatures when most of the molecules are in their vibrational ground state, tunneling across the small yet (classically) existent barrier increases the rate of the reaction. As seen from Figure 1c, the CVT + SCT Arrhenius plot for **3a**→**3b** crosses the linear CVT regime for $T > 150$ K. Notwithstanding the contribution from nonclassical reflection at room temperature, the reaction is extremely fast with and without a contribution from QMT.

Isotopic replacement of the two NH protons D is expected to decrease the rate of intermolecular hydrogen transfer by both zero-point energy effects and the less effective tunneling of D in comparison to H. At 298 K, $k^{H}_{CVT}(\mathbf{1a}\rightarrow\mathbf{1b})/k^{D}_{CVT}(\mathbf{1a}\rightarrow\mathbf{1b})$ and $k^{H}_{CVT}(\mathbf{2a}\rightarrow\mathbf{2b})/k^{D}_{CVT}(\mathbf{2a}\rightarrow\mathbf{2b})$ are 15.1 and 12.2, respectively. Small-curvature tunneling increases the KIE values with $k^{H}_{CVT+SCT}(\mathbf{1a}\rightarrow\mathbf{1b})/k^{D}_{CVT+SCT}(\mathbf{1a}\rightarrow\mathbf{1b})$ and $k^{H}_{CVT+SCT}(\mathbf{2a}\rightarrow\mathbf{2b})/k^{D}_{CVT+SCT}(\mathbf{2a}\rightarrow\mathbf{2b})$ being 54.4 and 16.9, respectively. Clearly the effects of QMT on KIE values are more impressive for **1a**→**1b** than that for **2a**→**2b**. To understand the difference between these two systems, Arrhenius plots of the KIE data are shown in Figure 2.

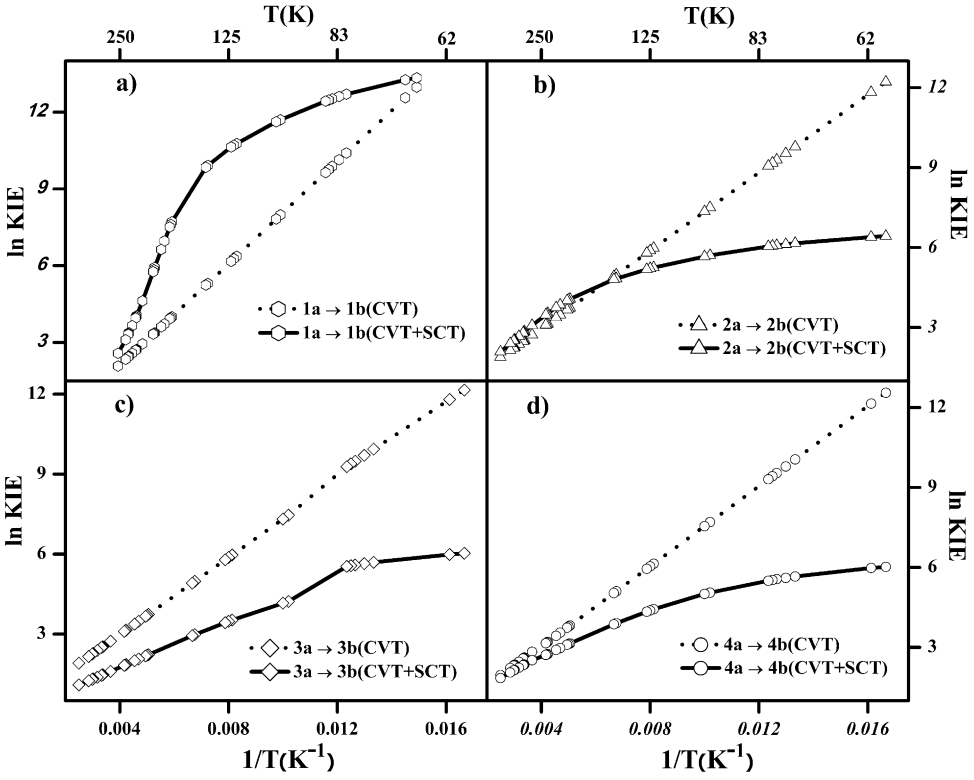

Figure 2. Arrhenius plots of the CVT and CVT + SCT KIE data for a) **1a**→**1b**, b) **2a**→**2b**, c) **3a**→**3b**, and d) **4a**→**4b**. $T = 60$–400 K.

The deviation from linearity of the CVT + SCT Arrhenius plot for KIE data is more pronounced in the case of **1a**→**1b** as the temperature is reduced. This deviation can be rationalized from the fact that the E_a (**1a**→**1b**) > E_a (**2a**→**2b**). At the high-temperature limit when tunneling is insignificant (for both H and D), the KIE value is closer to that of the linear regime of CVT calculations. With decreasing temperature, QMT begins to contribute significantly to the reaction rate, albeit more for H than D, and results in a convex deviation from the Arrhenius plot. However, for **2a**→**2b**, for which the barrier is smaller, both H and D tunnel efficiently and therefore lead to rather modest KIE values as a result of tunneling.[21,22] For example, at 298 K, the ratios of the transmission coefficients $\kappa^{H}_{SCT}(\mathbf{1a}\rightarrow\mathbf{1b})/\kappa^{D}_{SCT}(\mathbf{1a}\rightarrow\mathbf{1b})$ for H and D for **1a**→**1b** is 3.5 while that for **2a**→**2b**, is only 1.4. In the case of **2a**→**2b** for $T = 125$ K and below, $k^{H}_{CVT+SCT}(\mathbf{2a}\rightarrow\mathbf{2b})/k^{D}_{CVT+SCT}(\mathbf{2a}\rightarrow\mathbf{2b}) < k^{H}_{CVT}(\mathbf{2a}\rightarrow\mathbf{2b})/k^{D}_{CVT}(\mathbf{2a}\rightarrow\mathbf{2b})$. For example at 125 K, CVT and CVT + SCT KIE values for **2a**→**2b** are 359.5 and 183.9, respectively, and is observed in the reduced slope of the CVT + SCT Arrhenius plot in comparison to that of the CVT one at low temperatures. This reduction again is a consequence of the fact that at low temperatures, for reactions with smaller barriers, both H and D tunnel rather effectively, thereby reducing the difference between their activation energies. At 125 K, E_a^{H}(CVT)-E_a^{D}(CVT) is 1.5 kcal mol^{-1} while E_a^{H}(CVT+SCT)-E_a^{D}(CVT+SCT) is only 0.5 kcal mol^{-1} for **2a**→**2b**. As the barrier is reduced further for **3a**→**3b** and **4a**→**4b**, the CVT + SCT KIE values become smaller than the CVT KIE values at room temperature. This change is clearly observed in

Arrhenius plots for the CVT + SCT KIE having smaller slope than the CVT KIE Arrhenius plots in Figures 2c,d.

Direct experimental evidence for QMT in such intermolecular hydrogen-transfer reactions is unavailable. The only available example for such a transformation is the 2,3-dihydrothiazol-2-ylidene→thiazole reaction reported by Maier et al., as discussed previously.[13] At 298 K, we calculate $k_{CVT+SCT}$ and E_a(CVT+SCT) for **4a**→**4b** to be 1.27×10^{10} s^{-1} and 2.7 kcal mol^{-1}, respectively. QMT therefore leads to a minor enhancement of the reaction rate (~33 percent) compared to that of the classical CVT calculation. However, since the transformation was performed in an Ar matrix at 60 K, QRST CVT + SCT calculations were performed to accurately calculate the reaction rates at low temperatures (see the computational details in the Supporting Information). At 60 K, $k_{CVT+SCT}=1.67\times10^{6}$ s^{-1} with a very small activation energy of E_a(CVT+SCT) = 0.4 kcal mol^{-1}. The CVT rate of the reaction, $k_{CVT}=1.76\times10^{1}$ s^{-1} [E_a(CVT) = 3.0 kcal mol^{-1}], is five orders of magnitude lower. This difference is evident from the large curvature of the Arrhenius plot of the CVT + SCT rates with respect to CVT rates as seen in Figure 1d at low temperatures. Evidence for QMT at this temperature can also be derived from the CVT + SCT KIE value of 412.3, which is smaller than the quasiclassically calculated CVT KIE value of 2825 (where "quasiclassical" denotes quantized bound vibrations but no tunneling or nonclassical reflection) because of efficient tunneling by both H and D across the small barrier. Clearly, for the low temperature at which the experiments were performed, the reaction is extremely fast because of QMT and not because it occurs by passage over the barrier. This assessment is in agreement with the experimental observation that any attempt to isolate **4a** was unsuccessful and always led to the final product, **4b**. In fact, **4a** has been generated and detected only in the gas-phase by mass spectrometry,[23] and further corroborates our finding that a monomer of **4a** cannot form thiazole because the only available pathway for such a transformation proceeds through the intramolecular 1,2-hydrogen shift reaction which has an extremely high barrier (42.5 kcal mol^{-1} at M06-2X/6-31 + G(d,p) level of theory, see Table 1).

In summary, small-curvature tunneling calculations on the imidazole-2-ylidene→imidazole transformation, and related reactions, show that QMT has important consequences on the preferred intermolecular pathway. When the barrier is too shallow, as is the case for **3a**→**3b**, QMT decreases the forward rate of the reaction in comparison to that of the classical over-the-barrier route, even at room temperature, because of nonclassical reflection. To the best of our knowledge, experimentally verified examples where the tunneling transmission coefficient is less than unity at ambient temperatures (because the effect of nonclassical reflection dominates tunneling) are unknown and **3a**→**3b** is a case where it can be experimentally verified. Also, it is evident from our calculations that KIE (CVT) > KIE (CVT + SCT) at temperatures less than 125 K for **2a**→**2b** and even at room temperature for **3a**→**3b** and **4a**→**4b**. This trend is because a small barrier also leads to a smaller KIE value because of efficient tunneling by both H and D. The rapid 2,3-dihydrothiazol-2-ylidene→thiazole reaction is shown to proceed entirely by QMT in an Ar matrix at 60 K. We show that the generally accepted paradigm that QMT should increase the rate of the reaction and should also lead to large KIE values, is an over generalization and need not always be the case, particularly for reactions with small barriers.

Supporting Information. Computational Details, optimized geometries, energies, thermal corrections, and harmonic frequencies for **1–4**, and the transition structure connecting them, CVT and CVT + SCT rate constants from 50 to 400 K and calculation scheme for estimating barrier width (w).

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[17] The TS with two equivalent N–H···C hydrogen bonds is a second-order saddle point. All attempts to remove one of the two imaginary modes by relaxing along that transition vector converged to the structures with non-equivalent N–H···C hydrogen bonds. Previous calculations by Hu et al. also confirm this. See Ref. [14].
[18] Our scheme of estimating the barrier width assumes that for the most typical energy at which tunneling occurs at a particular temperature (RTE), the tunneling path is linear. This is only an approximation as CVT + SCT method includes contribution from tunneling via curved tunneling paths across the potential energy surfaces.
[19] For the same reaction (**1a**→**1c**) calculations at the canonical variation transition state theory (CVT), k(CVT) = 2.57×10^{-20} s^{-1} at 298 K. Therefore, even though QMT fastens the

reaction ~2000 times, it still remains too slow to be experimentally observed.

[20] Nonclassical reflection is known to decrease the rate of forward reactions compared to a classical over-the-barrier process: J. Zheng, R. J. Rocha, M. Pelegrini, L. F. A. Ferrao, E. F. V. Carvalho, O. Reberto-Neto, F. B. C. Machado, D. G. Truhlar, *J. Chem. Phys.* **2012**, *136*, 184310. However, such cases occur at very high temperature ($T > 1400$ K). In this case because of the very small barrier for **3a**→**3b**, $k_{CVT+SCT} < k_{CVT}$ at room temperature.

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