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A direct-dynamics study of proton transfer through water bridges in guanine and 7-azaindole

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To evaluate the efficiency of bridges of water molecules as proton conduits, multidimensional *ab initio* proton transfer rate constants are reported for complexes of guanine and 7-azaindole with one and two water molecules. These water molecules form hydrogen-bonded bridges between functional groups involved in tautomerization via proton transfer and catalyze this transfer. Structures and energies of the relevant stationary configurations are optimized at the second-order Møller–Plesset level and vibrational force fields are evaluated at the Hartree–Fock level. The proton transfer rate constants, calculated with the instanton method, show the effect of the structure and strength of the hydrogen bonds, reflected in couplings between the tunneling mode and the other vibrations of the complexes. The results indicate that strongly hydrogen-bonded, strain-free water bridges can serve as very efficient proton conduits. © *2000 American Institute of Physics.* [S0021-9606(00)52202-8]

I. INTRODUCTION

It is well recognized that proton transfer is a major component of many biological processes. Typically this transfer takes place across hydrogen bridges, which are present in abundance in all biological systems. During the transfer the proton is displaced over a distance of about 1–1.5 Å. It is known, however, that many biological processes, including passage through cell membranes, involve proton transfer over much longer distances.[1–5] It is also known that proteins play a key role in this long-range transfer, but the actual mechanism remains to be elucidated. From a thermodynamic point of view, it is clear that mechanisms that require a drastic rearrangement of the structure of the assisting protein are unlikely to be competitive.[2] Diffusion of a small species such as a hydronium ion[3] H_3O^+ is difficult to reconcile with the robustness inherent in biological functioning. The alternative is to assume that the proton that starts the journey is not the same as the one that reaches its destination: Instead of having one proton making N elementary steps, one can then have N protons each making a single step, as in the well-known Grotthus mechanism for proton transfer in ice. This requires a linked chain of hydrogen bridges undergoing a collective proton shift.

Proton transfer mechanisms of this kind have been studied by molecular dynamics simulations,[6–8] but these studies cannot give direct information on the transfer rate, nor have they established whether the collective transfer is coherent or incoherent. Studies of specific enzymatic reactions, such as carbonic anhydrase II, where proton transport involves a chain of at least two water molecules,[9,10] have focused on the structural rather than the dynamic aspects of the process. In general, very little is known about the rate of proton transfer in biological systems.

We showed in recent papers[11] that a single water molecule can serve as an efficient proton conduit in 7-azaindole and glycine, allowing coherent double proton transfer with rate constants of the order of 10^7-10^8 s^{-1} at room temperature. The transfer proceeds by synchronous quantum-mechanical tunneling of the protons to and from the water molecule, a motion that is strongly coupled to (and facilitated by) the vibrations of the bridgehead atoms. Actual transfer rate constants were calculated for net proton (and deuteron) transfer in a range of temperatures. In other papers we have studied the structural and energetic properties of solvated guanine tautomers in which one or two hydrogen-bonded water molecules can serve as proton transfer bridges.[12,13] In the present paper we compare the rate of double proton transfer through a single water molecule with that of triple proton transfer through a chain of two water molecules. For this study we have chosen two molecules of biological interest that can form cyclic complexes with water molecules: guanine and 7-azaindole. Their tautomerization reactions are illustrated in Fig. 1. 7-Azaindole is a molecule that has been associated with several biological models.[14–17] It exists in two forms, depending on which nitrogen atom carries a proton, and these forms are separated by a very high and wide barrier.[18,19] In protic solutions, however, tautomerization occurs rapidly.[15–17] The DNA base guanine has an oxo and a hydroxo form separated by a high and wide barrier; it has been shown[12] that the transition between these tautomers is catalyzed by water.

In both of these systems the large separation of the functional groups involved in the proton transfer reaction favors

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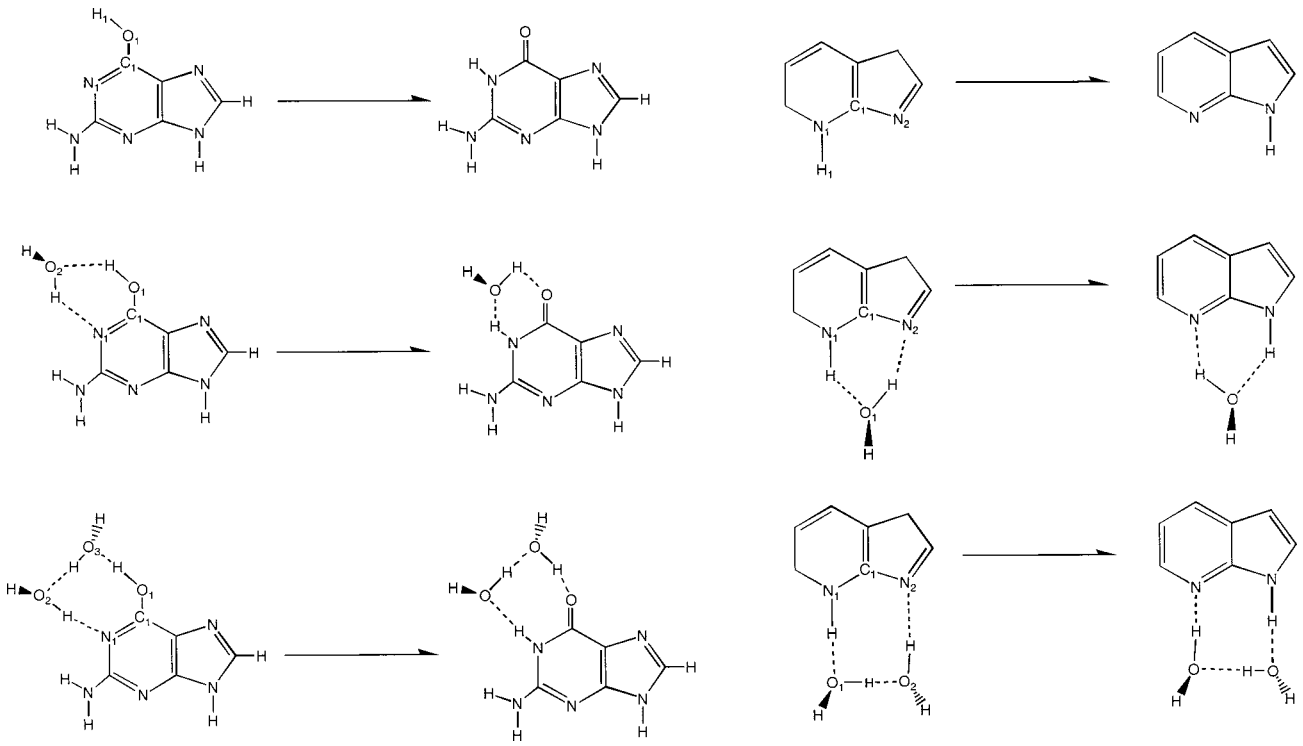

FIG. 1. Schematic representation of the tautomerization of guanine and its 1:1 and 1:2 complexes with water (left) and 7-azaindole and its 1:1 and 1:2 complexes with water (right). The species on the left of the arrow depict the tautomeric forms, which transform into the canonical form on the right. The numbering of the atoms refers to Table I.

transfer through a solvent bridge. The hydrogen bonds formed with a single bridging water molecule are nonlinear, which results in strain. This strain is expected to be reduced if the bridge consists of two water molecules, as illustrated in Fig. 1, but at the expense of adding another proton transfer step. Since it is not obvious which of these arrangements yields the faster transfer, we undertake to carry out such a comparison. For the tunneling calculations we use the instanton approach,[20–22] as implemented in the DOIT program,[22,23] which is very efficient and can handle systems of the size chosen at a reasonably high level of quantum chemistry.

The instanton approach is a quasiclassical method based on the least-action principle. The instanton path is the least-action trajectory for a given temperature, which implies that it is the dominant tunneling trajectory at that temperature. Although the exact instanton path is very difficult to calculate for a polyatomic molecule or complex, for rate constant calculations it is sufficient to calculate the corresponding multidimensional instanton action. An approximate expression for this action can be derived from the easily calculated one-dimensional tunneling rate constant through the introduction of appropriate couplings of the tunneling mode to the other (i.e., transverse) vibrational modes. If the couplings are taken to be linear in the transverse mode coordinates and if these modes are taken to be harmonic, this approximate instanton action is readily calculated from the structures, energies, and force fields of the stationary points along the reaction coordinate, which in turn are readily obtained from the output of standard quantum-chemical programs. In this paper we report the results of such calculations for 7-azaindole and guanine.

II. POTENTIAL-ENERGY SURFACES

To evaluate the potentials required for the application of the DOIT program,[23] we calculate the optimized structure and energy of the initial, final, and transition state of guanine and 7-azaindole, and their 1:1 and 1:2 complexes with water. From these results we construct potential energy surfaces for the tautomerization reactions in a form suitable for the evaluation of full-dimensional rate constants of these reactions in a wide range of temperatures.

The reaction coordinate in the instanton approach is not the minimum-energy path but the mode with imaginary frequency in the transition state, formally extended to the equilibrium configurations. Correspondingly the tunneling distance between the two equilibrium positions of the hydrogen atom is measured along this reaction coordinate. To calculate the appropriate potential-energy surface in terms of the normal coordinates of the transition state, our minimum requirements are knowledge of the energies, structures, and force fields of the three stationary states along the reaction path. Since absolute values for the rate constants are not crucial for the present purpose and since no experimentally observed kinetic data have been reported, the minimum requirements will suffice.

The level of the quantum-chemical calculations must be high enough to reveal the complex nature of the hydrogen bridges, since these govern the reaction path. Unfortunately, little is known about the level needed for an adequate description of, especially, the corresponding transition states. The highest level of theory explored thus far for guanine–water complexes is reported in our earlier guanine study.[12] It

TABLE I. Structural parameters of the hydrogen-bonded bridges involved in the tautomerization of 7-azaindole and guanine and their 1:1 and 1:2 complexes with water, calculated at the MP2/6-31G* level. *N* represents the canonical form, *T* the tautomeric form, and TS the corresponding transition state. Distances are in angstrom, angles in degrees.

		7-azaindole				Guanine		
		T	TS	*N*		*T*	TS	*N*
Isolated molecule								
	N_1N_2	2.399	2.193	2.405	O_1N_1	2.300	2.124	2.302
	$H_1N_1C_1$	117.0	74.9	124.0	$O_1C_1N_1$	120.0	106.3	118.6
	$N_1C_1N_2$	126.0	110.9	124.9	O_1N_2	2.314	2.336	2.339
	H_1N_2	2.611	1.444	2.718	H_1N_1	2.252	1.312	1.017
1:1 complex								
	N_2O_1	2.789	2.439	2.829	N_1O_1	2.318	2.296	2.305
	N_1N_2	2.403	2.378	2.407	$O_1C_1N_1$	120.4	119.3	120.5
	$N_1C_1N_2$	125.8	122.9	124.9	O_1O_2	2.741	2.410	2.811
	N_1O_1	2.777	2.451	2.882	N_1O_2	2.810	2.431	2.822
1:2 complex								
	N_2O_2	2.803	2.495	2.843	N_1O_1	2.320	2.319	2.303
	N_1N_2	2.412	2.414	2.415	$O_1C_1N_1$	121.2	122.1	120.9
	$N_1C_1N_2$	126.6	126.1	125.7	O_2O_3	2.757	2.415	2.719
	N_1O_1	2.785	2.501	2.862	N_1O_2	2.806	2.501	2.868
	O_1O_2	2.706	2.422	2.742	O_1O_3	2.720	2.443	2.797

amounts to structural optimization at the second-order Møller–Plesset[24] (MP2) level with the standard 6-31G* basis set combined with force field calculations at the structures optimized at the Hartee–Fock (HF) level with the same basis set. Higher levels of theory were tested via single-point calculations, but in the absence of suitable experimental data, there is no firm basis for a critical assessment of the results. Fortunately, the barrier height governing the transfer dynamics showed the same trends for the two guanine–water complexes at different levels of theory. Similarly, in earlier studies of tunneling splittings,[25] it was found that the isotope effect and the mode dependence of the splittings could be accounted for at the Hartree–Fock level, although reproduction of the absolute values of the splittings required scaling of the barrier height. Since for the systems under consideration no experimental rate constants are available, we adopt the same level of theory as that used in Ref. 12. Thus we perform the structural optimization at the MP2 level with the standard 6-31G* basis set, but calculate the force field at the structures optimized at the HF/6-31G* level. This compromise, adopted in view of the size of the systems, takes into account that the barrier height and tunneling distance are the main determinants of the tunneling rate, while the vibrational frequencies contribute in second order through the coupling corrections. The guanine calculations are reported and discussed in detail in Ref. 12. 7-Azaindole calculations were carried out at the same level by means of the GAUSSIAN 98 suite of programs.[26] No attempt was made to correct for basis-set superposition errors,[27] since they are expected to be roughly the same for the systems to be compared and hence will have at most a minor effect on the relative rate constants that are the aim of this study.

The principal structural parameters are summarized in Table I. In both guanine and 7-azaindole the tautomerization barrier is very high, namely about 36 and 51 kcal/mol, respectively, as shown in Table II. Correspondingly, it follows

TABLE II. Parameters related to the dynamics of tautomerization. The (mass-weighted) displacement along the reaction coordinate between the canonical (*N*) and tautomeric (*T*) forms is listed as the tunneling distance in Å $\text{amu}^{1/2}$. Energies are in kcal/mol, frequencies, scaled by 0.9, in cm^{-1}, rate constants in s^{-1}. The last row represents the rate constants obtained without coupling to the transverse modes.

	7-azaindole			Guanine		
	Molecule	1:1	1:2	Molecule	1:1	1:2
Barrier height	50.95	14.30	13.66	36.15	14.74	15.63
T–*N* energy gap	13.99	10.20	8.84	2.39	3.64	5.65
Tunneling distance	2.554	1.256	1.056	2.026	1.338	1.266
Imaginary frequency	2158*i*	1096*i*	949*i*	2120*i*	1920*i*	1113*i*
Effective frequency in the well	1334	3148	2968	1403	3228	2837
$k(0)$	0.97×10^{-26}	0.20×10^{6}	0.13×10^{6}	0.11×10^{-13}	0.51×10^{7}	0.60×10^{4}
$k(300)$	0.26×10^{-17}	0.12×10^{7}	0.18×10^{7}	0.86×10^{-5}	0.45×10^{8}	0.42×10^{6}
$k^0(300)$	0.73×10^{-20}	0.16×10^{8}	0.13×10^{9}	0.98×10^{-10}	0.39×10^{7}	0.85×10^{6}

from Table I that the structure of the transition state is strongly deformed relative to the equilibrium configurations. With tunneling distances of about 2 and 2.5 Å , respectively, it is to be expected that tautomerization through tunneling of protons with an effective mass of unity or higher will be extremely slow at room temperature.

In the complexes, one and two water molecules form stable hydrogen-bonded bridges between the functional groups involved in the tautomerization. For 7-azaindole the cyclic structure of these complexes has been confirmed by spectroscopic observations.[19] As shown in Table I, the effect of complexation on the structure of the stable configuration of the parent molecules is small, but the effect on the transition state is substantial; specifically, the structure of this state is much closer to that of the equilibrium structures than in the isolated molecule. Correspondingly the tautomerization barriers, listed in Table II, are much lower, namely in the range 14–16 kcal/mol, and the tunneling distances are in the range 1.0–1.3 Å amu$^{1/2}$, so that at room temperature tautomerization is expected to be rapid by a mechanism that involves collective motion of two or three protons.

With the calculated parameters we construct potential-energy surfaces in a form suitable for instanton calculations:

$$U(x,\mathbf{y}) = U(x) + \frac{1}{2}\sum_s \omega_s^2[(y_s)^2-(\Delta y_s)^2] + \frac{1}{2}\sum_a \omega_a^2[(y_a)^2-(\Delta y_a)^2] - x^2\sum_s C_s(y_s-\Delta y_s) - x\sum_a C_a(y_a\pm\Delta y_a), \tag{1}$$

where x represents the reaction coordinate, corresponding to the mode with imaginary frequency, and $\mathbf{y}_s$ and $\mathbf{y}_a$ represent the symmetric and antisymmetric components of the transverse coordinates, respectively, the sums running over all modes (with frequencies $\omega_{a,s}$) that are displaced between the stable configurations and the transition state. The values of the mass-weighted coordinates are given by $x=\mathbf{y}_{s,a}=0$ in the transition state and by Δx^i, $\Delta\mathbf{y}^i$, and Δx^f, $\Delta\mathbf{y}^f$ in the initial and final state, respectively. The symmetric and antisymmetric components of the vibrational displacements of the normal modes are defined by the linear combinations

$$\Delta\mathbf{y}_{s,a} = \tfrac{1}{2}(\Delta\mathbf{y}^f \pm \Delta\mathbf{y}^i). \tag{2}$$

The couplings assume the form

$$C_a = \omega_a^2\Delta y_a/\Delta x,\ C_s = \omega_s^2\Delta y_s/(\Delta x)^2, \tag{3}$$

where $\Delta x = \frac{1}{2}(\Delta x^f - \Delta x^i)$. We transform calculated interatomic distances into vibrational displacements through the relation

$$\Delta(x,\mathbf{y}) = \mathbf{r}\cdot\mathbf{L}, \tag{4}$$

where $\mathbf{r}$ is the vector of the mass-weighted atomic displacements between the transition state and the corresponding equilibrium configuration and $\mathbf{L}$ is the $3N\times(3N-6)$ matrix that relates the normal coordinates of the transition state to the mass-weighted Cartesian coordinates of the atoms.

To construct the potential near the initial equilibrium configuration, we carry out a transformation from the normal coordinates of the transition state, introduced as $\{x,\mathbf{y}\}$, to those of the initial equilibrium configuration, denoted by $\{\mathbf{z}\}$:

$$\{x,\mathbf{y}\} = \mathbf{G}\{\mathbf{z}\},\ x = \sum_k G_{1k}z_k,\ \sum_k G_{1k}^2 = 1, \tag{5}$$

so that the effective frequency along the reaction coordinate in the initial state is given by

$$\Omega_0^i = \left[\sum_k G_{1k}^2(\omega_k^0)^2\right]^{1/2}, \tag{6}$$

ω_k^0 being the normal mode frequencies in the initial state. A similar transformation for the final state yields the corresponding effective frequency Ω_0^f.

To evaluate the one-dimensional adiabatic barrier $U_A(x)$, we use the barrier height U_0 and the displacements Δx^i and Δx^f as components of the barrier width, together with the calculated curvatures at the stationary configurations. By definition, the points at which $U_A(x)$ is evaluated must obey the conditions $\partial U(x,\mathbf{y}_{a,s})/\partial\mathbf{y}_{a,s}=0$ for all modes $\mathbf{y}_{a,s}$, so that the gradient is directed along x. Since the DOIT code[23] evaluates the curvatures at the stationary points, the direction of this gradient is known near these points. Therefore a simple scheme to approximate the potential $U_A(x)$ for intermediate points is to connect the regions of the stationary points by their common tangent, i.e., the tangent at the parabolas corresponding to the imaginary frequency $i\omega^*$ of the transition state and $\Omega_0^{i,f}$ of the equilibrium configurations.

III. INSTANTON DYNAMICS

In our version of the instanton method[20–23] the tunneling rate constant is calculated from

$$k(T) = (\Omega_0^i/2\pi)e^{-S_I(T)}, \tag{7}$$

where Ω_0^i, the effective tunneling frequency in the tautomeric (metastable) equilibrium configuration, is given by Eq. (6) and $S_I(T)$, the multidimensional instanton action (in units $\hbar$), assumes the form

$$S_I(T) = \frac{S_I^0(T)}{1+\Sigma_s\delta_s(T)} + \alpha_s\sum_a \delta_a(T). \tag{8}$$

In this expression $S_I^0(T)$ is the one-dimensional instanton action along the reaction coordinate:

$$S_I^0(T) = 2\int_{x_1}^{x_2}\{2m_{\text{eff}}(x)[U_A(x)-E^*(T)]\}^{1/2}dx + \hbar E^*(T)/k_BT, \tag{9}$$

where $x_{1,2}$ are classical turning points for the energy $E^*(T)$ where the period of the motion in imaginary time it in the upside-down potential $-U_A(x)$ equals $\hbar/k_BT$. For numerical work it is advantageous, however, to calculate $S_I^0(T)$ from its relation through Eq. (7) to the standard semiclassical expression for the rate of one-dimensional tunneling

$$k^0 = Z_0^{-1}\int_{\hbar\Omega_0^i/2}^{U_0} P(E)e^{-E/k_BT}dE, \tag{10}$$

where Z_0 is the one-dimensional partition function, $P(E)$ is the quasiclassical barrier penetration factor, and the integral runs from the effective zero-point energy level in the initial state to the top of the barrier. To this rate constant we must add the zero-point contribution in the limit $T\rightarrow 0$, where $S_I^0(0)=2S_C(\hbar\Omega_0^i/2)$, i.e., twice the classical action for the zero-point energy level. In these expressions the effective mass of the tunneling particle (in dimensionless units) is given by

$$m_{\mathrm{eff}}(x)=1+\sum_a\ (C_a/\omega_a^2)^2+\sum_s\ (2xC_s/\omega_s^2)^2, \qquad (11)$$

where the summations are restricted to modes with a high frequency relative to the imaginary frequency. The lower-frequency transverse modes contribute via the correction terms $\delta_{a,s}$ in Eq. (5), which are expressed in terms of the linear couplings $C_{a,s}$ of Eq. (3) as detailed in Refs. 20–22. Note that the δ_a contribute a Franck–Condon factor to the transition and thus lower the rate of transfer, whereas the δ_s shorten the tunneling distance and lower the barrier so as to facilitate the transfer. The factor $\alpha_s\leqslant 1$ in Eq. (8) describes the modulation of the antisymmetric correction by the symmetric coupling.[20,28]

IV. RESULTS AND DISCUSSION

All proton transfer rate constant calculations were performed with the DOIT 1.2 program, a soon to be released upgraded version of the DOIT 1.1 program.[23] The main quantum-chemically calculated input parameters used in these calculations are listed in Table II. Since these parameters are sensitive to the level of quantum chemistry used and since no empirical calibration is available, the absolute values of the rate constants, which are also listed in Table II, should not be taken at face value. It is clear, however, that the rate of tautomerization in the two isolated molecules will be very low at room temperature and below. In practice, this process thus requires a catalyst such as water, which splits the long tunneling path into two or three shorter paths in which the protons move collectively, either coherently or incoherently. The instanton calculations indicate that coherent tunneling dominates for the four complexes considered here.

The calculated tautomerization rate constants for the 1:1 and 1:2 complexes of guanine and 7-azaindole with water are displayed in Figs. 2 and 3, respectively. To analyze these results, only the relative values of the rate constants are needed. In guanine double proton transfer through a bridge of one water molecule is much faster than triple proton transfer through a bridge of two water molecules, whereas in 7-azaindole both processes have very similar rates. To explain these observations, we start by relating the rate constants $k(T)$ to the one-dimensional tunneling rate constants $k^0(T)$, obtained by neglecting all couplings to transverse modes, i.e., by setting $\delta_{a,s}=0$ and $m_{\mathrm{eff}}=1$. This is equivalent to replacing the instanton action $S_I(T)$ by its one-dimensional approximation $S_I^0(T)$, which is mainly governed by three parameters, namely, the barrier height U_0, the exothermicity ΔE, and the imaginary frequency $i\omega^*$. These

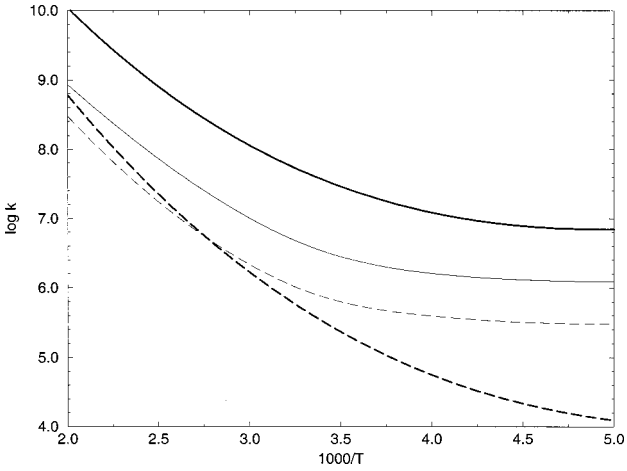

FIG. 2. Calculated tautomerization rate constants of guanine.H_2O (solid lines) and guanine.$(H_2O)_2$ (broken lines). The thick lines represent the full-dimensional results, the thin lines their one-dimensional approximations.

zero-order results are depicted by thin lines in Figs. 2 and 3. They show that the effect of the barrier height is directly reflected in the calculated zero-order rate constants, since $k^0(T)$ is larger for the 1:1 than for the 1:2 complex in guanine, whereas the reverse holds for 7-azaindole. Figure 4 shows the displacement vector of the mode with imaginary frequency, which sets the time scale for the motion under the barrier. Its direct effect is seen in the slower transfer in the 1:1 complex of 7-azaindole compared to that of guanine. The effect of the exothermicity is not immediately obvious, but that it must be important follows from the fact that it is related to the difference in the two hydrogen bonds each of these molecules forms with the complexed water molecules.

We can obtain a clearer picture of these effects by considering the coupling to transverse modes. Coupling to modes with a frequency that is high compared to the tunneling motion, represented by ω^*, increases the mass of the tunneling particle and thus makes the transfer more classical. The lower the imaginary frequency, the more modes fall into this high-frequency category and the stronger will be the effect. Coupling to the remaining low-frequency modes may either help or hinder the transfer, depending on whether the

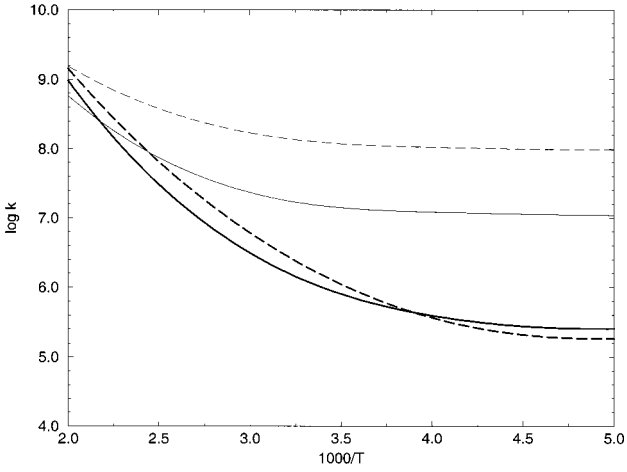

FIG. 3. Same as Fig. 2 for 7-azaindole.

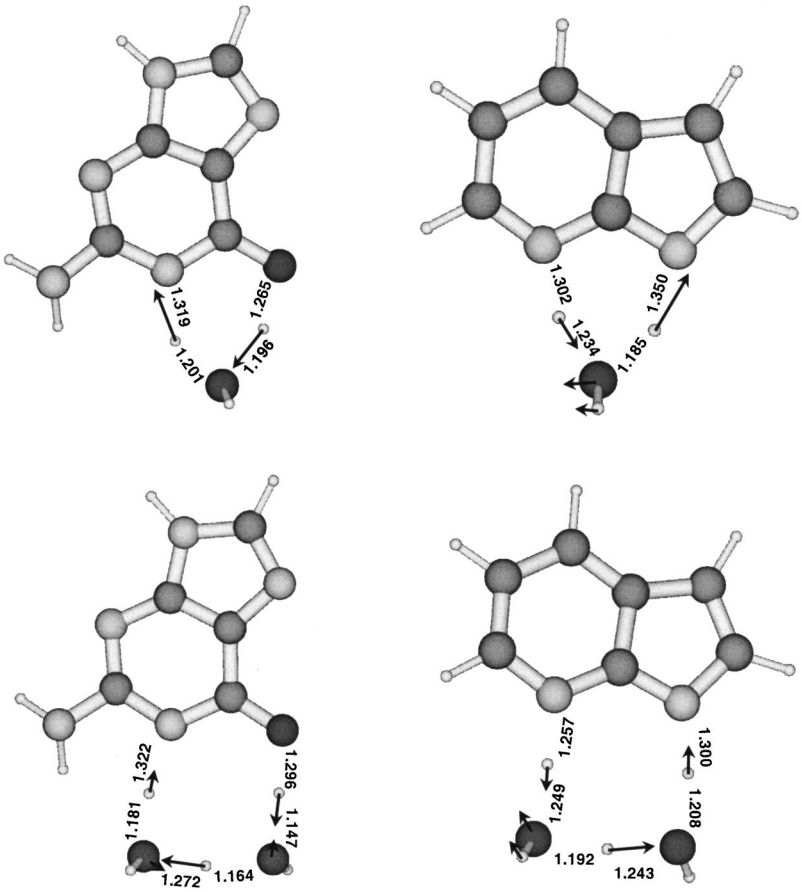

FIG. 4. Transition states of the guanine (left) and 7-azaindole (right) complexes. The interatomic distances and the displacement vectors of the mode with imaginary frequency illustrate the degree of synchronicity of the proton transfer.

mode is predominantly symmetric or antisymmetric with respect to the dividing plane of the transition state. On this basis the effect of the couplings on the transfer rate of the azaindole complexes can be readily understood. The key observation is that the two nitrogen atoms have very different basicities, reflected in the large exothermicity. As a consequence, the motions of the protons involved in the transfer lose their synchronicity and the tunneling mode acquires a large heavy-atom component, as indicated by the reduction of the imaginary frequency from about 2000 to about 1000 cm^{-1} upon complexation with water. This in turn leads to increased coupling with higher-frequency modes of the type illustrated in Fig. 5, resulting in an increase in the effective mass and a decrease in the tunneling rate. The effect is stronger in the 1:2 than in the 1:1 complex, in agreement with the number of coupled high-frequency modes in the two cases. In addition both complexes are subject to coupling with modes governing solvent reorganization between the initial and final states, as expected on the basis of the different basicities. This coupling contributes a Franck–Condon factor to the rate constant and is responsible for the fact that $k(T)$ increases more strongly with temperature than $k^0(T)$.

In the guanine.H_2O complex the difference in the relative stability is small, which indicates that the N···H···O and O···H···O potentials are not very different and allow synchronous transfer of the two protons. Correspondingly, the effective mass remains close to unity, the imaginary frequency is not much reduced by complexation, and the reor-

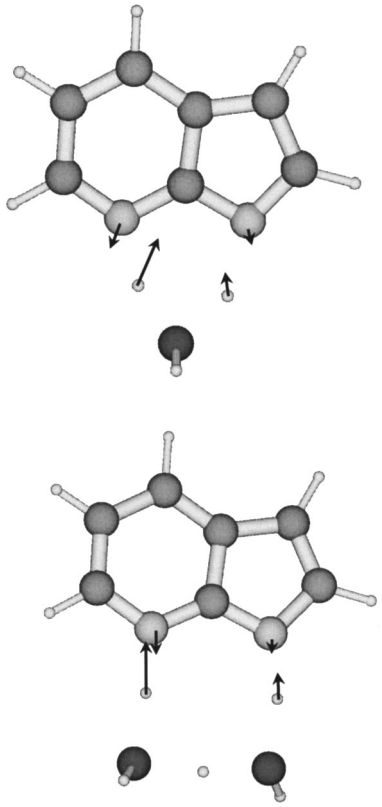

FIG. 5. Transverse normal modes of the transition state in the 7-azaindole complexes with displacement vectors of high-frequency modes that contribute strongly to the effective mass of the tunneling protons. For the 1:1 complex, the displayed mode has a frequency of 2259 cm^{-1} and contributes about 50% to Δm_s; for the 1:2 complex, the displayed mode has a frequency of 2242 cm^{-1} and contributes about 80% to Δm_s.

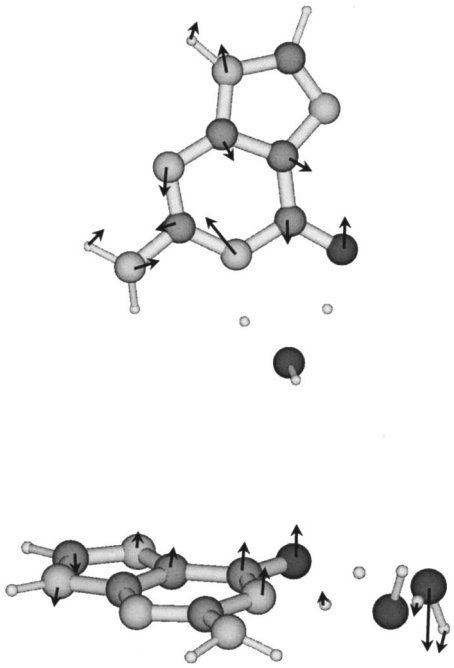

FIG. 6. Transverse normal modes of the transition state in the guanine complexes, where the displayed, predominantly symmetric, mode of 1120 cm^{-1} in the 1:1 complex helps the tunneling by contributing about 20% to δ_s, while the predominantly antisymmetric mode of 68 cm^{-1} in the 1:2 complex hinders tunneling by contributing about 30% to δ_a. The out-of-plane character of the latter mode shows the hydrogen-bonding effect of the (nonplanar) NH_2 group.

ganization of the water molecule is small. The coupling is therefore predominantly helping the transfer rate, the largest symmetric coupling contribution being that of the skeletal deformation mode depicted in Fig. 6, which changes the NCO bridgehead angle, thereby shortening the tunneling distance. The efficiency of this process explains why it has proved impossible to isolate the hydroxo form of guanine in protic solvents, although it is observed in the gas phase[29] and upon sublimation into cold matrices.[30]

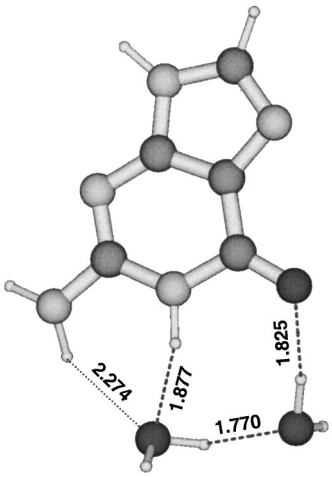

FIG. 7. Canonical configuration of guanine.$(H_2O)_2$, showing the presence of a weak hydrogen bond between the NH_2 group and one of the water molecules.

In the 1:2 complex of guanine with water the picture is complicated by the formation of an additional (weak) hydrogen bond between one of the water molecules and the NH_2 group, as shown in Fig. 7. This increases the exothermicity and breaks the synchronicity, as reflected in the increased effective mass due to coupling with high-frequency hydrogenic modes. In addition there is substantial reorganization of the water molecules, dominated by the low-frequency out-of-plane mode depicted in Fig. 6. As this mode illustrates, this reorganization is related to the weak hydrogen bond with the nonplanar NH_2 group. While the transfer of the two protons is far from synchronous, it remains coherent in the present case. Incoherent transfer in these systems would tend to require additional water molecules so as to stabilize an ion-pair intermediate. This is expected to be accompanied by substantial solvent rearrangement and therefore becomes more probable at high temperatures.

V. CONCLUSION

The main question investigated here is under which conditions a chain of water molecules can serve as an efficient conduit for protons. Although the present sampling of proton-transfer bridges is small, a clear pattern can be discerned by inspection of the structures and, especially, of the coupling with transverse modes. Collective proton transfer is fast and efficient if the hydrogen bonds are equivalent or nearly so. In that case the transfer will lead to a minimal rearrangement of heavy nuclei and the protons will be able to move synchronously. Spatial requirements are also important since crowding and strongly bent hydrogen bonds will reduce the transfer rate. These conclusions are derived from a comparison of relative rate constants in closely related complexes and should not depend on the absolute values of these rate constants.

In actual biological systems a driving force will be present that gives direction to the protons. In terms of the present approach, this means that the transfer will be exothermic. Since large exothermicities tend to reduce the synchronicity and hence interfere with efficient transfer, it is to be expected that for biological processes with a rate-determining proton-transfer step this exothermicity will be limited to relatively small values. This is indeed the case in the enzyme carbonic anhydrase II, referred to in Sec. I.[9,10] It appears that under these conditions collective proton transfer in strain-free, firmly anchored chains of hydrogen-bonded water molecules may be very fast, despite relatively high barriers.

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