

THE UTILIZATION OF TUNNEL EFFECTS FOR MECHANISTIC STUDIES OF HYDROGEN TRANSFER REACTIONS[†]

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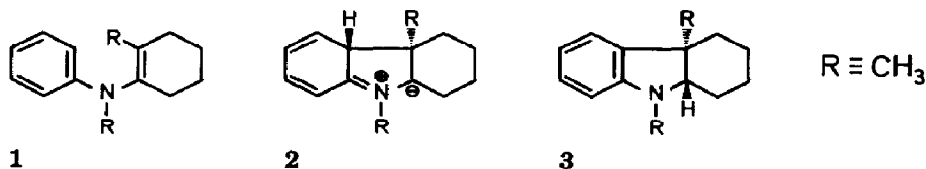
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Summary

The non-oxidative photocyclization of an *N*-aryl enamine and the enol-keto transition of several aromatic ketones were investigated flash photolytically. Large isotope effects and non-linear Arrhenius plots of the rate constants are interpreted as tunnel contributions to the hydrogen transfer reactions. The occurrence of proton tunnelling was used to distinguish between two possible routes of a sigmatropic hydrogen shift reaction and to investigate the mechanism of the enol re-ketonization reactions in detail. The existence of a pre-equilibrium between two enol rotamers is postulated and experimental evidence for its existence is presented.

1. Introduction

In deoxygenated non-polar solvents the enamine **1** is converted by light into the hexahydrocarbazole **3** via the zwitterionic intermediate **2**.



Chapman *et al.* [1] discovered this non-oxidative photocyclization reaction and investigated its mechanism by steady state methods. Flash experiments carried out in our laboratory [2] proved the existence of **2** as an intermediate in the reaction sequence. Recently, we were able to show [3] that the

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rate of the sigmatropic [1,4] hydrogen shift reaction $2 \rightarrow 3$ (rate constant k_H) is largely governed by a proton tunnel process at relatively high temperatures. Evidence for this tunnel reaction is a very large isotope effect when the migrating hydrogen atom in **2** is replaced by deuterium (rate constant k_D) and non-linear Arrhenius plots of k_H and k_D . The isotope effect $I(T) = k_H/k_D$ is temperature dependent and ranges from $I(293\text{ K}) = 10$ to $I(77\text{ K}) = 10^4$.

When we studied the re-ketonization reaction $5 \rightarrow 4$



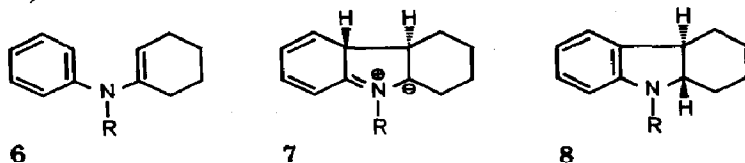
(rate constant k_{obs}) of flash photolytically enolized *o*-methylacetophenone **4**, curved Arrhenius plots of k_{obs} were again observed [4]. Furthermore, replacement of the reactive *o*-methyl group in **4** by a CD_3 group led to a large temperature-dependent isotope effect. We concluded from our findings that in this case also tunnelling contributes to the reaction $5 \rightarrow 4$.

Only very few kinetics data can be found in the literature which make proton tunnelling unambiguously evident. Attempts have been made by us [3, 4] and others [5] to design a quantum mechanical model for the calculation of proton transfer rate constants and to test its validity by comparing it with the available experimental data. In this paper this interesting subject is touched upon only briefly. We shall rather try to show (i) that the very existence of the tunnel reactions mentioned above can be used to solve a mechanistic problem which is not directly related to tunnelling and (ii) that it can lead to the proposal of a hypothesis which otherwise would perhaps not have been formulated and tested.

2. Results and discussion

2.1. Sigmatropic proton shifts

One position at the photochemically formed bridge of **2** is occupied by a methyl group. Thus, the pathway of the rearrangement $2 \rightarrow 3$ is pre-determined and can only be a sigmatropic [1,4] hydrogen shift. The situation is more complex if the parent enamine **6** is converted (via the zwitterion **7**) into **8**:



It has already been pointed out by Chapman *et al.* [1] that two mechanisms have to be considered in this case, *i.e.* either two [1,2] hydrogen shifts or one [1,4] hydrogen shift can take place when the zwitterion **7** decays (Fig. 1). Chapman *et al.* [1] attempted to distinguish between these two

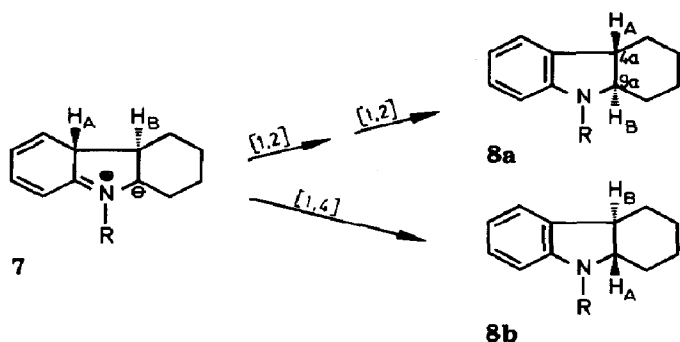


Fig. 1.

routes by comparing the nuclear magnetic resonance (NMR) photoproduct spectra of labelled and unlabelled **6** ($R \equiv \text{CH}_3$). However, it was not possible to determine accurately the deuterium content at the positions 4a and 9a of the final product(s) **8** by replacing the H_A atom of **7** (Fig. 1) by deuterium. Therefore, the question remained whether **8a** (deuterium atom at position 4a), **8b** (deuterium atom at position 9a) or both were formed.

Since the isotope effects observed with **1** are extremely large [3] (especially at low temperatures) and the reactions $1 \rightarrow 3$ and $6 \rightarrow 8$ are basically very similar, it appears that a kinetics study with appropriately labelled **6** is a much easier and more conclusive way to distinguish between the two routes in Fig. 1 than photoproduct analysis by NMR spectroscopy: replacement of H_A in **7** by deuterium should in any case give an isotope effect, but replacement of H_B should only give an isotope effect if two [1,2] hydrogen shifts take place. We therefore investigated compounds **6**, **6a** and **6b** ($R \equiv \text{C}_2\text{H}_5$)



flash photolytically. All measurements were carried out in a carefully dried and degassed mixture of isopentane-cyclopentane (4:1 by volume) as solvent.

On flashing 10^{-4} M solutions of **6**, **6a** and **6b** at different temperatures between 300 and 110 K, a transient with an absorption maximum at 490 nm is observed, as in the case of compound **1**. This transient decays in a first-order reaction (rate constants k , k_a and k_b for **6**, **6a** and **6b** respectively). In analogy [2, 3] with **2** we assign the zwitterionic structure **7** to this transient. The Arrhenius plots of all three rate constants are curved, as expected, and very similar to those given in ref. 3. However, *only* with compound **6a** is a (temperature-dependent) isotope effect $I_a(T) = k(T)/k_a(T)$ observed (e.g. $I_a(294 \text{ K}) = 20$, $I_a(200 \text{ K}) = 135$, $I_a(180 \text{ K}) = 316$). Compounds **6** and **6b** are kinetically indistinguishable, i.e. $I_b(T) = k(T)/k_b(T) = 1.0 \pm 0.3$ over the temperature range investigated (300 - 100 K).

From these kinetics findings it can safely be concluded that the H_B atom of 7 (see Fig. 1) does *not* participate in the reaction. Hence, only a [1,4] sigmatropic hydrogen shift takes place during the conversion of 7 into 8. The very close agreement of the k and k_b values at all temperatures so far investigated makes it very unlikely that [1,2] hydrogen shifts play a substantial role in the reaction.

2.2. Enol-keto tautomerization

The photoenolization reaction of *o*-methylacetophenone (4 → 5) and of a number of related compounds as well as the thermal re-ketonization reaction 5 → 4 (rate constant k_{obs}) have been extensively studied [6]. Since the enol 5 absorbs at longer wavelengths ($\lambda_{\text{max}} = 410 \text{ nm}$) than the ketone 4, the decay of 5, after flash excitation of 4, can be easily monitored and the decay rate constant k_{obs} can be accurately determined. As already mentioned above, we found [4] large isotope effects when the *o*-methyl group of 4 (rate constant $k_{\text{obs}}^{\text{H}}$) was replaced by CD₃ (rate constant $k_{\text{obs}}^{\text{D}}$). However, in analogy with the results described in Section 2.1, we expected a much more pronounced curvature in the Arrhenius plots of $k_{\text{obs}}^{\text{H}}$ and $k_{\text{obs}}^{\text{D}}$ than we actually observed, *i.e.* the rate constants k_{obs} at lower temperatures were several orders of magnitude smaller than predicted from the quantum mechanical calculation. To account for this discrepancy we assumed that a pre-equilibrium exists between two rotamers (5a and 5b) of the enol 5 (Fig. 2).

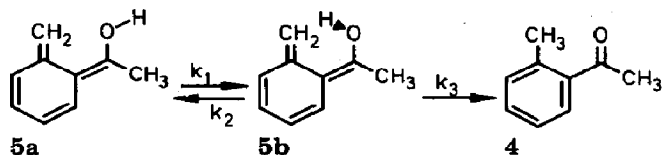


Fig. 2.

If the pre-equilibrium is established all the time (*i.e.* $k_2 \gg k_3$) and re-ketonization takes place only from rotamer 5b, the experimentally determined rate constant k_{obs} is given by $k_{\text{obs}} = k_1 k_3 / k_2$. We assume further that rotamer 5a is more stable than rotamer 5b because the OH group of 5a can be located in the plane of the molecule, which is not possible for 5b because of steric hindrance from the methylene group. Thus, the temperature dependence of the re-ketonization reaction will be governed not only by the reactive step k_3 but also by the difference ΔE in the stabilization energy of the two rotamers:

$$k_{\text{obs}}(T) = \frac{A_1}{A_2} \exp\left(-\frac{\Delta E}{RT}\right) A_3 \exp\left(-\frac{V_0}{RT}\right) \quad (1)$$

where A_1 , A_2 and A_3 are the frequency factors of k_1 , k_2 and k_3 respectively, $\Delta E = E_1 - E_2$ is the difference between the activation energies of k_1 and k_2 and V_0 is the activation energy of k_3 . If tunnelling contributes significantly to k_3 , this rate constant may no longer be expressed classically as in eqn. (1)

but rather by a reaction probability $P(T) = k_3(T)/A_3$ which has to be calculated quantum mechanically with an appropriate model [3, 4]:

$$k_{\text{obs}}(T) = A \exp\left(-\frac{\Delta E}{RT}\right) P(T) \quad (1a)$$

with $A \equiv A_1 A_3 / A_2$. From eqn. (1a) it follows that the "modified" experimental data $k_{\text{obs}}(T)/A \exp(-\Delta E/RT)$ have to be compared with the function $P_{\text{H}}(T)$ for protonated ketones and with the function $P_{\text{D}}(T)$ for deuterated ketones. To calculate $P(T)$ we used an Eckart potential to describe the shape of the tunnel barrier. The width d of the barrier is (within reasonable limits) an adjustable parameter and the height V_0 of the barrier is taken from the kinetics data at high temperatures (for details see ref. 4). When the values $\Delta E(5) = 20 \text{ kJ mol}^{-1}$, $A = 10^{15} \text{ s}^{-1}$, $d = 180 \text{ pm}$ and $V_0 = 40 \text{ kJ mol}^{-1}$ are assumed for the reaction $5 \rightarrow 4$, the agreement between experiment and the quantum mechanical calculation is excellent [4].

To test our rotamer hypothesis we investigated the ketones 9, 11, 13, 15 and 17 (Fig. 3). First, for the three ketones 9, 11 and 13, it is clear that the steric hindrance in the corresponding enol rotamers should become increasingly larger from 10a to 14a, whereas there should be no difference in this respect between the rotamers 10b, 12b and 14b. Hence, the difference $\Delta E(10)$ in stabilization energy between the rotamers 10a and 10b should be the largest, $\Delta E(14)$ should be approximately equal to zero and $\Delta E(12)$ should be somewhere in between. It should be mentioned that we investigated the tetralone 9 instead of using the data obtained already with *o*-methylacetophenone 4 because we wanted to make the "reactive moiety" of the ketones as similar as possible. Furthermore, *cis-trans* isomerization about the side-chain double bond, which is observed with 5, cannot take place. It is important to mention that, in spite of the rather drastic differences between the molecular structures of the enols 5 and 10, the absolute $k_{\text{obs}}(T)$ values of the re-ketonization reactions $5 \rightarrow 4$ and $10 \rightarrow 9$ are almost equal over the entire temperature range investigated (300 - 100 K). To test to what extent a change in the orientation between the methylene and the OH group of the enols influences the re-ketonization rate, we also compared the anthrone 11 with the dibenzosuberone 17 and, in addition, with the unlinked benzophenone derivative 15.

All five ketones are readily enolized on flash excitation. In Fig. 4 the Arrhenius plots of the re-ketonization reactions $10 \rightarrow 9$, $12 \rightarrow 11$ etc. of the light compounds (rate constant $k_{\text{obs}}^{\text{H}}(T)$) are depicted, and those of the deuterated ketones (rate constant $k_{\text{obs}}^{\text{D}}(T)$) are depicted in Fig. 5. The rate constants $k_{\text{obs}}(T)$ were determined with carefully degassed 10^{-4} M solutions of the ketones in a mixture of ether-isopentane-ethanol (5:2:5 by volume), as described elsewhere [4]. To facilitate the visualization of the isotope effect, one curve from Fig. 5 is shown (dotted line) in Fig. 4. Also included in Figs. 4 and 5 is the result of a quantum mechanical calculation of $P_{\text{H}}(T)$ and of $P_{\text{D}}(T)$ respectively (broken lines) with the parameters $V_0 = 40 \text{ kJ mol}^{-1}$ and $d = 180 \text{ pm}$.

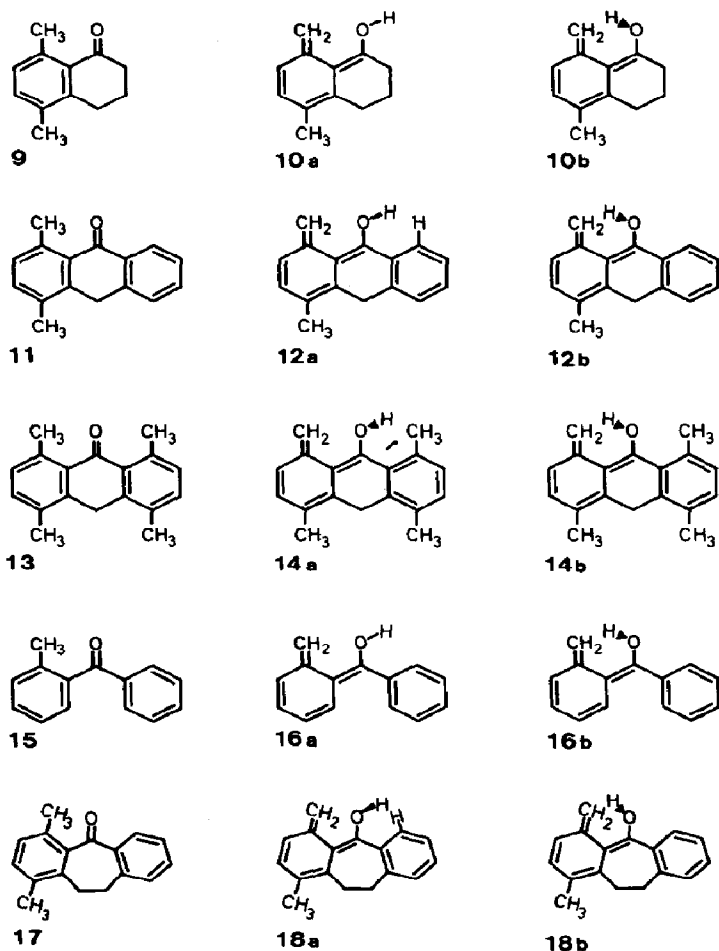


Fig. 3.

Inspecting Figs. 4 and 5 we note the following.

(1) All compounds exhibit a large and temperature-dependent isotope effect $I(T) = k_{\text{obs}}^{\text{H}}(T)/k_{\text{obs}}^{\text{D}}(T)$.

(2) The Arrhenius plots are not linear.

(3) From a comparison of the ketones 9, 11 and 13 it becomes quite evident that the speed of the re-ketonization reaction increases drastically from 9 to 13. At $T = 145$ K, for instance, the rate constant $k_{\text{obs}}^{\text{D}}$ (145 K) of ketone 13 is six orders of magnitude larger than that of 9 and ketone 11 lies in between (see Fig. 5). There is no doubt that this increase in rate is (at least in part) due to the decreasing difference ΔE in stabilization energy between the a- and b-type rotamers. This view is strongly supported by the fact that for ketone 13 the $k_{\text{obs}}^{\text{D}}(T)$ curve and the theoretical curve have the same shape without modification of the experimental data. We expect, as already mentioned, that in this case $\Delta E(14) \approx 0$ and that therefore eqn. (1a) reduces to $k_{\text{obs}}(T)/A \approx P(T)$, which is indeed the case when the composite "frequency factor" A is taken to be 10^{14} s^{-1} . The reaction of the un-

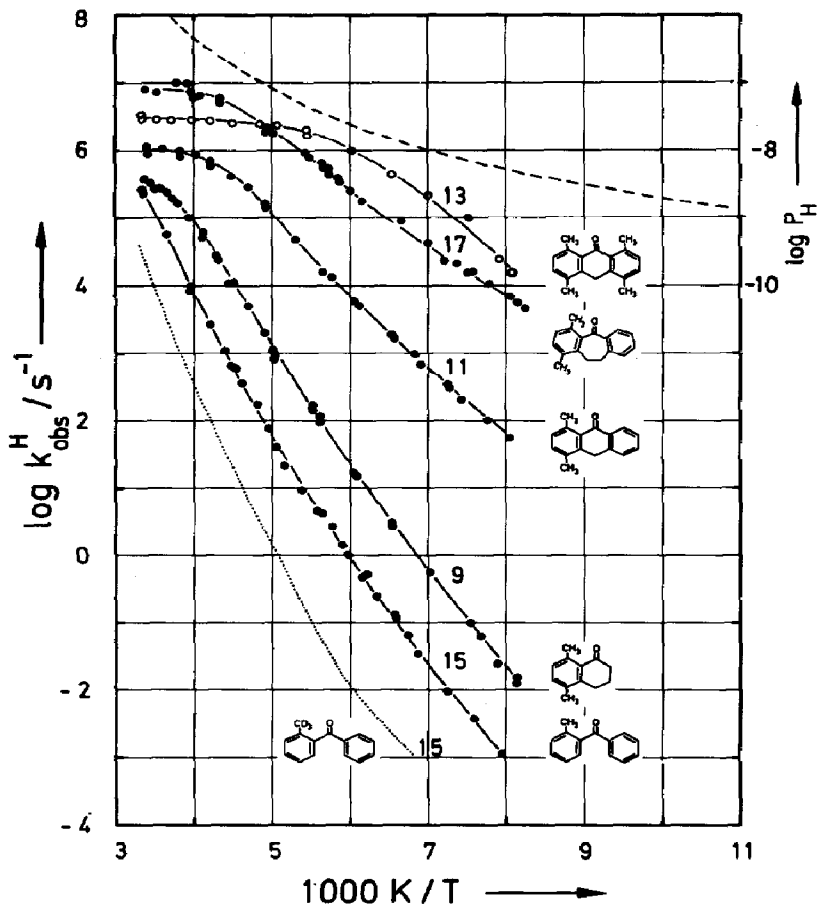


Fig. 4. Arrhenius plot (left-hand scale) of the re-ketonization reactions $10b \rightarrow 9$, $14b \rightarrow 13$ etc. (see Fig. 3) monitored at 400 nm (9), 450 nm (11), 450 nm (13), 410 nm (15) and 410 nm (17) (—) (for comparison, curve 15 of Fig. 5 (deuterated ketone) is included (.....)) and the quantum mechanically calculated (right-hand scale) (see text) hydrogen transfer probability $P_H(T)$ (---).

deuterated ketone 13 is already so fast that the *formation* of the enol becomes rate limiting. Therefore, in Fig. 4, curve 13 lies under the calculated function $P_H(T)$. In contrast with the approximately planar ketone 11 in which the two moieties of the molecule are linked by one CH_2 group, the two benzene rings of 17 are twisted out of plane by its $(\text{CH}_2)_2$ bridge. This non-planarity is apparently the reason why the re-ketonization $18b \rightarrow 17$ is faster than the analogous reaction $12b \rightarrow 11$. Opening of the bridge (ketone 15) leads to a drastic drop in the rate. Obviously, the rate of reaction is influenced not only by the difference ΔE in the stabilization energy but also by the orientation of the OH group with respect to the methylene group to which the hydrogen atom has to migrate. Since relatively small changes in the molecular geometry have such large effects on the rate constants, it can

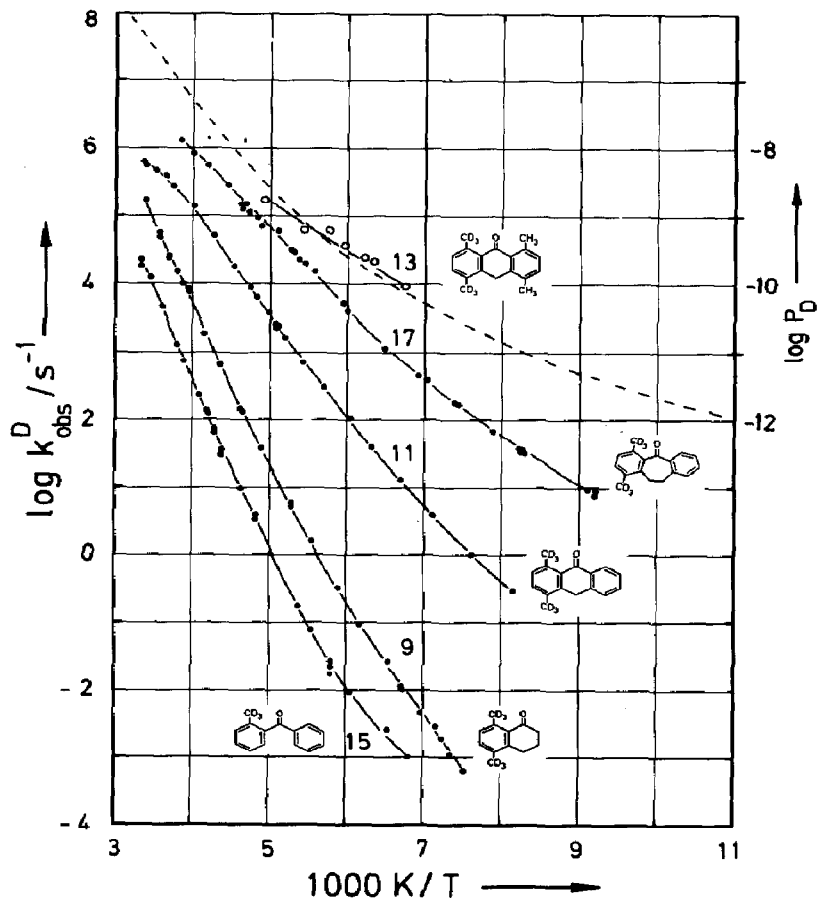


Fig. 5. Arrhenius plot (left-hand scale) of the re-ketonization reactions $10b \rightarrow 9$, $14b \rightarrow 13$ etc. (see Fig. 3) monitored at 400 nm (9), 450 nm (11), 450 nm (13), 410 nm (15) and 410 nm (17) (—) and the calculated (right-hand scale) deuterium transfer probability $P_D(T)$ (---).

be hoped that a more thorough analysis of the results presented in this paper may lead to a detailed description of the enol-keto tautomerization processes. As a first step in this direction we note that in agreement with eqn. (1a) the experimentally observed $k_{obs}(T)$ values of all five deuterated ketones and the protonated ketones 9, 11, 15 and 17 reduce to the function $P(T) = k_{obs}(T)/A \exp(-\Delta E/RT)$ (Figs. 4 and 5, broken lines) if we assume the values $\Delta E(16) = 25.5 \text{ kJ mol}^{-1}$, $\Delta E(10) = 20.0 \text{ kJ mol}^{-1}$, $\Delta E(12) = 11 \text{ kJ mol}^{-1}$, $\Delta E(18) = 3 \text{ kJ mol}^{-1}$, $\Delta E(14) = 0$, $A(10) = A(12) = A(16) = A(18) = 10^{15} \text{ s}^{-1}$ and $A(13) = 10^{14} \text{ s}^{-1}$. (The numbering of ΔE and A corresponds to the numbers in Fig. 3.) The decay of the protonated enol 14b is determined by its formation (see above).

Preliminary results suggest that $k_{obs}(T)$ depends not only on the molecular geometry of the enols but also on the solvent polarity and/or on the for-

mation of hydrogen bonds between the solute and the solvent. Further work in this direction is in progress.

Acknowledgments

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