structure II dominates in NADH and that the observed hindered rotation is that of the entire carboxamide group.

This argument does not lead to predictions of splitting and rate behavior, not does it suggest a conformational preference for the carboxamide. However, the behavior of NADH is clearly atypical, and, since the typical amides are all presumably characterized by the C–N hindered rotation, it is not unreasonable to propose an alternative for the atypical case.

Taking an entirely different tack, one might argue that the anomalous behavior of NADH is only apparent, and that the variation of peak separation with temperature is not due to rotational coalescence, but arises instead from specific chemical shift effects due to destacking. According to this argument, peak separation should continue to increase with stacking. However, peak separation is complete at −7 °C, whereas stacking is still incomplete at −25 °C, to judge from the dihydronicotinamide C_4-H resonance. Also, this argument does not explain the linearity of the Arrhenius plot. Finally, in NAD, which is estimated to be 15–20% stacked at 20 °C with a stacking enthalpy of −5 kcal/mol, the amide peak separation is virtually unchanged between 0 and 20 °C.[21]

In conclusion, the nature of the hindered rotation in NADH is an open question whose resolution will probably require further study. Even for "typical" amides, the origin of the chemical shift difference between cis and trans protons is poorly understood.[22]

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^{1}H NMR Spectroscopic Study of Cyclic Proton Exchange between Acetic Acid and Methanol in Tetrahydrofuran-d_8

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Abstract: The kinetics of the intermolecular proton exchange between methanol and acetic acid dissolved in tetrahydrofuran-d_8 have been studied by ^{1}H NMR line shape analysis. In the slow exchange range the line shapes of the carboxyl singlet and the methanol multiplets provide information about the proton-exchange rates between methanol and acetic acid and between molecules of methanol. In very carefully prepared samples of high purity no methanol self-exchange is observed. The proton-exchange rates between methanol and acetic acid were found to be proportional to the total concentrations of the reactants. The temperature dependence of the observed bimolecular rate constants is given by $k_{\text{obsd}} = \exp(18.6 \pm 0.7) \exp(-27 \pm 1.3 \text{ kJ mol}^{-1}/RT)$, $196 \leq T \leq 258$ K. The absence of methanol self-exchange and the kinetic law prove that the exchange takes place during one encounter of the reactants in a hydrogen-bonded intermediate which contains one molecule of acetic acid and one molecule of methanol. The rate-limiting step of the proton exchange is the proton transfer in this intermediate. The observed rate constants depend on the equilibrium constants of the formation of the active 1:1 complex from the dominating quasi-monomers which form a hydrogen bond with the solvent. The values of the activation parameters provide evidence that the proton exchange takes place in a cyclic 1:1 intermediate along a reaction pathway which does not involve a solvated ion pair as intermediate.

I. Introduction

The kinetics of intermolecular proton exchange in buffered mixtures of carboxylic acids and alcohols have been studied by Grunwald et al.[1-5] using dynamic ^{1}H NMR spectroscopy. In protic media ionic exchange mechanisms dominate which consist of successive proton-transfer reactions involving free solvated ions. However, side reactions involving only neutral molecules were also observed. There is evidence that this type of exchange takes place in cyclic hydrogen-bonded intermediates as shown, for example, in Scheme I. The number of participating alcohol molecules was found to vary between one and three. The question whether the exchange proceeds via an intimate ion pair or whether there is a concerted proton motion has been discussed in several papers,[2-7] and a stepwise mechanism was favored.[5,6]

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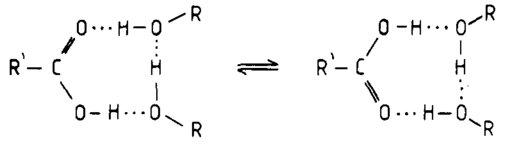
Scheme I



There is still a great interest in the question of synchronous or asynchronous proton motion in cyclic hydrogen-bonded systems.[8] By dissolving carboxylic acids and alcohols in aprotic media of low dielectric constants and by removing all catalysts from the system one may be able to suppress all ionic proton transfer. In such systems only the cyclic exchange mechanism should be important; hence, additional information about the reaction mechanism may be obtained. For example, it would be interesting to know more about the kinetic orders with respect to all reactants simultaneously, about the influence of hydrogen bonding on the reaction rates, and about the primary kinetic isotope effects. Denisov et al.[9] have used kinetic IR spectroscopy to study hydrogen-deuterium substitution reactions between different proton donors

$$\mathrm{ROH + R'OD \rightleftharpoons ROD + R'OH}$$

dissolved in carbon tetrachloride. However, the primary kinetic hydrogen-deuterium isotope effects cannot be determined by this method and it is difficult to distinguish between ionic and cyclic exchange mechanisms.

We have recently shown[10] that using ^{1}H NMR line shape analysis in the slow exchange range such a distinction can easily be made. In this paper, the kinetic results of a study of the proton exchange in the system acetic acid/methanol/tetrahydrofuran-d_8 (THF-d_8) will be reported and discussed.

II. Experimental Section

1. Preparation of Samples. The NMR samples had to be prepared very carefully in order to exclude air and moisture or other impurities that might be the cause of ionic proton transfer reactions. The following procedure was, therefore, adopted. The solvents were dried and stored in glass vessels which were attached to a vacuum line. By successive evaporation and condensation, part of the solvents was transferred into graduated traps which allowed volume measurements before the transfer into the NMR tube, also attached to the vacuum line.[11] In a final step the NMR tubes were sealed off. On the solvent vessels, traps, and tubes only greaseless stopcocks were employed. THF-d_8 (Sharp & Dohme, Munich) was dried and deoxygenated by adding anthracene-potassium to the vessel. Methanol and acetic acid were purified using standard methods and were dried over a freshly regenerated molecular sieve (Merck, 3 Å). No esterification reaction could be observed over a period of several months in very carefully prepared samples. However, the addition of traces of H_2SO_4 caused the formation of acetic acid methyl ester after a period of days as monitored by the NMR spectrum, which is consistent with the literature.[12]

2. Determination of Kinetic Data. The ^{1}H NMR spectra were recorded on a Varian HA-100 NMR spectrometer operating at 100 MHz. The kinetic data were obtained by simulation of the experimental spectra previously digitized. Since the spin system which is formed by the protons of methanol is of high order the calculations had to be based on the quantum mechanical density matrix formalism. We have recently[10] proposed a kinetic formulation of this theory in which the assumption of reaction mechanisms at the stage of the line-shape simulation is avoided. This is done by expanding the line-shape equation as a function of group exchange rate constants, $k_{rs}(i)$, of the spin group i between the environments r and s, of which i is an integral part. The computer program used for the line-shape calculations has been described in detail.[10] In the system methanol/acetic acid/THF-d_8 we have to consider two spin groups, A = H and B = CH_3O, and two environments, 1 = AB = $HOCH_3$[13] and 2 = A = CH_3COOH. The NMR line shape is then a function of the pseudo-first-order group exchange rate constants, $k_{11}(A)$, $k_{12}(A) = k_{21}(A) \cdot p_2/p_1$, and $k_{11}(B) = k_{11}(A) + k_{12}(A)$. The mole fractions, p_1 and p_2, were known from the concentrations, C_1 and C_2. The static line width, W_0, was determined by the inhomogeneity of the static magnetic field and could, therefore, be taken from the line width of the CH_3COOH signal at δ 1.90 ppm. The parameters which were varied during the simulations were $k_{11}(A)$, $k_{12}(A)$, the chemical shifts, δ_{CH_3OH}, δ_{CH_3OH}, and δ_{CH_3COOH}, and the coupling constant, J_{CH_3OH}.

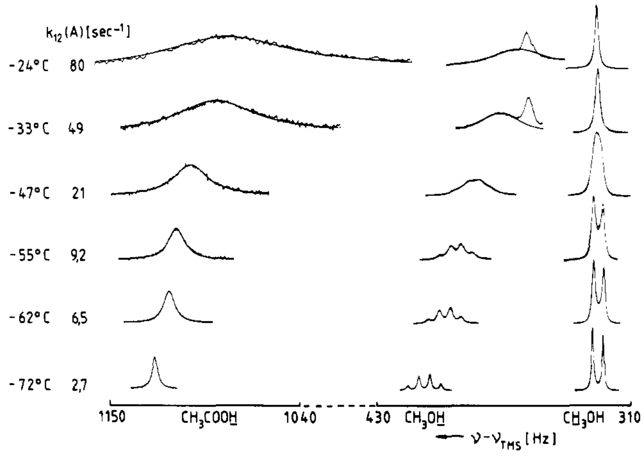


Figure 1. Superposed experimental and calculated 100-MHz ^{1}H NMR spectra of a mixture of 0.80 mol/L methanol and 0.29 mol/L acetic acid in tetrahydrofuran-d_8. The peak at $\nu - \nu_{Me_4Si} = 370$ Hz arises from solvent protons. For the definition of the group exchange rate constants, $k_{12}(A)$ and $k_{11}(A)$, see text. ν_{Me_4Si} is the resonance frequency of tetramethylsilane.

III. Results

A typical set of experimental and calculated ^{1}H NMR spectra of a sample which contained 0.8 mol/L methanol and 0.29 mol/L acetic acid is shown in Figure 1. Even at these high concentrations the region of slow proton exchange between acetic acid and methanol is easily reached as the temperature is lowered. The ^{1}H NMR spectra show then a sharp singlet at low field arising from the CH_3COOH site, a distorted quartet arising from the CH_3OH site, and a distorted doublet arising from the CH_3OH protons. Additionally, there is a singlet at δ 1.90 ppm produced by the CH_3COOH protons and two broad singlets at δ 3.6 and 1.7 ppm which arise from solvent protons. As the temperature is raised the fine structure of the methanol signals disappears. The CH_3OH doublet coalesces into a singlet and the CH_3OH lines as the CH_3COOH line broadens. The coalescence point of these two signals can be reached in THF-d_8 only at high concentrations and temperatures. It was established by simulation that in all carefully prepared samples the rate constants, $k_{11}(A)$, of proton exchange between molecules of methanol vanished

$$k_{11}(A) = 0 \qquad (1)$$

over the whole temperature range. The group exchange rate constants obeyed the relations

$$k_{12}(A) = k_{21}(A)p_2/p_1 \qquad (2)$$

and

$$k_{12}(A) = k_{11}(B) \qquad (3)$$

as is to be expected for the overall exchange reaction

$$\underset{(1)}{\mathrm{AB}} + \underset{(2)}{\mathrm{A^*}} \rightleftharpoons \underset{(1)}{\mathrm{A^*B}} + \underset{(2)}{\mathrm{A}}$$

not superposed by the overall self-exchange reaction

$$\mathrm{AB + A^*B \rightleftharpoons A^*B + AB}$$

Figure 2 shows the influence of a nonzero self-exchange rate constant, $k_{11}(A)$, on the NMR line shape. Two experimental spectra of Figure 1 are reproduced, but calculated with the

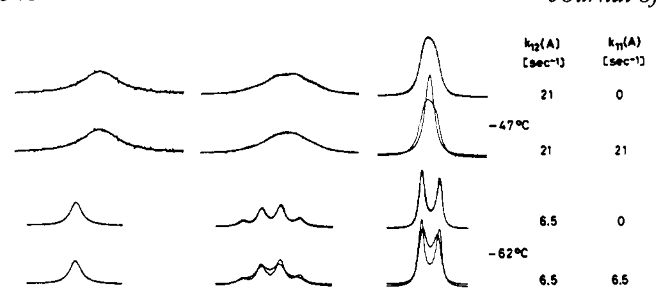


Figure 2. Superposed experimental and theoretical line shapes of the sample shown in Figure 1 at −47 and −62 °C. The upper curves are calculated for a 1:1 proton exchange between methanol and acetic acid, with $k_{11}(A) = 0$; the lower curves are calculated for a 1:2 exchange according to Scheme I with $k_{11}(A) = k_{12}(A)$.

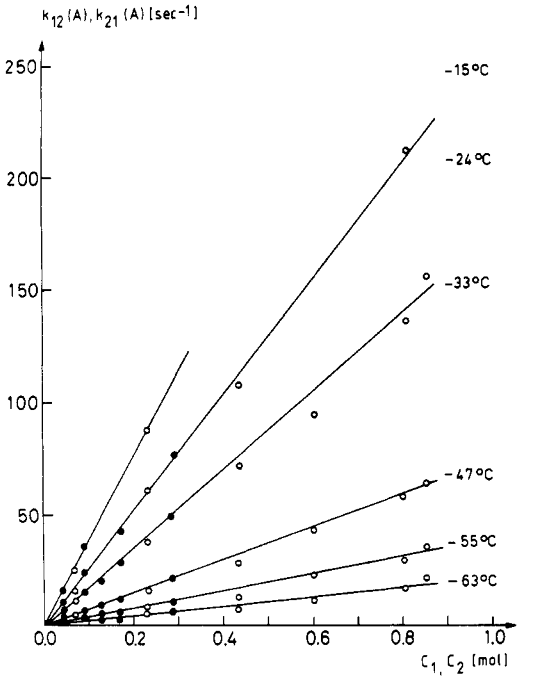


Figure 3. Pseudo-first-order group exchange constants $k_{12}(A)$ (open circles) as a function of the total concentration, C_2, of acetic acid and $k_{21}(A)$ (filled circles) as a function of the total concentration, C_1, of methanol at different temperatures. k_{obsd} is the observed bimolecular exchange rate constant.

values $k_{11}(A) = k_{12}(A)$, as is expected for the termolecular exchange process of Scheme I. The result is a considerable difference between the experimental and the calculated spectra. At higher temperatures it is no longer possible to extract any information on $k_{11}(A)$ from the line shape which is then entirely determined by $k_{12}(A)$ even if $k_{11}(A) \neq 0$.

In Figure 3, $k_{12}(A)$ is plotted against the total concentration, C_2, of acetic acid and $k_{21}(A)$ against the total concentration, C_1, of methanol. For the whole temperature range the relations

$$k_{12}(A) = k_{obsd}C_2 \tag{4}$$

and

$$k_{21}(A) = k_{obsd}C_1 \tag{5}$$

were fulfilled which is consistent with the observation of the validity of eq 1-3, if one remembers that $C_1/C_2 = p_1/p_2$. Therefore, one obtains a rate law of proton exchange between methanol and acetic acid which is of first order with respect to the total concentration of each reactant:

Table I. Bimolecular Rate Constants, k_{obsd}, of the 1:1 Proton Exchange between Acetic Acid and Methanol in THF-d_8 as a Function of the Temperature[a]

T/K	k_{obsd}/L mol^{-1} s^{-1}	T/K	k_{obsd}/L mol^{-1} s^{-1}
210	22 ± 5	240	160 ± 20
218	35 ± 5	249	250 ± 30
226	70 ± 10	258	350 ± 40

[a] The values are not corrected for the dependence of the concentrations on the temperature. However, such a correction does not exceed one-third of the experimental error of k_{obsd} and can, therefore, be neglected.

$$v = k_{obsd}C_1C_2 \tag{6}$$

Every time a proton is transferred from the methanol site to acetic acid another proton is back-transferred from acetic acid to methanol. No proton leaves a methanol molecule in order to jump to another methanol molecule without passing the acetic acid. The rate constants of the bimolecular exchange reaction, k_{obsd}, are listed in Table I. The Arrhenius curve is a straight line and obeys the equation

$$k_{obsd} = \exp(18.6 \pm 0.7)\exp(-27 \pm 1.3\ \mathrm{kJ\ mol^{-1}}/RT)$$
$$196 \leq T \leq 258\ \mathrm{K}$$

IV. Discussion

1. Proof of the Mutual Transfer of Two Protons during One Encounter of the Reactants. The rate law of the proton exchange and the relations between the group exchange rate constants show that the NMR line shape and, therefore, all kinetic parameters arise only from the exchange reaction

$$CH_3OH + CH_3COOH^* \rightleftharpoons CH_3OH^* + CH_3COOH$$

which involves one methanol molecule and one molecule of acetic acid. A priori, this reaction could take place via an ionic mechanism involving free solvated ions:

$$CH_3OH + CH_3COOH \rightleftharpoons CH_3OH_2^+ + CH_3COO^- \tag{7}$$

or via a nonionic or cyclic mechanism in which the reactants exchange their protons during one encounter:

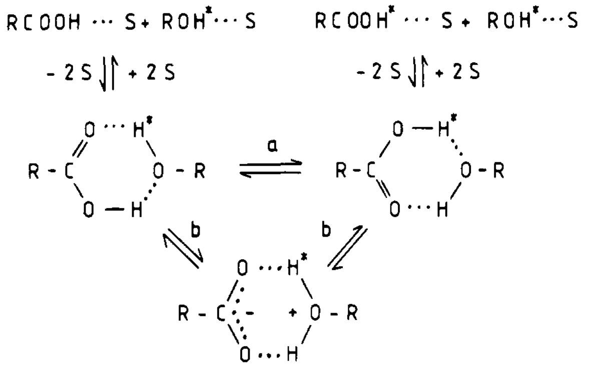
$$CH_3OH + CH_3COOH^* \overset{K'}{\rightleftharpoons} CH_3OH,CH_3COOH^*$$
$$\overset{k_{ex}}{\rightleftharpoons} CH_3OH^*,\ CH_3COOH$$
$$\rightleftharpoons CH_3OH^* + CH_3COOH \tag{8}$$

The ionic mechanism must be excluded here for the following reasons. The dissociation reaction of eq 7 is accompanied by a lot of different proton-transfer reactions, for example

$$CH_3OH_2^+ + CH_3OH \rightleftharpoons CH_3OH + CH_3OH_2^+$$
$$CH_3OH_2^+ + CH_3COOH \rightleftharpoons CH_3OH + CH_3C(OH)_2^+ \tag{9}$$
$$CH_3COO^- + CH_3OH \rightleftharpoons CH_3COOH + CH_3O^-$$

which presumably are faster than the dissociation step of eq 7. The presence of eq 9 should produce a nonzero value of the methanol self-exchange rate constant, $k_{11}(A)$. On adding a trace of sulfuric acid to our samples we found such nonzero values of $k_{11}(A)$.[10] The absence of ionic methanol self-exchange is, therefore, the proof for a cyclic exchange mechanism and the proof that the rate constants are not affected by an ionic mechanism which may arise from impurities or from a dissociation reaction. The zero values of $k_{11}(A)$ also prove the absence of a cyclic methanol self-exchange mechanism and exclude the participation of more than one methanol molecule in the exchange reaction. However, the NMR line shape gives

Scheme II



no information about the rates of cyclic proton exchange between molecules of acetic acid

$$\mathrm{CH_3COOH + CH_3COOH^*} \rightleftharpoons \mathrm{CH_3COOH^* + CH_3COOH}$$

because the resonance frequency of the proton is not altered during this reaction.

The low rate constants, k_{obsd}, show that the exchange process between methanol and acetic acid is not rate encounter controlled. Therefore, the rate-determining step must be the exchange in an appropriate hydrogen-bonded complex which is formed by one methanol molecule and one molecule of acetic acid as shown in eq 8. The concentration, c_{12}, of the active complex depends on the monomer concentrations, c_1 and c_2, of methanol and acetic acid:

$$K' = c_{12}/c_1c_2 \tag{10}$$

where K' is the equilibrium constant. The rate, v, of the proton exchange is then given by

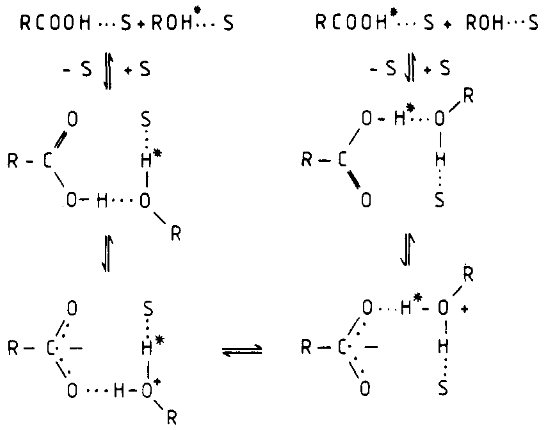
$$v = k_{\text{ex}}c_{12} = k_{\text{ex}}K'c_1c_2 = k_{\text{obsd}}C_1C_2 \tag{11}$$

Agreement with the experimental rate law of eq 6 is obtained by setting $C_1 \approx c_1$ and $C_2 \approx c_2$. The validity of these relations was proved by Gerritzen and Limbach[14] in a study of proton chemical shifts and the thermodynamics of the formation of hydrogen-bonded dimers and mixed 1:1 associates in the system acetic acid/methanol/THF-d_8. Acetic acid and methanol form strong hydrogen bonds with THF; the monomer species are then quasi-monomers which are hydrogen bonded to the solvent. The concentrations of all other species are so low that the observed rate constants are no longer affected by their presence.

2. Influence of Hydrogen Bonding with the Solvent on the Activation Parameters of Proton Exchange. According to Eigen's scheme of proton transfer[15] the proton donor must form a hydrogen bond with the base before the proton transfer can take place. Here, in addition, each reacting proton breaks its hydrogen bond to the solvent. If the two hydrogen bonds are formed between the reactants before the first proton is transferred, the active complex must have a cyclic hydrogen bonded structure, as shown in Scheme II. In the past, cyclic hydrogen bonded complexes have always been postulated as intermediates of proton transfer involving as many protons as neutral molecules.[1-5,16,17] A second possibility, shown in Scheme III, involves the mixed linear 1:1 solvent complexes. Here, a slow transfer of the first proton precedes the formation of the second hydrogen bond and the fast transfer of the second proton. The number of solvent molecules, n_{S}, liberated in the rate-determining step is $n_{\text{S}} = 2$ for the mechanism of Scheme II and $n_{\text{S}} = 1$ for the mechanism of Scheme III.

The true dimerization constant, K, of the formation of the active complex is given by

Scheme III



$$K = \frac{c_{12}c_{\text{S}}^{n_{\text{S}}}}{c_1c_2} \approx \frac{c_{12}C_{\text{S}}^{n_{\text{S}}}}{C_1C_2} \tag{12}$$

where the concentration of the free solvent which does not form a hydrogen bond is given by c_{S} and where the total solvent concentration is C_{S}. By combination of eq 10, 11, and 12 one obtains

$$k_{\text{obsd}} = \frac{k_{\text{ex}}K}{c_{\text{S}}^{n_{\text{S}}}} \approx \frac{k_{\text{ex}}K}{C_{\text{S}}^{n_{\text{S}}}} \tag{13}$$

In principle, c_{S} is a function of C_1 and C_2; k_{obsd} should, therefore, depend slightly on C_1 and C_2. However, one can show that these variations of k_{obsd} are smaller than the experimental error of k_{obsd}. From eq 13 one deduces that the energy of activation, $E_{\text{a(obsd)}}$, is the sum of the energy of activation of the proton transfer in the active complex, $E_{\text{a(ex)}}$, and the enthalpy, ΔH, of its formation:

$$E_{\text{a(obsd)}} = E_{\text{a(ex)}} + \Delta H \tag{14}$$

Similarly, the observed frequency factor, A_{obsd}, depends on the frequency factor of the proton transfer, A_{ex}, and the entropy, ΔS, of the formation of the active complex, and on n_{S} and C_{S}:

$$\ln A_{\text{obsd}} = \ln A_{\text{ex}} + \Delta S/R - n_{\text{S}} \ln C_{\text{S}} \tag{15}$$

Equations 14 and 15 define in a more quantitative way the statement of Grunwald et al.[2] that the concentration of the active species in which the exchange takes place is lower than the total concentrations of the reactants. Some interesting conclusions on the solvent dependence of the proton-exchange rates may be obtained from these equations. In a solvent such as THF, which acts as hydrogen-bond acceptor, the number of hydrogen bonds is maintained during the formation of the active complex. Thus, K, as defined in eq 12, is ~1 and ΔH and ΔS are close to zero, as could be shown for the formation of the species $\mathrm{CH_3COOH \cdots CH_3OH \cdots THF}$.[14] The same arguments apply to the formation of the cyclic 1:1 associate. Equation 12 shows that this species is formed to a less extent than the linear associates because of the greater value of n_{S}. Thus, with $C_{\text{S}} = 12.3$ mol L^{-1} we obtain values of $\ln A_{\text{ex}}(n_{\text{S}} = 2) \approx 21$, $\ln A_{\text{ex}}(n_{\text{S}} = 1) \approx 21$, and $E_{\text{a(ex)}} \approx E_{\text{a(obsd)}}$.

By contrast, if one uses an inert solvent, and if one measures the proton lifetimes in the true monomers, lower frequency factors and lower energies of activation should be observed. The reactants form hydrogen bonds before proton exchange, resulting in negative and nonzero values of ΔH and ΔS. This is one possible explanation of the values $E_{\text{a}} = 21$ kJ mol^{-1} and $\ln A = 15.7$ found by Denisov et al.[9] for the hydrogen–deuterium substitution reaction

$$\mathrm{CH_3COOD + CH_3CH_2OH} \rightleftharpoons \mathrm{CH_3COOH + CH_3CH_2OD}$$

using carbon tetrachloride as solvent. Though deuterium transfer is involved, the energy of activation is lower than for the reaction studied here. However, an energy of activation of about 8 kJ $\mathrm{mol^{-1}}$ found by Denisov et al.[9] for the hydrogen-deuterium substitution reaction between water and ethanol in CCl_4 and the extremely low frequency factor of $\ln A = 8.8$ cannot be explained by eq 14 and 15, but probably arise from an ionic exchange mechanism. It is well known[18] that chlorinated hydrocarbons decompose under the action of daylight, producing traces of hydrochloric acid by reaction with proton donors.

3. Reaction Pathway in the Active Complex. Besides the exchange mechanism of Scheme III we must discuss two possible reaction pathways in a cyclic 1:1 associate according to Scheme II. The first is a more or less coupled proton motion which is faster than solvent reorientation. An asynchronous motion leads over a nonsolvated "ion pair". The second is an asynchronous proton motion coupled to solvent reorientation with a solvated ion pair or transition state as intermediate (pathway b). In discussing the reaction pathways of similar reactions as studied here, Grunwald[3a] found evidence against a solvated ion pair mechanism. The probable lifetime of an ionized species was estimated to be shorter than the time required to reach an equilibrium state of solvation.

We reach a similar conclusion by comparing the experimental entropies of activation $\Delta S^{\ddagger}_{\mathrm{obsd}}(298\ \mathrm{K}, n_{\mathrm{S}} = 2) \approx -54\ \mathrm{J\,K^{-1}\,mol^{-1}}$ and $\Delta S^{\ddagger}_{\mathrm{obsd}}(298\ \mathrm{K}, n_{\mathrm{S}} = 1) \approx -79\ \mathrm{J\,K^{-1}\,mol^{-1}}$ to the entropy, $\Delta S_i(\mathrm{THF})$, estimated for the formation of solvated ion pairs according to Scheme II, pathway b, and to Scheme III. The ionization entropy of acetic acid in methanol is given by $\Delta S_i\ (\mathrm{methanol}) = -141\ \mathrm{J\,K^{-1}\,mol^{-1}}$, calculated from the data of Bolton et al.[19] and taking into account the concentration of the solvent. Caldin and Mateo[20] have shown that the enthalpy and the entropy of the formation of the ion pair between 4-nitrophenylnitromethane and tetramethylguanidine decreases as the dielectric constant, ϵ, of the medium decreases. Since THF has a lower dielectric constant ($\epsilon = 7.39$) than methanol ($\epsilon = 32.7$), one expects, by analogy, a value of about $\Delta S_i(\mathrm{THF}) \approx -220\ \mathrm{J\,K^{-}\,mol^{-1}}$. The values of $\Delta S^{\ddagger}_{\mathrm{obsd}}$ are much more positive than the value of $\Delta S_i(\mathrm{THF})$ and even of $\Delta S_i(\mathrm{methanol})$. The proton exchange is faster than expected for any of the solvated ion pair mechanisms. Thus, pathway a of Scheme II, which leads over mixed cyclic 1:1 intermediates between methanol and acetic acid, is the most probable reaction mechanism; there is no need for solvent reorientation in the "transition state", which would produce a large negative entropy of activation. The "transition state" may be one or several more or less quantized vibrational states from which the fast proton motion proceeds in a spontaneous manner. The frequency factor $\ln A_{\mathrm{ex}}(n_{\mathrm{S}} = 2) = 24$ is not in contradiction to a proton motion which proceeds by tunneling from excited vibrational levels. We have recently[8] found values of $\ln A_1 = 26.5$ and $A_0 = 5\ \mathrm{s^{-1}}$ for synchronous hydrogen tunneling between the first excited NH stretching levels and for the reaction between the ground states, respectively.

We hope that more information on the presence of tunneling and the degree of coupling of the proton motion can be obtained from the determination of the primary kinetic hydrogen-deuterium isotope effects. Such experiments can be carried out now that the existence of a cyclic proton exchange mechanism between methanol and acetic acid in THF has been established.

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