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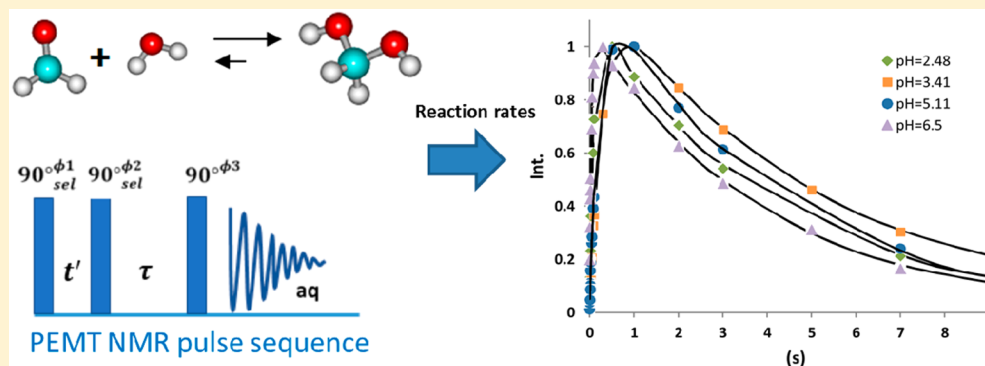
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NMR Studies of the Equilibria and Reaction Rates in Aqueous Solutions of Formaldehyde

Michal Rivlin, Uzi Eliav, and Gil Navon*

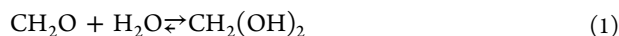
School of Chemistry, Tel Aviv University, Ramat Aviv, Tel Aviv, 69978, Israel



ABSTRACT: Formaldehyde has an important role in the chemical industry and in biological sciences. In dilute aqueous solutions of formaldehyde only traces of the molecular formaldehyde are present and the predominant species are methylene glycol and in lower concentrations, dimethylene glycol. The chemical equilibria and reaction rates of the hydration of formaldehyde in H₂O and D₂O solutions at low concentrations were studied by ¹H and ¹³C NMR at various conditions of pH (1.8–7.8) and temperature (278–333 K). These measurements became possible by direct detection of formaldehyde ¹³C and ¹H peaks. The equilibrium and rate constants of the dimerization reaction of methylene glycol were also measured. The rate constants for both the hydration and the dimerization reactions were measured by a new version of the conventional selective inversion transfer method. This study, together with previous published work, completes the description of dynamics and equilibria of all the processes occurring in dilute aqueous formaldehyde solutions.

INTRODUCTION

Aqueous solutions of formaldehyde ("formalin") have a central role in the chemical industry and in biological sciences.^{1,2} Upon dissolution, formaldehyde undergoes fast hydration to form methylene glycol (HOCH₂OH) (major species), which partially undergoes a much slower dimerization reaction^{3–5} to dimethylene glycol (HOCH₂OCH₂OH) (minor species), leaving only traces of the molecular formaldehyde,^{3,4,6} CH₂O:



The literature data on the chemical equilibrium constant of the hydration of formaldehyde (eq 1) were obtained from the carbonyl specific UV-absorption at approximately 290 nm,^{7–9} pulse polarography,^{10,11} thermochemical data,¹² or from the ratio of the hydration and dehydration rate constants that were determined by independent methods.^{13,14} The dehydration rate constants of methylene glycol were measured by several groups by chemical trapping of formaldehyde by hydrazine derivatives and measuring the hydrazine products spectrophotometrically.^{15–17} Direct determination of the hydration equilibrium constant and its kinetics by NMR are clearly desirable. Thus, one of the goals of the current study is to identify the ¹H and ¹³C signals of formaldehyde in aqueous solutions and to

perform direct measurements of the kinetics and equilibrium constants of the hydration reaction of formaldehyde (eq 1).

The chemical equilibria and kinetics rates of the polyoxymethylene glycol formation, were previously studied by ¹³C NMR by Hahnenstein et al.⁴ and Gaca et al.,⁵ following the changes in concentrations of the species after dilution of aqueous formaldehyde solutions. In the present work the kinetics among the chemical species were measured by magnetization transfer NMR techniques under conditions of chemical equilibrium.

For this purpose the hydration and dimerization reactions were studied by several NMR chemical exchange methods that were best suited to the exchange region, including saturation transfer and new versions of the conventional selective inversion transfer method.

EXPERIMENTAL METHODS

As described earlier,¹⁸ formaldehyde solutions were prepared from paraformaldehyde powder (>0.95 g/g, Merck, Germany) that was depolymerized by dissolution in H₂O (or D₂O), containing 0.01 M sodium phosphate buffer pH 7.4, which was

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kept at a temperature of 333 K for time periods ranging from 3 h for the low formaldehyde concentrations, to 3 days for the high formaldehyde concentrations.¹⁹ All experiments were performed at concentrations up to 2.4 M. Above this concentration precipitation of paraformaldehyde occurred, unless methanol was added.

All H₂O solutions were prepared using doubly distilled water. The deuterium oxide solutions contained min 99.98 atom % D. (BIOLAB, Jerusalem, Israel). The presence of paramagnetic impurities, such as Mn, Fe, and Cu, was ruled out by atomic absorption analysis. Furthermore, the same results were obtained for formaldehyde samples that were prepared following sublimation of paraformaldehyde or formaldehyde solutions that were passed through Chelex chelating ion-exchange resin, indicating no effect of impurities on the results.

NMR Spectra. The spectra were acquired with Bruker 9.39 and 11.74 T NMR spectrometers using a 5 mm multinuclei probe. To ensure full relaxation of all species, relaxation delay times of 60 and 20 s were used for the ¹H NMR and ¹³C NMR measurements, respectively. The temperature was controlled to within ± 0.1 K.

The kinetic of the hydration/dimerization reaction of formaldehyde solutions in D₂O was measured using ¹H and ¹³C NMR with a modified version of the standard²⁰ inversion transfer method, denoted as phase encoding magnetization transfer (PEMT) (eq 3). In this pulse sequence the selective 180° in the standard inversion transfer method²⁰ is replaced by two selective 90° pulses whose phases are cycled as given in eq 3.

$$(90^{\circ\phi_1}_{\text{sel}}) - t' - (90^{\circ\phi_2}_{\text{sel}}) - \tau - (90^{\circ\phi_3}_{\text{sel}}) - \text{acq} \quad (3)$$

$$\phi_1 = 0^\circ 180^\circ 0^\circ 180^\circ, 0^\circ 180^\circ 0^\circ 180^\circ$$

$$\phi_2 = 0^\circ 0^\circ 180^\circ 180^\circ, 0^\circ 0^\circ 180^\circ 180^\circ$$

$$\phi_3 = 0^\circ 0^\circ 0^\circ 0^\circ, 90^\circ 90^\circ 90^\circ 90^\circ, 180^\circ 180^\circ 180^\circ 180^\circ, \\ 270^\circ 270^\circ 270^\circ 270^\circ$$

$$\phi_{\text{receiver}} = 0^\circ 180^\circ 180^\circ 0^\circ, 90^\circ 270^\circ 270^\circ 90^\circ, 180^\circ 0^\circ 0^\circ 180^\circ \\ 270^\circ 90^\circ 90^\circ 270^\circ$$

where t' is a short time interval between the two 90° selective pulses allowing the change of the pulses' phases. In this method, one of the species is selectively excited, labeling its magnetization with rf phases ϕ_1 and ϕ_2 . A suitable phase cycling selects the magnetization of the excited species and of the transferred magnetization to the exchanging partners.

For the pulse sequence shown in eq 3, the following expression could be written assuming that the exchange rate is faster than the longitudinal relaxation rates:²¹

$$M_A(t) = M_0^A p_A \{ \exp(-R_1 t) - \exp(-k_{\text{ex}} t) \} \quad (4)$$

$$M_B(t) = M_0^B [p_A \exp(-k_{\text{ex}} t) - p_B \exp(-R_1 t)]$$

where

$$k_{\text{ex}} = k_{\text{BA}} + k_{\text{AB}} \quad R_1 = p_A R_{1A} + p_B R_{1B}$$

$$R_{1A} = 1/T_{1A} \quad R_{1B} = 1/T_{1B}$$

$$p_A = k_{\text{BA}}/(k_{\text{BA}} + k_{\text{AB}}) \quad p_B = k_{\text{AB}}/(k_{\text{BA}} + k_{\text{AB}})$$

$$p_A + p_B = 1$$

This method has the advantage over the standard inversion transfer method in that the signal at $t = 0$ is very small and is not affected by the B₁ inhomogeneities. Thus, it requires only three parameters for the analysis instead of the four required for the inversion transfer method. In addition, the method filters out peaks that are not related to the exchange process. In the inversion transfer method, peaks that are not involved in the exchange process are present in the spectrum, and in cases where the intensity of these signals is much larger than those that are involved in the exchange process they may obscure the latter ones.

The PEMT technique is not applicable in conditions where the exchange rate is slow and is of the order of T_1 . In such cases the saturation transfer method (ST) is the preferred technique (Figure 1).

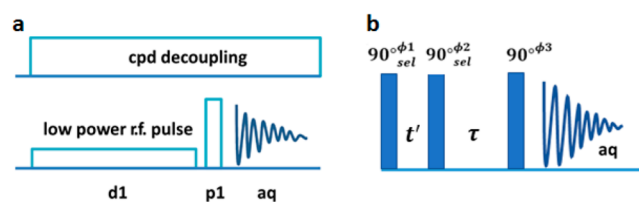


Figure 1. Pulse scheme for the ST (a) and PEMT (b) techniques.

In this technique, one of the peaks is saturated, and the decline of the exchanging signal is monitored. According to Gupta and Redfield,²² one can calculate the exchange lifetime, τ_A , by the following equation:

$$\tau_A = T_{1A} \frac{M_Z^A/M_0^A - M_Z^B/M_0^B}{1 - M_Z^A/M_0^A} \quad (5)$$

where A is the observed peak and B is the irradiated one. M_Z and M_0 are the longitudinal magnetizations with and without irradiation, respectively. Since the signal intensity is proportional to M_Z , the ratio M_Z/M_0 is obtained from the ratio of the signal intensities in the presence and absence of the irradiation. T_{1A} is the longitudinal relaxation time of signal A in the absence of exchange.

In the present work the signal (of peak B) was completely saturated and the effect of the saturation on the other peak was monitored. The intensity of the irradiation was chosen so that the irradiated signal was completely saturated. Then a simplified form of eq 5 with $M_Z^B/M_0^B = 0$ can be used. Under conditions of full saturation of one of the signals eq 5 yields

$$M_0^A/M_Z^A = k_{\text{AB}} T_{1A} + 1 \quad (6)$$

$$M_0^B/M_Z^B = k_{\text{BA}} T_{1B} + 1 \quad (7)$$

where k_{AB} and k_{BA} are the exchange rate constants of the two species and T_{1A} , T_{1B} are the longitudinal relaxation times in the absence of exchange. The latter relaxation times were obtained by combining the results of the saturation transfer experiments with those of inversion recovery experiments under the condition where either signal B or A are completely saturated and are given by the following expressions:

$$1/T_{1A}^S = k_{\text{AB}} + 1/T_{1A} \quad (8)$$

$$1/T_{1B}^S = k_{\text{BA}} + 1/T_{1B} \quad (9)$$

where T_{1A}^S and T_{1B}^S are the relaxation times of species A and B under saturation. Equations 6–9 constitute four equations with four unknown parameters, enabling the calculation of the rate constants.

RESULTS

The proton NMR spectrum of formaldehyde in D_2O is shown in Figure 2. Four peaks are depicted: Three are assigned to the

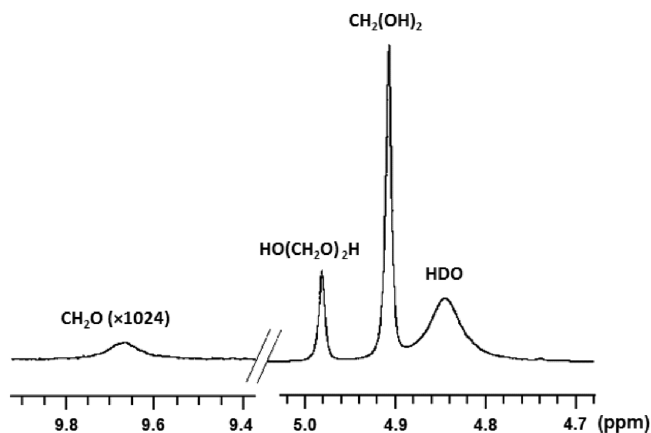


Figure 2. 1H NMR spectrum of 2.4 M formaldehyde in a solution of 0.01 M phosphate buffer, pH 7.4, in D_2O ($T = 298\text{ K}$, $B_0 = 11.74\text{ T}$). The chemical shifts were calibrated by using DSS (0 ppm).

CH_2 groups of the formaldehyde, the methylene glycol and the dimethylene glycol as indicated in the spectrum. The fourth peak is attributed to the residual peak of water (HOD). This assignment is in agreement with the previous report of Le Botlan²³ except that the formaldehyde signal, which is present at very small amounts ($<0.03\%$ at pH = 7.4, $T = 298\text{ K}$), was not reported previously.^{4,6,9}

^{13}C NMR spectra of aqueous solutions of 99% ^{13}C -enriched formaldehyde are shown in Figures 3 and 4. The assignment of

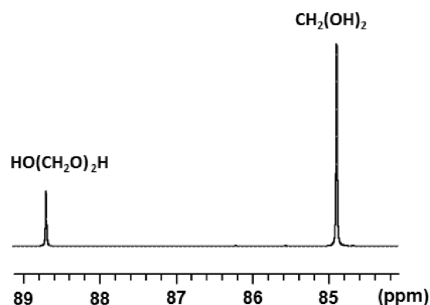


Figure 3. Decoupled ^{13}C NMR spectrum of 99% ^{13}C enriched 2.4 M formaldehyde in D_2O solution (0.01 M phosphate buffer, pH = 3.7, $T = 298\text{ K}$, $B_0 = 11.74\text{ T}$). The chemical shifts were calibrated by using dioxane (67.19 ppm).

the ^{13}C signals was based on the intensity ratios in the decoupled spectra (Figure 3) and on the chemical shift of the dimer which is expected to be at a lower field to that of the monomer due to the etheric bond (Figure 3), in agreement with previous reports.^{6,23} For the observation of the ^{13}C signal of formaldehyde the solution was slightly acidic (pH = 3.7) in order to minimize line broadening due to chemical exchange (Figure 4). The 1:2:1 triplet that collapsed by proton decoupling centered at 9.66 ppm validates the assignment of

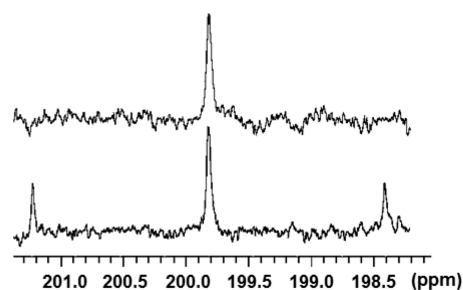


Figure 4. ^{13}C NMR proton coupled (lower spectrum) and proton-decoupled ^{13}C NMR (upper spectrum) of 99% ^{13}C enriched 2.4 M formaldehyde in a D_2O solution (0.01 M phosphate buffer, pH = 3.7, $T = 298\text{ K}$, $B_0 = 11.74\text{ T}$). The chemical shifts were calibrated by using dioxane (67.19 ppm). The spectrum was recorded with a delay of 40 s, an acquisition time of 1.49 and 256 scans, $\Delta\nu_{1/2}(\text{formaldehyde}) = 3.3\text{ Hz}$.

this signal to the residual formaldehyde. The assignment was further verified by a selective C–H correlation HMQC pulse sequence; selective excitation of the ^{13}C nuclei at 199.8 ppm showed a correlation to the 1H peak at 9.66 ppm. The observed ^{13}C chemical shift of 199.8 ppm for aqueous formaldehyde is slightly higher than that reported in organic solvents, that is, 196.7 and 194 ppm in dimethyl ether and THF, respectively.^{24,25} Having a well-resolved 1H and ^{13}C NMR spectra for the formaldehyde, the monomer and dimer enabled the measurements of the equilibrium and the rate constants among all these species.

Measurements of Equilibrium Constants. The equilibrium constants for the hydration reaction (eq 1), $K_{eq(hyd)}$, and the dimerization reaction (eq 2) $K_{eq(dimer)}$, given by in eqs 10 and 11, were determined by independent measurements of the integrated intensities of the 1H and ^{13}C signals.

$$K_{eq(hyd)} = \frac{X_{monomer}}{X_{formaldehyde}X_{D_2O}} \quad (10)$$

$$K_{eq(dimer)} = \frac{X_{dimer}X_{D_2O}}{X_{monomer}^2} \quad (11)$$

where X stands for mole fractions.

While for ^{13}C the peak areas were obtained by direct integration, the areas of the 1H peaks were obtained by Lorentzian line fitting due to their considerable overlap, as shown in Figure 5. The NOE enhancement for the ^{13}C spectra measured at 298 K was 2.5 for both the monomer and the dimer. It was further assumed that the NOE was the same for all species at all temperatures.

The results of the equilibrium constants of the hydration, $K_{eq(hyd)}$, and the dimerization $K_{eq(dimer)}$, reactions measured by both 1H and ^{13}C spectra at different pH values and temperatures are summarized in Figure 6. It should be noted that the results taken from the 1H and ^{13}C spectra fall on the same curve despite the different experimental setup. The equilibrium constants of the hydration and the dimerization reactions were found to be independent of pH. As can be seen from Figure 6, $K_{eq(hyd)}$ of formaldehyde decreases with temperature, giving a reaction enthalpy of $\Delta H^\circ = -39.0\text{ kJ/mol}$. The average value obtained for $K_{eq(hyd)}$ at 293 K was 2.10×10^3 .

The temperature dependence of the chemical equilibrium constants for the dimerization reaction is rather weak, giving a

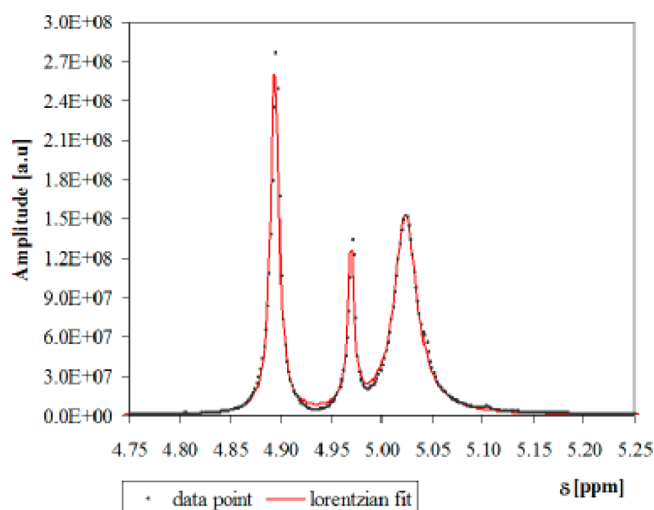


Figure 5. Result of the Lorentzian fit to ^1H NMR spectrum of 2.4 M formaldehyde in D_2O solution (0.01 M phosphate buffer, pH = 7.4, $T = 281$ K, $B_0 = 9.39$ T). The points represent the experimental amplitude, while the solid line represents the best fit to the data. $R^2 = 0.990$.

reaction enthalpy of $\Delta H^\circ = 1.2$ kJ/mol. The results for $K_{\text{eq(dimer)}}$ of H_2O formaldehyde solutions were 6.54 ± 0.65 at a temperature of 298 K and 5.4 ± 0.74 at a temperature of 327 K. Measurements that were done in D_2O solutions yielded $K_{\text{eq(dimer)}}$ values of 9.08 ± 1.42 at $T = 298$ K, and 9.43 ± 0.52 at $T = 327$ K (Figure 6). These results correspond to the isotope effect $K(\text{D}_2\text{O})/K(\text{H}_2\text{O})$ of 1.4 and 1.7 at $T = 298$ K and $T = 327$ K, respectively.

^{13}C NMR Measurements of the Dimerization Reaction Rate. The ^{13}C NMR spectral lines of the monomer and the dimer (Figure 3) are very narrow (below 1 Hz), indicating very slow exchange between the two species and prohibiting the measurement of their rate using the line width. Thus, the techniques used here to measure the exchange rates are based on measuring changes of the longitudinal magnetization, that is, saturation transfer,^{22,26,27} and magnetization transfer methods that involve selective excitation, which is applicable when the exchange rate is larger than the longitudinal relaxation rate. For that purpose we devolved a modified version of the standard inversion transfer method, denoted as phase encoding magnetization transfer (PEMT), which is described in details in the methods section. Following the equations of this method, for the case of the dimerization reaction, species A was defined as the monomer and species B as the dimer.

As can be seen from Figure 7a the pair of selective 90° pulses (on the dimer) yields no signal for the monomer (species A) at time zero. As the exchange progresses, there is a buildup of the signal of the monomer concomitantly with the decay of the dimer's magnetization. From the rise time of the monomeric signal we have obtained an exchange rate of 490 ms, while the initial rate of decay of the dimer's signal was fitted to an exchange rate of 380 ms. The decay of both signals at longer times is dominated by the longitudinal relaxation ($T_{1A} = 7.0$ s, $T_{1B} = 7.8$ s).

From the measurements of the monomer and the dimer data, one may note that τ_{ex} and T_1 should be the same, since $k_{\text{ex}} = k_{\text{AB}} + k_{\text{BA}}$ and the exchange is much faster than T_1 . (k_{AB} and k_{BA} are the exchange rate constants of the monomer and dimer, respectively.) The numbers obtained from the dimer data

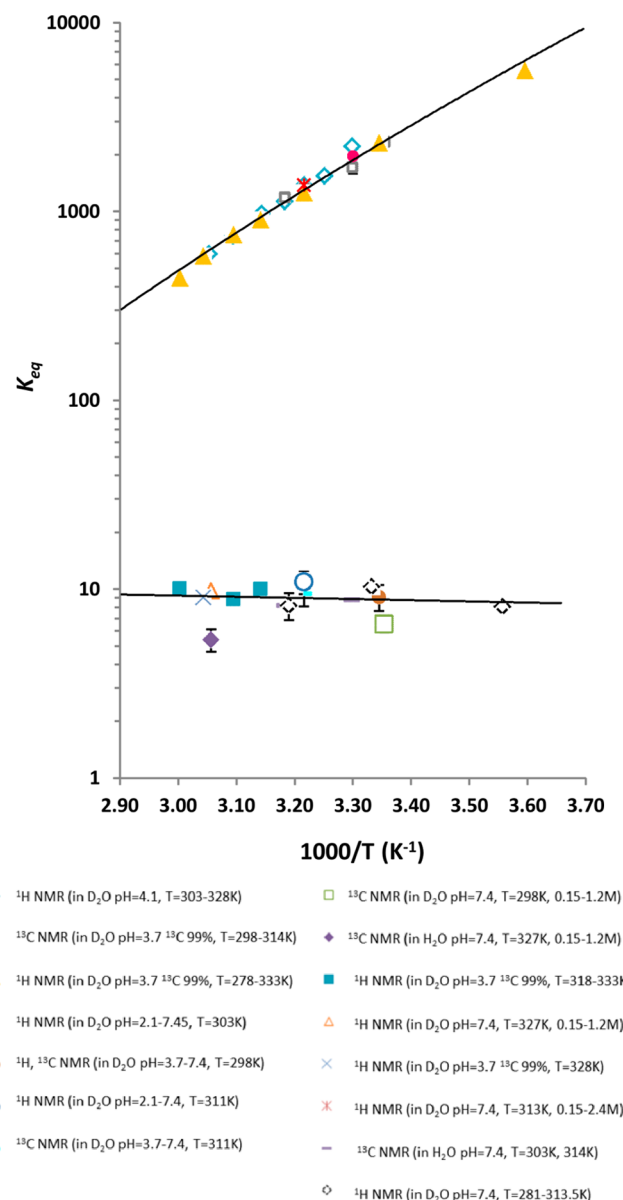


Figure 6. Temperature dependence of the equilibrium constants of the hydration (eq 1, upper curve) and dimerization (eq 2, lower curve) reactions, for a 2.4 M formaldehyde solution (0.01 M phosphate buffer, $B_0 = 11.74$ T).

(Figure 7b) are less reliable since they are obtained from a sum rather than a difference of decay rates, and since the signal SNR is lower compared to that of the monomer.

The PEMT technique is not applicable when the exchange rate is slow and is of the order of T_1 . In such cases the saturation transfer method (ST) is the preferred technique. In the ST method, the dimer signal (peak B) was completely saturated and the effect of the saturation on peak A was monitored. The intensity of the irradiation was chosen so that the irradiated signal was completely saturated. Then, a simplified form of eq 5 with $M_Z^B/M_0^B = 0$ can be used. For ^{13}C peaks this is possible without direct saturation of the other peak due to the large separation (3.7 ppm, 2 kHz) between the dimer and the monomer peaks, which is much larger than the r.f amplitude used in the current study (91 Hz).

Under the conditions of 1.2 M aqueous formaldehyde solution, (0.01 M phosphate buffer, pH = 7.4 $T = 298$ K), the

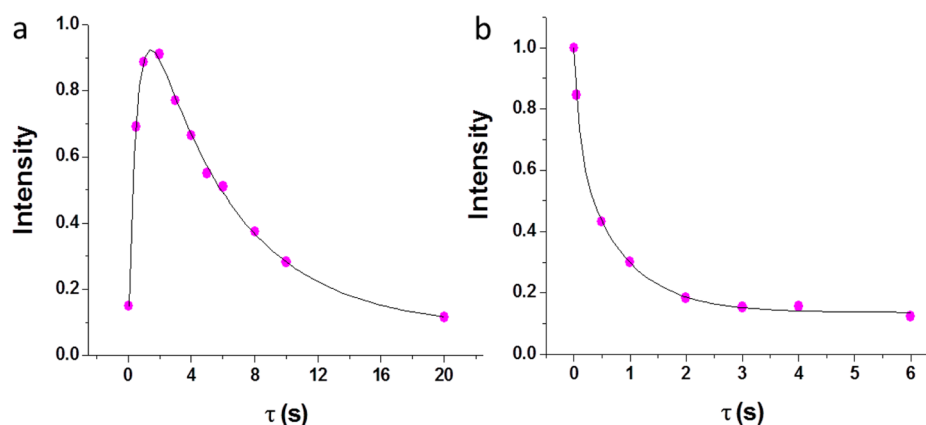


Figure 7. ^{13}C NMR results of the PEMT experiment on the exchanging methylene carbons of the monomer (species A) (Figure 7a) and dimer (species B) (Figure 7b) at 327 K. The points represent the observed intensities as a function of the exchange time τ , while the solid lines represent the biexponential best fit to the data. The dimer was selectively excited while the effect of the exchange was detected on the peak of the monomer. The lengths of the selective and the nonselective pulses were 20 ms and 22 μs , respectively.

experiment, in which signal B was saturated using a 6 s saturation pulse, yielded $M_Z^A/M_0^A = 0.91$, $T_{1A}^A = 3.5$ s, and on the basis of eqs 6 and 8 $T_{1A} = 3.8$ s and $k_{AB} = 0.026 \text{ M}^{-1} \text{ s}^{-1}$ were calculated. Similarly, when signal A was saturated $M_Z^B/M_0^B = 0.85$, $T_{1B}^B = 1.4$, and on the basis of eqs 7 and 9, $T_{1B} = 1.6$ s and $k_{BA} = 0.11 \text{ s}^{-1}$ were calculated.

Having measured the forward and backward reaction rates for the dimerization reaction it is possible to get an additional and independent way of evaluating the equilibrium constants, simply by taking the ratio of these reaction rate constants.

The equilibrium constants for the dimerization reaction were calculated from these values according to eq 12:

$$K_{\text{eq(dimer)}} = k_{BA}/k_{AB} = 2\tau_{AB}/\tau_{BA} \quad (12)$$

For a 1.2 M aqueous formaldehyde solution, the calculated values of k_{BA} and k_{AB} yield $K_{\text{eq(dimer)}} = 8.6$. This result agrees with the completely independent evaluation of $K_{\text{eq(dimer)}}$ obtained by direct integration of ^{13}C and ^1H peaks given above (Figure 6).

In Table 1, the ST and PEMT results are given for a 2.4 M formaldehyde solution at different temperatures.

Table 1. Temperature Dependence of the Dimerization and the Reverse Reaction (eq 2) Rate Constants and the Longitudinal Relaxation Times (2.4 M Formaldehyde in D_2O Solution, 0.01 M Phosphate Buffer, pH = 7.4, $B_0 = 9.39$ T)

expt	T (K)	τ_{ex} (s)	k_{AB} ($\text{M}^{-1} \text{s}^{-1}$)	k_{BA} (s^{-1})	T_{1A} (s)
ST	298	133.3 ^a	0.0014	0.006	3.7
ST	308	15.4 ^a	0.012	0.054	5.2
PEMT	316	4.2	0.043 ^b	0.195 ^b	7.1
PEMT	327	0.4	0.446 ^b	2.054 ^b	7.8

^aCalculated by the expression $1/\tau_{\text{ex}} = k_{AB} + k_{BA}$. ^bCalculated from experimental data for τ_{ex} and $K_{\text{eq(dimer)}}$ using the expression $1/\tau_{\text{ex}} = k_{AB} + k_{BA}$ and eq 12.

The reaction rate constant for the dimerization reaction has a very steep dependence on the temperature (Table 1). The general agreement between the two methods of rate measurement, as evident in the overall linearity of the data, is apparent (Figure 8), corresponding to activation energies of 155 and 157 kJ/mol for k_{AB} and k_B , respectively.

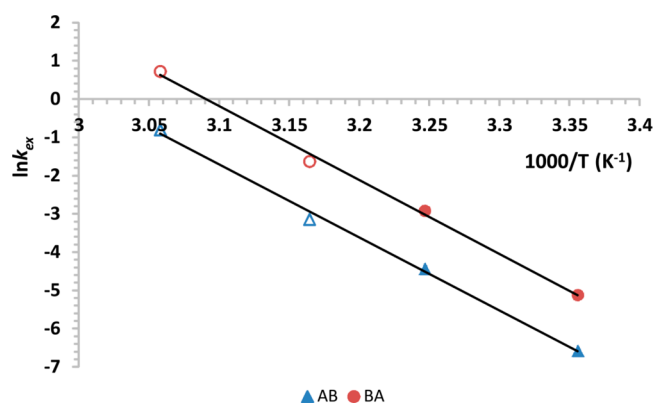


Figure 8. Arrhenius plot of the dimerization and the reverse reaction (eq 2) rate constants k_{AB} and k_{BA} calculated by the PEMT and the ST methods for 2.4 M formaldehyde in D_2O solution (0.01 M phosphate buffer, pH = 7.4). Points represent experimental data: unfilled characters, PEMT; filled characters, ST; lines represent linear fits.

The Temperature Dependence of the ^{13}C Chemical Shifts of the Monomer and the Dimer. The ^{13}C chemical shift of the formaldehyde monomer and dimer in a 1.2 M formaldehyde solutions at the temperature range of 281–316 K is given in Figure 9. From the linear fit we have deduced that the temperature dependence of the shift is 0.6×10^{-2} ppm/K and 1.1×10^{-2} ppm/K for the monomer and dimer, respectively. The shift was to a lower field with increasing temperature. Le Botlan et al.²³ reported somewhat higher values for the temperature dependence of the ^{13}C chemical shifts in highly concentrated (42.8%) solutions of formaldehyde in H_2O , i.e. an increase of 0.29 and 0.40 ppm upon a temperature change of 30 K, corresponding to 0.97×10^{-2} and 1.33×10^{-2} ppm/K for the monomer and the dimer, respectively.

The significant stronger temperature dependence of the ^{13}C chemical shift for the dimer compared to that of the monomer is very striking and possibly stems from an exchange with a conformation which is unique to the dimer (see Discussion).

^1H NMR Measurements of the Hydration Reaction Rate of Formaldehyde. The high resolution ^1H NMR spectrum of 2.4 M formaldehyde in D_2O (pH = 7.4) exhibits a broad resonance at 9.66 ppm, assigned to the CH_2O , which is similar to $\delta = 9.53$ ppm in THF,²⁸ and 9.61 ppm in MeCN.²⁹

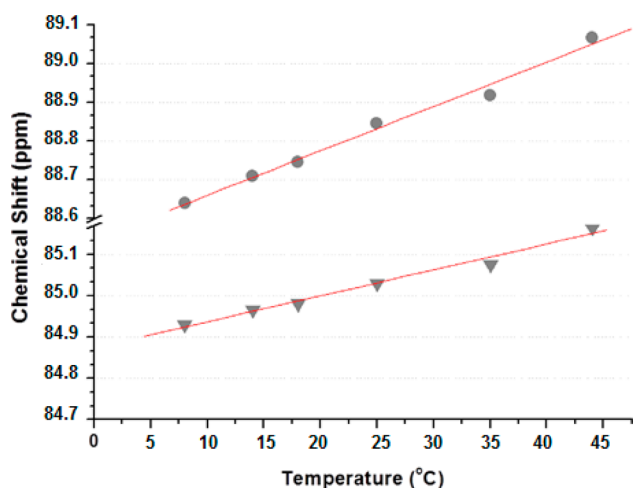


Figure 9. Temperature dependence of the dimer (●) and monomer (▼) chemical shifts for 1.2 M formaldehyde in D_2O solution (0.01 M buffer phosphate, pH= 7.4, containing 0.14 M of acetone which was used as chemical shift reference $\delta(^{13}C) = 33.0$ ppm, $B_0 = 11.74$ T). R^2 (dimer, monomer) = 0.995, 0.991. The solid lines represent linear fits.

The line width of this signal over the temperature range of 281–327 K increases from 12 to 96 Hz. This increase can be partially explained as resulting from faster exchange rates between formaldehyde and its hydrates at higher temperatures. This interpretation is supported by the observation that the formaldehyde line width in organic solvents (such as $CDCl_3$), where there is no chemical exchange, is only 0.5 Hz.

The exchange rate of formaldehyde and its hydrates were obtained by using the PEMT method shown in eq 3 except that the third pulse was a selective pulse applied to the formaldehyde peak. The reason for this modification is the very small formaldehyde peak intensity relative to that of its hydrates. Thus, the use of a selective pulse improves the SNR due the dynamic range, and eliminates problems related to the overlap of the formaldehyde peak with those of its hydrates. Examples of the PEMT results for a few pH values are given in Figure 10, and a plot of the resulting rate constants as a function of pH is shown in Figure 11.

Both acid and base catalysis are seen in Figure 11, however owing to the small number of experimental points the corresponding rate constants could not be determined from these results.

It should be noted that k_{ex} is the sum of the hydration k_{hyd} and the dehydration k_{dehyd} rate constants:

$$k_{ex} = k_{hyd} + k_{dehyd} \quad (13)$$

which are related to each other by

$$k_{dehyd}/k_{hyd} = K_{eq} \quad (14)$$

The two rate constants were calculated for each temperature from k_{ex} using eqs 13 and 14, and the values of K_{eq} given in Figure 6. The results at a pH of 7.4 are given in Figure 12, and the activation energies obtained are 54.5 and 86.2 kJ/mol for the hydration and the dehydration reactions, respectively.

$$k'_{hyd}(s^{-1}) = 2.07 \times 10^5 \sqrt{[OH^-]} + 2405[H^+] + 5$$

The apparent rate constant k'_{hyd} , that can be calculated from the line width ($k'_{hyd} = \pi\Delta\nu_{1/2}$) of the formaldehyde signal in the pH range of 1–8, is given in Figure 13. The dependence of k'_{hyd} on

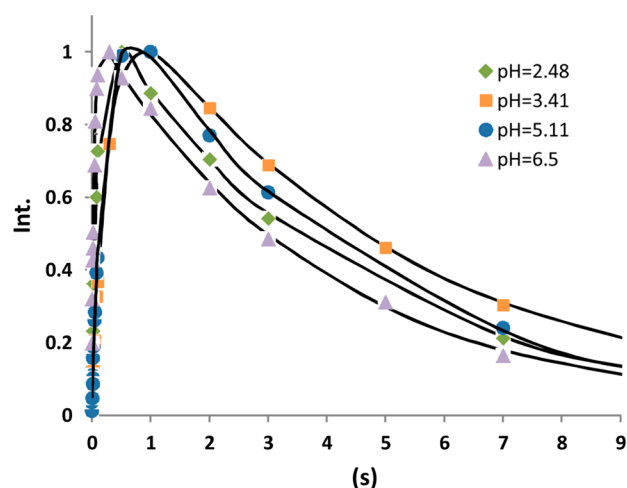


Figure 10. Examples of the 1H NMR results obtained by the modified PEMT experiments describing the exchange between formaldehyde and the hydrates (eq 1) at different pH values. 2.4 M formaldehyde solution in D_2O (0.01 M phosphate buffer, $T = 298$ K, $B_0 = 11.74$ T). The points represent the observed intensities as a function of time τ (eq 4), while the solid lines represent biexponential best fit to the data. The hydrates were selectively excited, and the exchange was monitored by following the formaldehyde peak intensity by the application of a selective pulse to it. The lengths of the selective pulses were 3–4 ms.

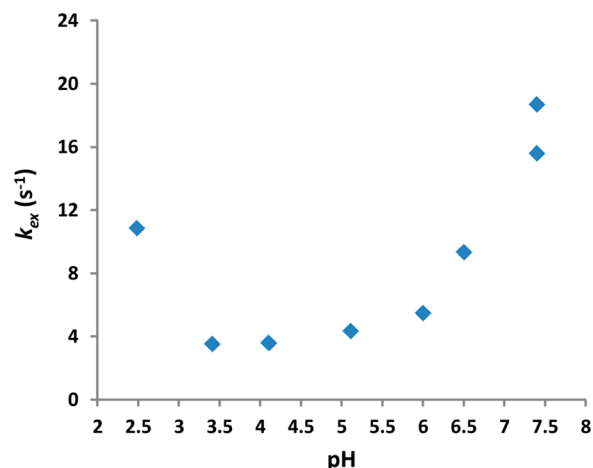


Figure 11. pH dependence of k_{ex} obtained by the modified PEMT method for 2.4 M formaldehyde in D_2O solution (0.01 M phosphate buffer, $T = 298$ K, $B_0 = 9.3$ T).

the pH could not be fitted to a simple acid and base catalytic process but rather to the square root of the hydroxide concentration. The apparent rate constant that can be calculated from the line width (Figure 13) is much larger than that obtained from the PEMT experiment (Figure 11). The discrepancy between these two experiments is more pronounced at higher pH values. It decreases with the temperature: at pH 7.4 the ratio between the rate constants obtained by the two methods, k'_{hyd}/k_{hyd} decreases from 6 at 298 K to 2 at 327 K. A possible explanation for the excess broadening over that expected from the exchange rate constant is an exchange of the formaldehyde with a minor species that is either chemically shifted or is very broad. Such a process may contribute to the line width of the formaldehyde without affecting its exchange rate with the methylene glycol. To test the possibility that these species are formaldehyde molecules

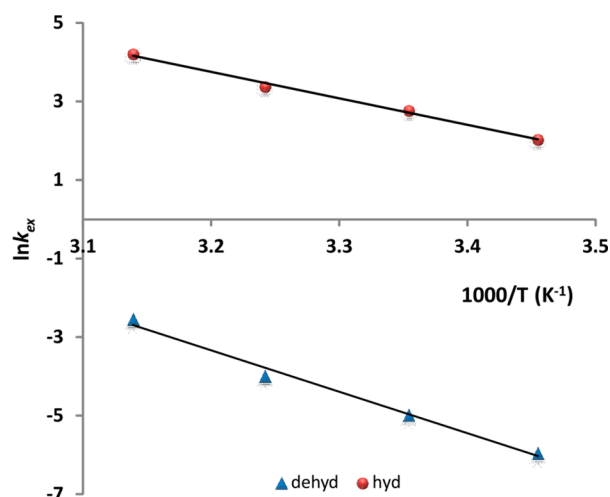


Figure 12. Arrhenius plot of formaldehyde reversible hydration rate constants (k_{hyd} , k_{dehyd}) (eq 1) calculated from the modified PEMT method, for 2.4 M formaldehyde in D_2O solution (0.01 M buffer phosphate, pH = 7.4, $B_0 = 9.3$ T). The solid lines represent linear fits.

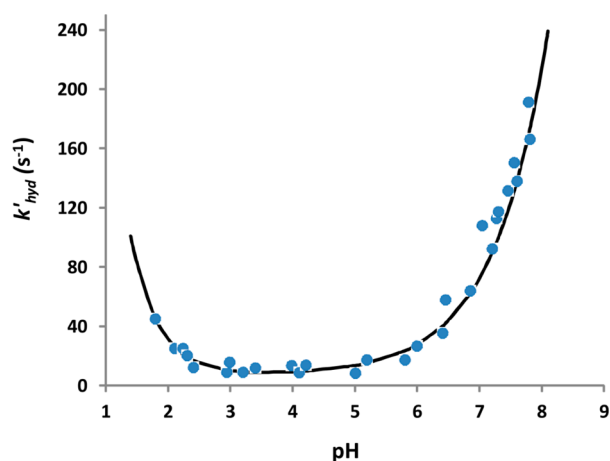


Figure 13. k'_{hyd} obtained from the line width of the formaldehyde signal as a function of pH. The exchange rate was estimated from the formaldehyde line width using the expression $k'_{\text{hyd}} = \pi \Delta\nu_{1/2}$, while $\Delta\nu_{1/2}$ is the line width at half height after subtraction of the monomer line width in order to remove field inhomogeneity effects (for 2.4 M formaldehyde in D_2O solution, 0.01 M phosphate buffer, $T = 298$ K, $B_0 = 11.74$ T).

adsorbed to the glass tube, the exchange rates and the line widths were measured using quartz NMR tubes. However, the results were the same as those in glass NMR tubes. Thus, the source of this effect, as well as the proportionality of the excess broadening to the square root of the hydroxide concentration, is still waiting for an explanation.

DISCUSSION

The ^{13}C and ^1H NMR studies of the dynamics and chemical exchanges presented in this paper illustrate the usefulness of NMR in studying reactions of aqueous formaldehyde solutions. To the best of our knowledge, this is the first report of the ^1H and ^{13}C signals of formaldehyde in aqueous solutions. Direct measurements of the formaldehyde peak, both by ^{13}C and ^1H NMR, allowed quantitative calculations of its hydration equilibrium constants. The average value obtained for K_{eq} at 293 K was 2.10×10^3 (Figure 6). This value is in good

agreement with the value of $K_{\text{eq}} = 2.33 \times 10^3$ (at $T = 293$ K) obtained by Valenta¹¹ using pulse polarography, and was considered by Bell and Evans¹⁶ as the most reliable result. Other reported values were 2.22×10^3 (at 298 K)^{7–9} and 2.19×10^3 (at 293 K)⁹ from the carbonyl specific UV-absorption, and 2.22×10^3 (at 295 K)¹⁵ and 1.59×10^3 (at 293 K)¹⁴ from the ratio of the hydration and dehydration rate constants that were determined by two independent methods.

The equilibrium constant of the hydration reaction determined in this work shows no pH dependence, but is strongly dependent on the temperature, with an enthalpy of $\Delta H^\circ = -39.0$ kJ/mol. The reaction enthalpy reported in the literature for the hydration reaction varies from -21.4 to -39.4 kJ/mol. The value obtained in this work is consistent with previous reports of Bryant and Thompson¹² who derived an expression for $K_{\text{eq(hyd)}}$ from a consistent set of thermochemical data, and reported $\Delta H^\circ = -38.9$ kJ/mol. Zavitsas et al.⁹ obtained $\Delta H^\circ = -35.2 \pm 2.1$ kJ/mol from the carbonyl specific UV absorption at approximately 290 nm. However, this technique is hampered by the assumption that the molar absorption coefficient is solvent independent.³⁰

The rate constants for the hydration and dehydration reactions obtained in the present work by the PEMT technique in D_2O solutions are $k_{\text{hyd}} = 4.0$ s⁻¹ and $k_{\text{dehyd}} = 1.7 \times 10^{-3}$ s⁻¹ at pH 4 ($T = 298$ K). At that pH but in H_2O solutions Sutton and Downes¹⁵ reported a value of $k_{\text{hyd}} = 9.8$ s⁻¹ by following the rate of formation of semicarbazone after irradiation of semicarbazide and methanol solutions by a beam of 2 Mev electrons. Most determinations of the dehydration rate constants of methylene glycol were obtained indirectly by trapping the formaldehyde formed with hydrazine derivatives and following spectrophotometrically the increase in absorbance in hydrazones.^{15–17} Their results were 5.1×10^{-3} s⁻¹ at 298 K, 4.4×10^{-3} s⁻¹ at 295 K, and 4.2×10^{-3} s⁻¹ at 298 K. Thus, the literature values for both k_{hyd} and k_{dehyd} were larger by a factor of about 2.5 than our reported values. This discrepancy can be at least partially explained by an isotope effect since our results were obtained in D_2O solutions. For comparison $\text{H}_2\text{O}/\text{D}_2\text{O}$ kinetic isotope effects of 3.6 and 3.9 were reported by Pocker³¹ for the hydration and the dehydration reactions of acetaldehyde, respectively.

The equilibrium constants of the dimerization reaction determined in this work were found to slightly decrease with temperatures between 298 and 327 K (Figure 6), and with an enthalpy of $\Delta H^\circ = 1.2$ kJ/mol. Hahnenstein et al.⁶ reported enthalpy below 5 kJ/mol for formaldehyde in H_2O . The results for $K_{\text{eq(dimer)}}$ of H_2O formaldehyde solutions of 6.54 ± 0.65 at $T = 298$ K agree with those published by Hahnenstein et al., who reported a value of $K_{\text{eq(dimer)}} = 6.7$ at the same temperature obtained by ^{13}C NMR spectroscopy for very concentrated formaldehyde solutions.^{4,6} Earlier works reported values of $K_{\text{eq(dimer)}} \sim 4.5$ (^1H NMR)³² and 5.7 (^{13}C NMR).³³

A combination of ^{13}C NMR methods, each best suited to the exchange regions, has been shown to be applicable to determine the exchange rate between the methylene glycol and dimethyl glycol molecules. The rate constants at a pH value of 7.4 were in the range of 1.4×10^{-3} to 0.45 M⁻¹ s⁻¹ and 6×10^{-3} to 2.05 s⁻¹ for the dimerization and the reverse reaction, respectively, at $T = 298$ – 327 K. Hasse et al.³ and Hahnenstein et al.⁴ used two independent methods to measure the kinetics of the dimerization reaction: NMR spectroscopy and high-resolution densimetry. Their studies cover aqueous formaldehyde solutions with pH values lower than 7. Considering

the fact that the rate constants strongly depend on temperature and pH and go through a minimum (U-shaped), the rate constants increase strongly at pH = 7.4 (pD = 7.8). Yet, there is insufficient information in order to compare the results. Ott et al.³⁴ used flow ¹H NMR spectroscopy measured rate constants of $1.74 \times 10^{-3} \text{ s}^{-1}$ at $T = 293 \text{ K}$ and $5.24 \times 10^{-3} \text{ s}^{-1}$ at $T = 323 \text{ K}$, for the reverse reaction at a pH value of 6.89. The comparison with our results is not valid owing to the differences in the pH values and the solvent (H_2O vs D_2O).

As was shown in the Results section (Figure 9), the ¹³C chemical shifts of the monomer, and in particular that of the dimer molecules, were significantly dependent on temperature. This can be explained by another equilibrium and may indicate an exchange among several conformations. On the basis of the density functional theory calculations, Kua et al.³⁵ suggested cyclical structures that involve two water molecules for both the monomer and the dimer. To explain the larger temperature dependence of the ¹³C chemical shift of the dimer we would like to propose an exchange with a new cyclic conformation which is unique to the dimer (Figure 14). This structure is

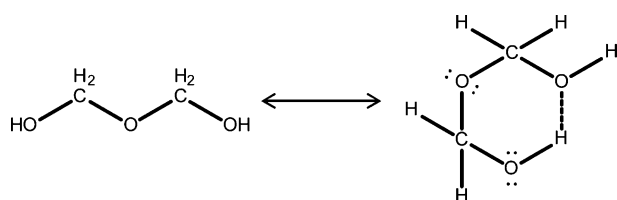


Figure 14. Hypothetical description of new equilibrium for the dimer molecule.

stabilized by intramolecular hydrogen bonding and does not involve the participation of water molecules. Equilibrium between open and cyclic conformers can very well result in a temperature dependence of the chemical shift.

CONCLUSIONS

The reaction rates and equilibrium constants of the hydration and dimerization of formaldehyde were obtained by several conventional and modified ¹³C and ¹H NMR methods (Table 2). A broad temperature and pH range were covered. The

present work, together with our previous work which described the proton exchange of the monomer with water, completes the comprehensive picture of all the equilibrium constants and the kinetic rate constants of formaldehyde in aqueous solutions—from the hydration of the molecular formaldehyde to give the monomer, the dimerization of the latter, and finely the exchange between the hydroxyl protons of the monomer and water.

AUTHOR INFORMATION

Corresponding Author

*E-mail: navon@post.tau.ac.il. Tel: +972(3)6408156.

Notes

The authors declare no competing financial interest.

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Table 2. Summary of the Kinetics Parameters That Were Measured for Aqueous Formaldehyde Solutions ($T = 293 \text{ K}$, pH = 7.4, in D_2O and H_2O) in This Work and in Earlier Publication (*295 K, **298 K)

	$\text{CH}_2\text{O} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_2(\text{OH})_2$		$2\text{CH}_2(\text{OH})_2 \rightleftharpoons \text{HOCH}_2\text{OCH}_2\text{OH} + \text{H}_2\text{O}$	
	value	ref	value	ref
K_{eq}	2.10×10^3	this work	6.54 ± 0.65	**this work (in H_2O)
	2.33×10^3	11,16	6.7	**4,6 (in H_2O)
	2.22×10^3	**7–9,11,16	4.5	**32 (in H_2O)
	2.19×10^3	9	5.7	**33 (in H_2O)
	2.22×10^3	*15		
	1.59×10^3	14		
ΔH_0 (kJ/mol)	−39.0	this work	1.2	this work
	−38.9	12	<5	6
	−35.2 ± 2.1	9		
rate constants (s^{-1})	4.0	**this work (pH = 4, in D_2O)	1.4×10^{-3} ($\text{M}^{-1} \text{s}^{-1}$)	
	9.8	**15 (pH = 4, in H_2O)		
reverse rate constants (s^{-1})	1.7×10^{-3}	**this work (pH = 4, in D_2O)	6×10^{-3}	**this work (pH = 7.4, in D_2O)
	5.1×10^{-3}	**15 (pH = 4, in H_2O)	1.741×10^{-3}	34 (pH = 6.89, in H_2O)
	4.4×10^{-3}	*16 (pH = 4, in H_2O)		
	4.2×10^{-3}	**17 (pH = 4, in H_2O)		

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