# Ketonization equilibria of phenol in aqueous solution<sup>1</sup>

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Abstract: The two keto tautomers of phenol (1), cyclohexa-2,4-dienone (2) and cyclohexa-2,5-dienone (3), were generated by flash photolysis of appropriate precursors in aqueous solution, and the pH-rate profiles of their enolization reactions,  $2 \rightarrow 1$  and  $3 \rightarrow 1$ , were measured. The rates of the reverse reactions,  $1 \rightarrow 2$  and  $1 \rightarrow 3$ , were determined from the rates of acid-catalyzed hydron exchange at the *ortho-* and *para*-positions of 1; the magnitude of the kinetic isotope effect was assessed by comparing the rates of hydrogenation of phenol-2*t* and -2*d*. The ratios of the enolization and ketonization rate constants provide the equilibrium constants of enolization,  $pK_E(2, aq, 25^{\circ}C) = -12.73 \pm 0.12$  and  $pK_E(3, aq, 25^{\circ}C) = -10.98 \pm 0.15$ . Combination with the acidity constant of phenol also defines the acidity constants of 2 and 3 through a thermodynamic cycle. These ketones are remarkably strong carbon acids:  $pK_a(2) = -2.89 \pm 0.12$  and  $pK_a(3) = -1.14 \pm 0.15$ . They disappear by proton transfer to the solvent with lifetimes,  $\tau(2) = 260 \,\mu s$  and  $\tau(3) = 13$  ms, that are insensitive to pH in the range from 3-10.

Key words: proton transfer, tautomers, flash photolysis, kinetic isotope effect, pH-rate profiles.

**Résumé** : Opérant en solution aqueuse, on a généré les deux tautomères cétoniques du phénol (1), la cyclohexa-2,4diénone (2) et la cyclohexa-2,5-diénone (3), par photolyse éclair de précurseurs appropriés et on a mesuré les profils pH de la vitesse pour leurs réactions d'énolisation,  $2 \rightarrow 1$  et  $3 \rightarrow 1$ . On a déterminé les vitesses des réactions inverses  $1 \rightarrow 2$  et  $1 \rightarrow 3$  à partir des vitesses d'échange d'hydron acidocatalysées dans les positions *ortho*- et *para*- de 1; on a évalué l'amplitude de l'effet isotopique cinétique en comparant les vitesses d'hydrogénation du phénol-2*t* et -2*d*. Les rapports des constantes de vitesse d'énolisation et de cétonisation permettent d'arriver aux constantes d'équilibre d'énolisation, p $K_E(2, aq, 25^{\circ}C) = -12,73 \pm 0,12$  et  $pK_E(3, aq, 25^{\circ}C) = -10,98 \pm 0,15$ . Une combinaison avec la constante d'acidité du phénol permet de définir aussi les constantes d'acidité de 2 et de 3 à travers un cycle thermodynamique. Ces cétones sont des acides carbonés relativement forts:  $pK_a(2) = -2,89 \pm 0,12$  et  $pK_a(3) = -1,14 \pm 0,15$ . Elles disparaissent par transfert de proton vers le solvant avec des temps de vie,  $\tau(2) = 260 \,\mu s$  et  $\tau(3) = 13 \,\mu s$ qui sont insensibles au pH entre 3 et 10.

Mots clés : transfert de proton, tautomères, photolyse éclair, effet isotopique cinétique, profils pH-vitesse.

[Traduit par la Rédaction]

# Introduction

Twenty years ago, we reported on the observation of acetophenone enol by flash photolysis and determined the acidity constant of the enol from the pH–rate profile of its ketonization in aqueous solution (1). That work was a sideline of studies aimed primarily at the characterization of diradical intermediates in Norrish Type 2 reactions, and would not have been pursued, had Prof. A.J. Kresge not visited Basel and convinced us that the photochemical approach to study enol kinetics should be further exploited. Thus began a growing friendship and continued collaboration with the un-

This paper is dedicated to Jerry Kresge in recognition of his many achievements in chemistry.

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<sup>1</sup>Tautomerization of phenols, part 2; see ref. 3 for part 1. <sup>2</sup>Author to whom correspondence may be addressed. Telephone: +41 61 267 38 42. Fax: +41 61 267 38 55. e-mail: wirz2@ubaclu.unibas.ch beatable research team of Jerry Kresge and his wife, Yvonne Chiang. On the scientific side, we were rewarded by participating in the kinetic and thermodynamic characterization of the enolization equilibria of a representative selection of carbonyl compounds over the last two decades (2).

The protomeric equilibria of thermodynamically stable enols have received less attention. Phenol (1) is much more stable than its keto tautomers cyclohexa-2,4-dienone (2) and cyclohexa-2,5-dienone (3), because proton transfer from oxygen to carbon disrupts  $\pi$ -conjugation of the phenyl ring. Nevertheless, keto tautomers of phenols are frequently invoked as reactive intermediates, e.g., in the Photo-Fries rearrangement, the Kolbe-Schmitt and Reimer-Tiemann reactions, in electrophilic substitutions of phenols, and in the oxidative metabolism of aromatic compounds ("NIH-shift"). In preliminary work (3), we generated cyclohexa-2,4dienone (2) by flash photolysis and observed the kinetics of its enolization,  $2 \rightarrow 1$ , in acidic and neutral aqueous solutions. The rate constant of ketonization,  $k^{K}(1 \rightarrow \hat{2})$ , was estimated from the rate of deuteration of 1 in 1 N D<sub>2</sub>SO<sub>4</sub> at 80°C. Combination with the rate constant of enolization,  $k^{\rm E}(2 \rightarrow 1)$ , provided a preliminary estimate of the equilibrium constant of enolization of **2** in aqueous solution,  $K_E \equiv [1]/[2] = k^E(2 \rightarrow 1)/k^K(1 \rightarrow 2) \approx 10^{(13 \pm 1)}$ . We now report the

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Scheme 1.



complete pH-rate profile of the enolization reaction  $2 \rightarrow 1$ in aqueous solution and an accurate value for  $K_{\rm E}$ . A brief study of the other keto tautomer of 1, cyclohexa-2,5-dienone (3), is included. The photoreactions that were used to generate dienones 2 and 3 are shown in Scheme 1.

# Results

# Continuous irradiation of compounds 4–6

Direct irradiation of bicyclo[2.2.2]oct-2-ene-5,7-dione (4) eliminates ketene to yield 2 as a primary product that tautomerizes to phenol (3). Oxadi- $\pi$ -methane rearrangement is the predominant reaction initiated by triplet sensitization of 4 (4). Irradiation of tricyclo[6.2.1.0<sup>2,7</sup>]undeca-5,9-dien-4-one (5) or tricyclo[6.2.1.0<sup>2,7</sup>]undeca-4,9-dien-3-one (6) also gave phenol as a major photoproduct that was identified by GC–MS analysis. The flash photolysis experiments described below provided direct evidence that phenol is formed via the primary photoproducts 2 and 3 after light-induced cycloelimination of cyclopentadiene from 5 and 6, respectively, as indicated in Scheme 1.

# Flash photolysis; rates of enolization of the keto tautomers 2 and 3

Aqueous solutions of compounds 4-6 were flashed with 25 ns pulses from an excimer laser operated on XeCl (200 mJ per pulse, 308 nm), or 20 µs pulses from a conventional electric discharge flashlamp of up to 1000 J electrical energy. The cycloadducts 4 and 5, presumed to be photochemical precursors of 2, both gave rise to weak transient absorption in the range of 280-330 nm. The decays of these transients obeyed first-order kinetics with rate constants depending on pH and buffer concentrations. Degassing had no influence on the yield or lifetime of the transient intermediates. Ketones 4 and 5 are sensitive to base, but decomposition was sufficiently slow to permit measurements in freshly prepared, weakly basic solutions. The decay rates of the 300 nm transients produced from 4 and 5 were equal, within the limits of error, in neutral water ( $k_{obs} = 3800 \pm 300 \text{ s}^{-1}$ ) and faster, but again equal, in 2.0 mM aqueous KOH (7600  $\pm$  800 s<sup>-1</sup>).

Because 4 gave somewhat stronger transient signals and was available in larger quantity, this precursor was used to collect a more extensive set of data at various pH ( $25^{\circ}$ C, ionic strength I = 0.1 M, Table 1). The resulting pH–rate

**Fig. 1.** pH–rate profile for the enolization of 2,4-cyclohexadienone (**2**) in aqueous solution at 25.0°C and I = 0.10 M.



profile of the enolization reaction  $2 \rightarrow 1$  is shown in Fig. 1. As is well known from many studies of ketone enolization (2), the rate of enolization is accelerated by acid and by base, but, unlike the behavior of simple ketones, the pH-independent contribution dominates the overall reaction over a large range,  $3 \le pH \le 10$ . The solid line corresponds to function [1], which was fitted to the observed rates of enolization by nonlinear least-squares adjustment of the parameters  $k_{H^+}^E$  and  $k_{OH^-}^E$  the rate coefficients for acid and base catalysis, and  $k_0^E$  for the reaction catalyzed by the solvent (Table 2). The dissociation constant of water at ionic strength I = 0.1 M was taken as  $K_w = 1.59 \times 10^{-14}$  M<sup>2</sup> (5). Weighting of the data was not required, because the relative errors of the observed rate constants, and hence, standard errors of log ( $k_{obs}$ ) values, were approximately constant.

[1] 
$$\log (k_{obs}^{E}/s^{-1}) = \log \{(k_{0}^{E} + k_{H^{+}}^{E}[H^{+}] + k_{OH^{-}}^{E}K_{w}/[H^{+}])/s^{-1}\}$$

Acetate and tris(hydroxymethyl)methyl amine (Tris) buffers were used to determine some rate constants at pH values around 5 and 8. The decay rates increased linearly with buffer concentration, and the intercepts obtained by least-squares fitting of these individual plots are given in Table 1. From the slopes of the buffer dilution plots only general base catalysis is detectable,  $k_{Ac} = (9.5 \pm 0.4) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{\text{Tris}} = (1.8 \pm 0.2) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ . Solvent isotope effects (Table 2) were found to be in the normal direction ( $k_{\text{H}} > k_{\text{D}}$ ) for the decay rate constants  $k_0^{\text{E}}$  of cyclohexa-2,4-dienone and of its 6,6-dideuterated derivative **2**- $d_2$ , but strongly inverse on the coefficient  $k_{\text{H}^+}^{\text{E}}$  of the acid-catalyzed reaction.

Flash photolysis of **6** gave very weak transient absorption around 250 nm, which is the wavelength expected for the absorption of 2,5-cyclohexadienone (**3**) (**6**). Eight traces were averaged for each measurement to improve the signalto-noise ratio. Due to the instability of **6** to base, experiments were limited to acidic and neutral solution. The decay rates of **3** were more than an order of magnitude slower than those of **2** (Table 1). The rate coefficients  $k_0^E$  and  $k_{H^+}^E$  for **3** were determined by nonlinear least-squares fitting of eq. [1] (omitting the last term for base catalysis), and are also given in Table 2.

Table 1.	Rates c	of enolization	of 2 and 3	3 in aqueous	solution at	$25.0 \pm$	0.1°C.
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Compound	Acid/base	Buffer ratio	Conc./M	$\log ([H^+]/M)$	$k_{\rm obs}^{\rm E}/(10^3 \ {\rm s}^{-1})$	No. of expts.
2	HClO <sub>4</sub>		0.100	1.00	73.6 ± 1.9	а
2	HCl		0.100	1.00	$60.8 \pm 1.5$	10
2	HC1		0.050	1.30	$30.6 \pm 0.7$	10
2	HC1		0.032	1.50	$18.5 \pm 0.3$	10
2	HC1		0.010	2.00	$7.65 \pm 0.08$	10
2	HC1		0.005	2.30	$5.80\pm0.08$	10
2	HC1		0.0025	2.60	$4.80 \pm 0.06$	10
2	HC1		0.001	3.00	$4.00 \pm 0.06$	10
2	HAc/NaAc	5.00	0.02-0.10	$3.87^{b}$	$3.82 \pm 0.15^{e}$	18
2	HAc/NaAc	1.584	0.01-0.09	$4.37^{b}$	$3.90 \pm 0.06^{e}$	23
2	HAc/NaAc	0.500	0.01 - 0.09	$4.87^{b}$	$3.98 \pm 0.07^{e}$	24
2	HAc/NaAc	0.159	0.01 - 0.09	$5.36^{b}$	$3.99 \pm 0.10^{e}$	18
2	HAc/NaAc	0.050	0.01 - 0.09	$5.87^{b}$	$3.95 \pm 0.03^{e}$	23
2	HCl/Tris	1.12	0.01 - 0.10	$8.07^{c}$	$3.80 \pm 0.15^{e}$	25
2	KOH		0.002	$11.10^{d}$	$7.59 \pm 0.17$	10
2	KOH		0.004	$11.40^{d}$	$12.0 \pm 0.6$	10
2	_			≈6	$3.83 \pm 0.04$	5
2		(D <sub>2</sub> O)	_	≈6	$2.67 \pm 0.02$	6
$2-d_2$			_	≈6	$0.58 \pm 0.01$	5
$2-d_2$	_	(D <sub>2</sub> O)		≈6	$0.40 \pm 0.01$	9
3	HC1		0.020	1.70	$0.62 \pm 0.07$	8
3	HCl		0.005	2.30	$0.224 \pm 0.010$	8
3				≈6	$0.079 \pm 0.004$	8

<sup>a</sup>Value calculated from the regression line of an Arrhenius plot (data in Table 4).

<sup>b</sup>Calculated using the thermodynamic acidity constant  $pK_a^{\circ} = 4.76$  (38), and activity coefficients recommended by Bates (5) to give the concentration quotient  $pK_{a,c}(I = 0.1 \text{ M}) = 4.57$ .

<sup>c</sup>Calculated from  $pK_{a,c}(I = 0.1 \text{ M}) = 8.12$  (39).

<sup>*d*</sup>Calculated from the nominal base concentration with  $K_w(I = 0.1 \text{ M}) \equiv [\text{H}^+][\text{HO}^-] = 1.59 \times 10^{-14}$  (ref. 5).

<sup>c</sup>Intercept of buffer dilution plot. From the slopes of the buffer dilution plots only general base catalysis is detectable,  $k_{Ac} = (9.5 \pm 0.4)10^3 \text{ M}^{-1} \text{ s}^{-1}$ ,  $k_{Tris} = (1.8 \pm 0.2)10^5 \text{ M}^{-1} \text{ s}^{-1}$ .

**Table 2.** Rate constants of enolization and ketonization at  $25 \pm 0.1$  °C, I = 0.10 M.

Reaction	Rate coefficient	$k/s^{-1}$	$k(H_2O)/k(D_2O)$
2  ightarrow 1	$k_0^{\mathrm{E}}$	$(3.8 \pm 0.1)10^3$	$1.43 \pm 0.03^{a}$
$2\text{-}d_2 \rightarrow 1$	$k_0^{\mathrm{E}}$	$(5.8 \pm 0.1)10^2$	$1.45 \pm 0.05^{a}$
2  ightarrow 1	$k^{ m E}_{ m H^{+}}$	$(5.4 \pm 0.3)10^5 \text{ M}^{-1}$	$0.50 \pm 0.05^{b}$
2  ightarrow 1	$k_{OH}^{E}$ -	$(2.0 \pm 0.3)10^{6} \text{ M}^{-1}$	
3  ightarrow 1	$k_0^{\mathrm{E}}$	$80 \pm 8$	
3  ightarrow 1	$k^{ m E}_{ m H^{+}}$	$(2.8\pm0.9)10^4M^{-1}$	
1  ightarrow 2	$k_{ m H^{+}}^{ m K}$	$(1.01\pm0.28)10^{-7}M^{-1}$	
1  ightarrow 3	$k_{ m H^{+}}^{ m K}$	$(2.96 \pm 0.27)10^{-7} \text{ M}^{-1}$	

<sup>*a*</sup>Average from  $\geq$ 5 measurements each in H<sub>2</sub>O and D<sub>2</sub>O (no buffer); 25°C, I = 0.1 M.

<sup>b</sup>Average from 9 measurements each of HCl/H<sub>2</sub>O and DCl/D<sub>2</sub>O at matching nominal acid concentrations in the range of 0.02–0.1 N; 23°C, I = 0.1 M.

# Isotope exchange kinetics; rates of ketonization

At room temperature the exchange of the aromatic hydrogen atoms of 1 is slow. Solutions of phenol-2*d* and phenol-2*t* in 0.1 N HClO<sub>4</sub> were kept at 80.0  $\pm$  0.5°C, and the loss of their deuterium or tritium label to the solvent was monitored by 400 MHz <sup>2</sup>H NMR and by scintillation counting, respectively (Table 3). Details of the procedures are given in the experimental section. The analysis of these data to determine the isotope effect and to extrapolate to the rate constant  $k_{H^+}^K$  for the acid-catalyzed ketonization reaction  $1 \rightarrow 2$  is now described.

Acid-catalyzed exchange of aromatic hydrogen proceeds by a two-step reaction mechanism with a C-protonated intermediate (7), Scheme 2. Solutions of the substrate 2-L in H<sub>2</sub>O are assumed to be dilute, such that that the second step,  $2\text{-L}^+ \rightarrow 1 + \text{L}^+$ , is practically irreversible. Following the notation

Reaction	Symbol	$k_{ m obs}/{ m s}^{-1}$	Acid	Acid conc./M	<i>T</i> /K
$1-2t \rightarrow 1$	$k^{-\mathrm{T}}$	$(5.63 \pm 0.03)10^{-7}$	HClO <sub>4</sub>	0.10	353.2
$1 - 2d \rightarrow 1$	$k^{-D}$	$(9.04 \pm 0.55)10^{-7}$	$HClO_4$	0.10	353.2
$1 \rightarrow 1\text{-}2d$	$k^{D_2}$	$(3.22 \pm 0.03)10^{-5}$	DCl	1.00	353.2
$1 \rightarrow 1-2d$	$k^{D_2}$	$(1.11 \pm 0.01)10^{-5}$	DCl	1.00	343.2
$1 \rightarrow 1\text{-}2d$	$k^{D_2}$	$(3.48 \pm 0.03)10^{-6}$	DCl	1.00	333.2
$1 \rightarrow 1$ -4d	$k^{D_4}$	$(5.39 \pm 0.05)10^{-5}$	DCl	1.00	353.2
$1 \rightarrow 1$ -4d	$k^{D_4}$	$(1.93 \pm 0.02)10^{-5}$	DCl	1.00	343.2
$1 \rightarrow 1$ -4d	$k^{D_4}$	$(7.02 \pm 0.07)10^{-6}$	DCl	1.00	333.2

Table 3. Isotopic exchange rates of phenol.

Scheme 2.



used by Kresge and Chiang (7), the rate coefficients shown in Scheme 2 carry two superscripts to facilitate the bookkeeping of isotope effects. The *right-hand superscript* designates the isotope involved in the hydron transfer reaction between C2 and the solvent (*primary isotope effect*). The *left-hand superscript* designates the spectator isotope remaining on C2 during this reaction (*secondary isotope effect*).

Dissociation equilibria of oxygen acids are, in general, established more rapidly than those of carbon acids (8). Accordingly, we assume that OH dissociation of  $2-L^+$  (the vertical reaction shown in Scheme 2) is faster than hydron dissociation from carbon to form 1 or 1-L (horizontal reactions). This assumption conforms to the accepted mechanism for hydronium-ion-catalyzed enolization of simple carbonyl compounds, which consists of rapid and reversible hydronation of the substrate on oxygen followed by ratedetermining removal of a carbon-bound hydron by a molecule of water (9). Application to the present case might be questioned on the grounds that CH dissociation of 2-L<sup>+</sup> is thermodynamically favored over OH dissociation by 2.3RT  $\times$  pK<sub>E</sub> which, as we shall see below, amounts to 72.6  $\pm$  0.7 kJ mol<sup>-1</sup>. However, we have recently shown that even larger thermodynamic bias is insufficient to overcome the kinetic preference for OH dissociation (10). Moreover, the inverse solvent isotope effect observed on the acid-catalyzed enolization of 2 ( $k_{\rm H}/k_{\rm D}$  = 0.5, Table 2, row 3) is strong evidence for pre-equilibrium protonation on oxygen.

If OH dissociation of  $2-L^+$  is faster than CH dissociation, then carbon protonation is the rate-determining step in acidcatalyzed ketonization of  $1 \rightarrow 2$ , and the rate constant of this process is given by eq. [2]. The statistical factor of 2 arises because the ketonization rate constant  $k_{\rm H^+}^{\rm K}$  refers to protonation at either of the *ortho* positions C2 or C6, whereas  ${}^{\rm H}k_{\rm H}^{\rm H}$  refers to protonation at C2 only.

[2] 
$$k_{\text{II}^+}^{\text{K}} = 2^{\text{H}} k_1^{\text{H}}$$

Carbon protonation does, however, not fully determine the rate of isotopic exchange, because only a fraction of the protonated intermediate **2**-L<sup>+</sup> eventually loses the label by dissociating to **1** + L<sup>+</sup>. The rates of the forward reaction (loss of label) and backward reaction (retention of label) are of the same order of magnitude,  ${}^{\rm H}k_2^{\rm L} \approx {}^{\rm L}k_2^{\rm H}$ . Since protonation of **1**-L is much slower than the subsequent steps,  ${}^{\rm L}k_1^{\rm H}[{\rm H}^+] << {}^{\rm H}k_2^{\rm L} + {}^{\rm L}k_2^{\rm H}$ , the steady-state (Bodenstein) approximation is applicable to **2**-L<sup>+</sup>, and the observed rate constant for acid-catalyzed loss of label L may be expressed as the product of the rate constant of C-protonation of **1**-L, the proton concentration, and the partitioning ratio of intermediate **2**-L<sup>+</sup>, eq. [3].

[3] 
$$k_{obs}^{-L} = {}^{L}k_{1}^{H}[H^{+}] \frac{{}^{H}k_{2}^{L}}{{}^{H}k_{2}^{L} + {}^{L}k_{2}^{H}}$$

The ratio of the experimental rate constants of detritiation and dedeuteration in aqueous acid of a given concentration is then given by eq. [4].

$$\begin{bmatrix} 4 \end{bmatrix} \qquad \frac{k_{obs}^{-T}}{k_{obs}^{-D}} = \frac{{}^{T}k_{l}^{H}}{{}^{D}k_{l}^{H}} \frac{{}^{H}k_{2}^{T}}{{}^{H}k_{2}^{T} + {}^{T}k_{2}^{H}} \frac{{}^{H}k_{2}^{D} + {}^{D}k_{2}^{H}}{{}^{H}k_{2}^{D}} \\ = \frac{{}^{T}k_{l}^{H}}{{}^{D}k_{l}^{H}} \frac{1 + {}^{D}k_{2}^{H} {}^{H}k_{2}^{D}}{1 + {}^{T}k_{2}^{H} {}^{H}k_{2}^{T}}$$

Our goal is to calculate the rate constant for acidcatalyzed ketonization of 1,  $k_{\text{H}^+}^{\text{K}}$ , from the observed rates of dedeuteration and detritiation,  $k_{\text{obs}}^{-\text{D}}$  and  $k_{\text{obs}}^{-\text{T}}$ . Extrapolation from observed isotope exchange rates  $k_{\text{T}}$  and  $k_{\text{D}}$  to  $k_{\text{H}}$  is commonly done on the basis of the Swain relation (eq. [5]) (11). However, eq. [4] contains contributions from both primary and secondary kinetic isotope effects. In a detailed study of acid-catalyzed hydron exchange in 1,3,5trimethoxybenzene, Kresge and Chiang (7) have established that the Swain relation gives reliable results when it is applied individually to primary and secondary isotope effects.

$$[5] \qquad (k_{\rm H}/k_{\rm D})^{1.442} = k_{\rm H}/k_{\rm T}$$

The first factor on the right-hand side of eq. [4],  ${}^{T}k_{1}^{H}/{}^{D}k_{1}^{H}$ , is a purely secondary isotope effect: hybridization of carbon atom 2 changes from  $sp^{2}$  to  $sp^{3}$  upon protonation (step 1 in Scheme 2), which influences bonding to the isoto-

**Table 4.** Temperature dependence of the rate constants of enolization of **2** in 0.1 N HClO<sub>4</sub>.

$\log (k_{\rm obs}^{\rm E}/{\rm s}^{-1})$	t/°C
4.85 ± 0.02	$25.0 \pm 0.1$
$5.05 \pm 0.02$	$37.0\pm0.1$
$5.21 \pm 0.02$	$47.0\pm0.1$
$5.37 \pm 0.02$	$62.5\pm0.2$
$5.49 \pm 0.02$	$71.0\pm0.2$
$5.59 \pm 0.02$	$79.0\pm0.3$

pic label L. Such secondary isotope effects are known to be inverse, and to have a relatively constant value of about 12% per deuterium atom, i.e.,  ${}^{\rm H}k_1^{\rm H}/{}^{\rm D}k_1^{\rm H} = 0.88 \pm 0.04$  (7, 12). The factor  ${}^{\rm T}k_1^{\rm H}/{}^{\rm D}k_1^{\rm H}$  can then be estimated using the Swain relation

$$\begin{bmatrix} 6 \end{bmatrix} \qquad \frac{{}^{\mathrm{T}}k_{\mathrm{I}}^{\mathrm{H}}}{{}^{\mathrm{D}}k_{\mathrm{I}}^{\mathrm{H}}} = \frac{{}^{\mathrm{T}}k_{\mathrm{I}}^{\mathrm{H}}}{{}^{\mathrm{H}}k_{\mathrm{I}}^{\mathrm{H}}} \frac{{}^{\mathrm{H}}k_{\mathrm{I}}^{\mathrm{H}}}{{}^{\mathrm{D}}k_{\mathrm{I}}^{\mathrm{H}}} = \left(\frac{{}^{\mathrm{D}}k_{\mathrm{I}}^{\mathrm{H}}}{{}^{\mathrm{H}}k_{\mathrm{I}}^{\mathrm{H}}}\right)^{(1.442-1)}$$
$$= (0.88 \pm 0.04)^{-0.442} = 1.06 \pm 0.02$$

The fractions appearing in the second term of eq. [4] are a product of primary and secondary isotope effects. In the numerator we have  ${}^{\mathrm{D}}k_{2}^{\mathrm{H}}/{}^{\mathrm{H}}k_{2}^{\mathrm{D}} \equiv x$ . By application of the Swain relation we obtain  ${}^{\mathrm{T}}k_{2}^{\mathrm{H}}/{}^{\mathrm{H}}k_{2}^{\mathrm{T}} = x^{1.442}$ , and eq. [4] is replaced by eq. [7].

[7] 
$$\frac{k_{\rm obs}^{-\rm T}}{k_{\rm obs}^{-\rm D}} = (1.06 \pm 0.02) \frac{1+x}{1+x^{1.442}}$$

The experimental rate constants for detritiation and dedeuteration of 1-2*l* at 80°C in 0.1 N HClO<sub>4</sub> are given in Table 3. Equation [7] can be solved for *x* by iterative approximation to give  $x = 4.1 \pm 0.5$ . Insertion of *x* into eq. [3] (L = D) gives  ${}^{D}k_{1}^{H} = k_{obs}^{-D}(1 + x)/[H^{+}]$  and using  ${}^{H}k_{1}^{H} = {}^{D}k_{1}^{H}(0.88 \pm 0.04)$ , we can replace eq. [2] by eq. [8], in which the desired rate constant of ketonization is expressed fully in terms of experimentally determined quantities

[8] 
$$k_{\text{H}^+}^{\text{K}} = 2k_{\text{obs}}^{\text{-D}}(x+1)(0.88 \pm 0.04)/[\text{H}^+]$$

We obtain  $k_{\text{H}^+}^{\text{K}}(353 \text{ K}) = (8.1 \pm 1.3)10^{-5} \text{ M}^{-1} \text{ s}^{-1}$  for the rate constant of acid-catalyzed ketonization,  $\mathbf{1} \rightarrow \mathbf{2}$ . The error limits were determined by propagation of the standard errors of the experimental data and of the assumed range for the secondary isotope effect, taking account of the high covariance between *x* and  $k_{obs}^{-D}$  through eq. [7].

# Temperature dependence of the kinetic data

Flash photolysis of **4** in 0.1 N aqueous HClO<sub>4</sub> was done at various temperatures from 25 to 80°C (Table 4). The rate constants accurately obeyed the Arrhenius equation,  $k = A \exp(-E_a/RT)$ , and linear regression of log  $(k_{obs}^{\rm E}/{\rm s}^{-1})$  vs. 1/*T* gave the Arrhenius parameters log  $(A/{\rm s}^{-1}) = 9.58 \pm 0.11$  and  $E_a = 27.0 \pm 0.7$  kJ mol<sup>-1</sup>. The rate coefficient for the acid-catalyzed enolization of **2** at 80°C is calculated as  $k_{\rm H^+}^{\rm E} = k_{\rm obs}^{\rm C}/[{\rm H}^+] = (3.94 \pm 0.06)10^6 {\rm M}^{-1} {\rm s}^{-1}$  from this regression. Combination with the rate constant of ketonization provides the equilibrium constant of enolization of **2** at this temperature,  $K_{\rm E}(353 {\rm K}) = k_{\rm H^+}^{\rm E}/k_{\rm H^+}^{\rm K} = (3.94 \pm 0.06)10^6/(8.1 \pm 1.3)10^{-5} = (4.9 \pm 0.8)10^{10}$ ,  $pK_{\rm E}(353 {\rm K}) = -10.69 \pm 0.07$ .

The temperature dependence of the isotopic exchange rates was determined by monitoring the deuteration of phenol in 1 N DCl/D<sub>2</sub>O at 60.0, 70.0, and  $80.0 \pm 0.5^{\circ}C$  by 300 MHz <sup>1</sup>H NMR. This was easier than repeating the dedeuteration of phenol-2d at several temperatures, and at the same time, provided exchange rates at C4 of phenol. Secondary isotope effects from isotopic substitution at positions remote from the site of protonation (C4 and C6 for deuteration at C2) have been demonstrated to be negligible (7). The resulting exchange rate constants  $k^{D_2}$  and  $k^{D_4}$  are given in Table 3. These values are two to three times higher than those obtained in preliminary work by deuteration of phenol in 1 N  $D_2SO_4$  at the same temperature (3). The discrepancy may in part be attributed to incomplete dissociation of  $D_2SO_4$  in 1 N solution. Linear least-squares regression of log  $(k/s^{-1})$  vs. 1/T gave the Arrhenius parameters log  $(A/s^{-1}) = 11.61 \pm 0.13$  and  $E_a = 109 \pm 1 \text{ kJ mol}^{-1}$  for ortho-deuteration, and log  $(A/s^{-1}) = 10.47 \pm 0.32$  and  $E_a =$  $100 \pm 2 \text{ kJ mol}^{-1}$  for *para*-deuteration. The rate constants calculated for 25°C from these regressions are  $k^{D_2} = (3.47 \pm$  $(0.16)10^{-8} \text{ M}^{-1} \text{ s}^{-1}$  and  $k^{D_4} = (1.02 \pm 0.12)10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ .

The ratio between the rate constant of ketonization  $1 \rightarrow 2$ , eq. [8], and the observed rate constant of *ortho*-deuteration amounts to  $k_{\rm H^+}^{\rm K}/k^{\rm D_2} = (8.1 \pm 1.3)10^{-5}/(3.22 \pm 0.03)10^{-5} =$  $2.5 \pm 0.4$  at 80°C. This factor is a compound of primary and secondary isotope effects of the substrate as well as ionic strength and isotope effects of the solvent. The temperature dependence of this factor is estimated from the formula  $k_{\rm H^+}^{\rm K}/k^{\rm D_2} = \exp(-\Delta E_0/RT)$ , assuming that it may be attributed to a single dominant zero-point vibrational energy difference  $\Delta E_0$ . That is an overly crude assumption, but the correction of +0.4 for extrapolation to room temperature is small; the ratio resulting for 25°C is  $k_{\rm H^+}^{\rm K}/k^{\rm D_2} = 2.9 \pm 0.8$  (the error margin was increased by 0.4, the amount of the above correction), and the rate constant for acid-catalyzed ketonization  $1 \rightarrow 2$  at 25°C is then calculated as  $k_{\rm H^+}^{\rm K} = (2.9 \pm 0.8)(3.47 \pm 0.16)10^{-8} = (1.01 \pm 0.28)10^{-7}$  M<sup>-1</sup> s<sup>-1</sup>. The same factor was used to calculate the acid-catalyzed rate constant of ketonization  $1 \rightarrow 3$ ,  $k_{\rm H^+}^{\rm K} = (2.9 \pm 0.8)k^{\rm D_4} = (2.96 \pm 0.27)10^{-7}$  M<sup>-1</sup> s<sup>-1</sup>.

# Discussion

#### Evidence for keto tautomers of phenol

In a review article on the theory of unsaturated and aromatic compounds, published in 1899, Thiele (13) speculated that the propensity of phenol (1) and its anion to undergo substitution and oxidation reactions might be attributed to rapid equilibration of 1 with the transient keto forms 2 and 3. At that time, the concepts of protomerism, as in Scheme 3, and mesomerism, Scheme 4, were not clearly distinguished. From the present viewpoint, it is clear that the ketonization of phenol, Scheme 3, is much too slow to explain the reactivity of phenol towards, e.g., bromine, but mesomeric charge delocalization, as shown in Scheme 4, is still used to explain the enhanced reactivity of phenolate at the *ortho* and *para* positions.

Only 2 years later, Lapworth (14) put forth the hypothesis that bromocyclohexadienones are the primary products formed in the aqueous bromination of phenol to rationalize the exclusive bromination of 1 at the *o*- and *p*-positions.

Scheme 3.



These bromocyclohexadienone intermediates were detected 15 years ago by Tee et al. (15) using the stopped-flow technique. Cyclohexadienones were also proposed (16) and later characterized (17, 18) as intermediates in the Photo–Fries rearrangement of aryl esters. 4-Benzylcyclohexa-2,5-dienone was identified by CIDNP as a transient intermediate in the photorearrangement of benzyl phenyl ether; it had a half-life of about 4 s in cyclohexane (19).

4*H*-Keto tautomers of heavily substituted phenols have been isolated in crystalline form (20). The tautomers of parent phenol, cyclohexa-2,4-dienone (2), and cyclohexa-2,5dienone (3), were generated by flash vacuum pyrolysis of suitable Diels–Alder adducts, trapped at 77 K, and characterized by their IR and UV spectra (21). Pentaammineosmium complexes of 1-3 have been identified, and it was shown that all three tautomeric complexes are of comparable thermodynamic stability (22).

In the present work, cyclohexadienones 2 and 3 were formed by flash photolysis of suitable precursors (4-6, Scheme 1) in aqueous solution, which allowed their enolization rates to be measured directly. The transient formed by flash photolysis of 4 has previously been identified as cyclohexa-2,4-dienone (2) based on the observed decay kinetics, the position of its absorption (the first  $\pi,\pi^*$  absorption band of stable cyclohexa-2,4-dienones is around 300 nm, log  $\epsilon \approx 3.7$  (6)), the identification of phenol as the final product, and the formation of 1,3,5-hexatrienone upon irradiation of 4 in a glassy matrix (3). The present finding that precursor 5 gives the same transient intermediate (absorption and pH-dependent decay rate) confirms that assignment. Formation of cyclohexa-2,5-dienone (3) from precursor **6** was assumed by analogy, and that is supported by the observed transient kinetics and the identification of phenol as the final product.

# Thermochemistry of cyclohexadienone-phenol tautomerization

Several thermochemical estimates have been reported for the protomeric equilibria of phenol (1) with ketones 2 and 3 (Scheme 3):  $\Delta_{(2 \text{ or } 3)\to 1}G^{\ominus}$  (g, 298 K) = -18.6 kcal mol<sup>-1</sup> was obtained from a bond additivity scheme (23), and  $\Delta_{2\to 1}G^{\ominus}(\text{aq}, 298 \text{ K}) = -13 \pm 3 \text{ kcal mol}^{-1}$  from estimates of the aqueous protonation equilibria for each tautomer to the



common cation (24).  $\Delta_{2\rightarrow 1}H^{\ominus}(g, 298 \text{ K}) = -15.2 \text{ kcal mol}^{-1}$  is obtained using Benson's group increments (25). Tee and Iyengar (15) predicted  $\Delta_{3\rightarrow 1}G^{\ominus}(aq, 298 \text{ K}) = -15 \text{ kcal mol}^{-1}$  based on an earlier estimate of the pK for C-protonated phenol. Shiner et al. (26) generated the cyclohexadienones **2** and **3** by pyrolytic cycloreversion of their formal Diels–Alder adducts with cyclopentadiene, compounds **5** and **6**, and measured their gas phase acidities by the flowing afterglow technique. The derived heats of tautomerization,  $\Delta_{2\rightarrow 1}H^{\ominus} = -6 \pm 3$  and  $\Delta_{3\rightarrow 1}H^{\ominus} = -10 \pm 3 \text{ kcal mol}^{-1}$  are, however, not compatible with present data.

From the present data, the enolization constant of **2** at 25°C is determined as the ratio of the enolization and ketonization rate constants given in Table 2,  $K_{\rm E}(\mathbf{2}, aq, 298 \text{ K}) = k_{\rm H^+}^E/k_{\rm H^+}^K = (5.4 \pm 0.3)10^5/(1.01 \pm 0.28)10^{-7} = (5.4 \pm 1.5)10^{12}$ ,  $pK_{\rm E} = -12.73 \pm 0.12$ . This value, and the acidity constant of phenol,  $pK_{\rm a}^{\rm E}(\mathbf{1}, 298 \text{ K}) = 9.84 \pm 0.02$  (expt. sect.), form two legs of a thermodynamic cycle, from which the C–H acidity constant of ketone **2** can be calculated,  $pK_{\rm a}^{\rm K} = pK_{\rm E} + pK_{\rm a}^{\rm E} =$  $-2.89 \pm 0.12$  (Scheme 5). It turns out that ketone **2** is one of the strongest carbon acids known (27).

The enthalpy of enolization can be calculated by the second-law method from the temperature dependence of the enolization constant, d ln  $K_{\rm E}/dT = \Delta_{\rm E} H^{\ominus}/RT^2$ ,  $\Delta_{\rm E} H^{\ominus} = 2.303R[pK_{\rm E}(T_2 = 353 \text{ K}) - pK_{\rm E}(T_1 = 298 \text{ K})]/(1/T_2 - 1/T_1) = -74.8 \pm 5.1 \text{ kJ mol}^{-1}$ . The standard free energies of enolization are  $\Delta_{\rm E} G^{\ominus}(\text{aq}) = 2.303RT \times pK_{\rm E}(353 \text{ K}) = -72.3 \pm 0.5 \text{ kJ mol}^{-1}$  at 353 K and  $-72.7 \pm 0.7 \text{ kJ mol}^{-1}$  at 298 K. The entropy of enolization,  $\Delta_{\rm E} S^{\ominus}(\text{aq}, 298 \text{ K}) = -7 \pm 16 \text{ J K}^{-1} \text{ mol}^{-1}$ , is very small, too small to be reliably determined from these values. In our preliminary communication (3), we had estimated the temperature dependence of the enolization constant by neglecting the temperature dependence of the enolization constant by neglecting the temperature dependence of the free energy of enolization  $\Delta_{\rm E} G^{\ominus}$ , i.e., by assuming  $\Delta_{\rm E} S^{\ominus} \approx 0$ .

The enolization constant of 2,5-cyclohexadienone **3** is similarly obtained as the ratio of the corresponding acidcatalyzed rate constants of enolization and ketonization (Table 2),  $K_{\rm E}(298 \text{ K}) = k_{\rm H^+}^{\rm E}/k_{\rm H^+}^{\rm K} = (9.5 \pm 3.2)10^{10}$ , p $K_{\rm E} = -10.98 \pm 0.15$  (Scheme 6).

The thermochemical data obtained in this work are summarized in Table 5. Note that the acidity constants  $pK_a^E$  and  $pK_a^K$  reported here are concentration quotients determined at ionic strength I = 0.1 M. The experimental enolization constants are in reasonable, though not perfect, agreement with the results of density functional calculations given in Table 6. The (gas phase) enolization constants predicted by these calculations are  $pK_E(2) = -10.4$  and  $pK_E(3) = -9.8$ .

**Table 5.** Thermochemical data (aq,  $25^{\circ}$ C, I = 0.1 N).

Reaction	$pK_{\rm E}$	pK <sup>K</sup> <sub>a</sub>	$pK_a^E$	$\Delta_{\rm E} H/({\rm kJ~mol^{-1}})$	$\Delta_{\rm E}S/({\rm J~K^{-1}~mol^{-1}})^a$
2  ightarrow 1	$-12.73 \pm 0.12$	$-2.89 \pm 0.12$	$9.84 \pm 0.02$	$-74.8 \pm 5.1$	-2.6
$3 \rightarrow 1$	$-10.85 \pm 0.29$	$-1.01 \pm 0.30$	$9.84~\pm~0.02$	$-61.9 \pm 6.2^{b}$	-1.2

<sup>a</sup>Calculated B3LYP/6-31G\* (g, 298 K), cf. Table 6.

<sup>b</sup>Calculated from  $pK_E$  assuming  $|\Delta_E S(aq)| \le 20 \text{ J K}^{-1} \text{ mol}^{-1}$ .

Table	6.	Results	of	ab	initio	calculations. <sup>a</sup>
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Compound	Method	$-E_0$ /hartree	Enthalpy/hartree <sup>b</sup>	$S^{\ominus}/(J \text{ K}^{-1} \text{ mol}^{-1})$
1	B3LYP/6-31G*	-307.464 865	0.111 231	74.55
2	B3LYP/6-31G*	-307.441 132	0.110 405	77.14
3	B3LYP/6-31G*	-307.442 838	0.110 618	75.76
1	6-31G*	-305.558 063	0.117 496	73.58
2	6-31G*	-305.538 575	0.117 177	75.63
3	6-31G*	-305.541 889	0.117 385	74.65

<sup>a</sup>Gaussian 94.

<sup>b</sup>Thermal correction to enthalpy including zero-point vibrational energy.

Scheme 6.



#### Exchange kinetics and kinetic isotope effects

Isotope exchange rates of phenol in aqueous sodium hydroxyde were already determined in 1936 by Ingold et al. (28). These authors used 2.2 M solutions of phenol and found that the exchange rate reached a maximum when the concentration of NaOH was about half that of phenol. Hydron transfer from phenol as a general oxygen acid to phenolate as a carbon base was identified as the dominant mechanism for exchange under these conditions. In the present work, hydron exchange experiments were done with dilute solutions and under acid catalysis. Note that, from the data given in Tables 2 and 5, base is predicted to reduce the rate of hydron exchange in dilute aqueous solutions. The rate of hydrogen exchange at carbon 2 of phenol in strong base, pH >>  $pK_a^E(1)$ , is given by  $k_0'^K = k_{OH}^E - K_w/K_a^K$ =  $4 \times 10^{-11} \text{ s}^{-1}$  at 25°C. This is more than an order of magnitude less than the rate calculated for the same process in neutral solution,  $k_0^{\text{K}} = k_0^{\text{E}} K_a^{\text{E}} / K_a^{\text{K}} = 7 \times 10^{-10} \text{ s}^{-1}$ , because the reaction of protons with phenolate accelerates ketonization at pH < 12 until proton catalysis saturates at pH  $\approx pK_a^E$  = 9.84.

The method used to assess the magnitude of the kinetic isotope effects and to determine the rate constants of ketonization from the observed rates of hydron exchange of phenol in aqueous acid closely follows previous work of Kresge and Chiang (7) and was described in the results section. Some of the observed kinetic isotope effects deserve mention. The four decay rates determined for 2 and  $2-d_2$  in

 $H_2O$  and  $D_2O$  (Table 2) give two closely similar values for the predominantly primary kinetic isotope effect,  $k(2-h_2)/k(2-d_2) = 6.6 \pm 0.2$ , and for the compound (secondary and medium) solvent isotope effect,  $k(H_2O)/k(D_2O) =$ 1.44  $\pm$  0.03. Both of these values are consistent with the mechanism assigned to the pH-independent enolization of ketone 2: rate-determining hydron transfer from carbon to solvent water. A crude a priori estimate for the solvent isotope effect,  $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) \approx 1.5$ , is obtained by assuming  $K_a^{\text{K}}(\text{H}_2\text{O})/K_a^{\text{K}}(\text{D}_2\text{O}) \approx 1/l^3 = 3$  (l = 0.69 is the fractionation factor for the hydronium ion (29)) and application of the Brønsted equation  $k(H_2O)/k(D_2O) = [K_a^K(H_2O)/K_a^K(D_2O)]^{\alpha}$ with  $\alpha \approx 0.35$  (2b). Finally, the inverse isotope effect observed on the acid-catalyzed enolization of 2-L (Table 2, row 3), shows that OH fission of  $2-L^+$  (vertical reaction in Scheme 2) is faster than CH or CL fission, in spite of a strong thermodynamic bias for the latter.

The range covered by experimental data on keto-enol protomeric equilibria is nearly doubled by the present measurements of phenol ketonization: enolization constants now extend over a range of about 30 orders of magnitude, and the corresponding rate constants vary by about 20 orders of magnitude. The free-energy relationship between these quantities is clearly curved, and the curvature defines the intrinsic barrier of proton transfer to the  $\beta$ -carbon atom of enols  $\Delta G_0^{\ddagger}$  = 57 kJ mol<sup>-1</sup> (2*b*). Similar values have been determined previously from curvature in Brønsted plots (30, 31). The pHindependent, spontaneous dissociation of 2 as a carbon acid,  $k_0^{\rm E} = 3.8 \times 10^3 \, {\rm s}^{-1}$ , dominates the pH-rate profile of 2 (Fig. 1) from pH 3 to 10. On the other hand, the contribution of this mechanism to the pH-rate profiles for the enolization of simple ketones such as acetophenone is barely noticeable (31), because carbon protonation of enolates is so highly exergonic that these rates approach the diffusional limit.

# **Experimental**

#### General

All concentrations are nominal values referring to 25°C. No corrections were applied for volume expansion at higher

temperatures. The required, small corrections would affect acid-catalyzed rate constants of enolization and ketonization by the same factor that would cancel in their ratio, the enolization constant.

## Materials

Samples of tricyclo[6.2.1.0<sup>2,7</sup>]undeca-5,9-dien-4-one (**5**) and tricyclo[6.2.1.0<sup>2,7</sup>]undeca-4,9-dien-3-one (**6**) were obtained as a gift from Dr. C. Shiner, University of Colorado, Boulder (23), and samples of 5,7-dioxobicyclo[2.2.2]octane-2,3-dicarboxylic acid from Profs. M. Demuth, MPI Göttingen, and C.A. Grob, University of Basel.

Phenol-2d was synthesized from 2-bromophenol as described by Tashiro et al. (32). <sup>1</sup>H NMR indicated >90% deuteration at the 2-position. The same procedure was used to synthesize phenol-2t: NaOH (500 mg) was dissolved in 1 mL of tritium-enriched water and 520 mg of 2-bromophenolate (2.7 mmol) was added. CuAl catalyst (125 mg, Ventron, Karlsruhe) was added. The solution was stirred vigorously for 30 min. The catalyst was removed by filtration. The solution was acidified with 2 N HCl whereupon phenol precipitated. The aqueous solution was extracted with 10 mL of ether. The organic extract was dried with Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated at room temperature under a stream of  $N_2$ . The residue was sublimed in vacuo (<1 Pa) at room temperature. A sample containing 0.6 mg (6.4 µmol) of phenol-2t had an activity of 1750 Bq on a calibrated scintillation counter which corresponds to a tritium content of 0.25 ppm.

Bicyclo[2.2.2]oct-7-ene-2,5-dione (4) was prepared by oxidative bisdecarboxylation of 5,7-dioxobicyclo[2.2.2]octane-2,3-dicarboxylic acid, samples of which were obtained as gifts from Profs. Grob (33) and Demuth (5). The following, improved method was taken from the thesis of Weitemeyer (34).  $Pb(OAc)_4$  (18 g) was added to a stirred solution of the diacid (4.48 g) in pyridine (60 mL) which was immersed in a water bath at 20°C. The yellow solution slowly turned orange to deep red under evolution of CO<sub>2</sub>. After an hour, the solution was gently warmed to 40°C until the gas evolution ceased after 90 min. CHCl<sub>3</sub> (200 mL) was added and the mixture shaken with 40 mL of cold 20% HCl. The precipitate was removed and washed with CHCl<sub>3</sub>. The combined organic phases were washed four times with 40 mL of 20% HCl until the color was removed, neutralized with NaHCO<sub>3</sub>, and dried. Evaporation of the solvent left a brown-red solid residue which was chromatographed on silica with an 80:20 mixture of hexane and diethyl ether and sublimed at 90°C in vacuo to give 560 mg (20.6%) of 4 as colorless crystals.

A sample of **4** (50 mg) was deuterated in 2 mL of D<sub>2</sub>O containing 0.1 g of NaOD. The solution turned yellow. After 10 min the diketone was extracted with ether. The organic phase was washed with D<sub>2</sub>O, evaporated to dryness, and sublimed at 80°C in vacuo, giving off-white crystals of **4**-6,6,8,8- $d_4$  (40 mg). <sup>1</sup>H NMR (D<sub>2</sub>O) & 2.8 (m, <0.01 H), 3.8 (m, 1 H, > CH-), 6.8 ppm (m, 1 H, -CH=); solvent peak (HDO) & 5.0 ppm. MS: 141 (8.8), 140 (100, M<sup>+</sup>), 139 (9.1).

#### Isotopic exchange experiments

The samples of phenol-2*d* (7 NMR tubes containing 0.5 mL, 0.04 M) and phenol-2*t* (20 mL, 0.007 M) in 0.1 N HClO<sub>4</sub> were heated simultaneously in a thermostat bath that

was kept at  $80.0 \pm 0.1^{\circ}$ C. Deuterium loss from phenol-2*d* in samples removed periodically from the bath was determined by integration of the two peaks observed in the <sup>2</sup>H NMR spectra, at  $\delta$  1.13 (HDO) and at 1.28 ppm (phenol-2*d*). The first six samples covered two half-lives, the last was drawn after seven half-lives.

Deuteration rates of phenol in 1.0 N DCl in  $D_2O$  were determined by 300 MHz <sup>1</sup>H NMR. The NMR tubes (10 for each temperature) were heated in a water bath which was held at 80.0, 70.0, or  $60.0 \pm 0.1^{\circ}C$ , removed at appropriate time intervals, and stored at in a refrigerator until all samples had been collected. The signal of the *meta* hydrogens ( $\delta = 7.4$  ppm; dd,  $J_{2,3} = J_{3,4} = 7$  Hz, 2H) was used as an internal standard. First-order exponential decays were fitted to the integrated signal intensities of the *ortho* ( $\delta = 6.9$  ppm; d,  $J_{2,3} = 7$  Hz, 2H) and *para* ( $\delta = 7.1$  ppm; t,  $J_{3,4} = 7$  Hz, 1H) hydrogens (Table 3).

The contents of phenol-2t were determined by liquid scintillation counting of 31 aliquots of 0.5 mL containing 7 mM of phenol which were drawn periodically over three halflives of the exchange reaction. A final sample was measured after 10 half-lives. The aliquots were extracted with 4 mL of diethyl ether to separate the tritiated phenol from the tritium that had exchanged into water. To correct for variations  $(\pm 10\%)$  in the efficiency of the extraction, the absorbance of each extract was measured at 274 and 281 nm, and the radioactivity of the samples were normalized by these absorbances. In this way, the standard error of single measurements was reduced to about 3%. The activity of the samples was determined by scintillation counting on a Packard scintillation analyzer CA 2000 using 1,4-bis(5-phenyl-2oxazolyl)benzene (POPOP) and Packard emulsifier 299 as scintillation reagents. Prior to the measurements, the instrument was calibrated with a standard of known activity.

#### **Flash photolysis**

All kinetic measurement were done with water-jacketed quartz cells which were kept at  $25.0 \pm 0.1^{\circ}$ C unless stated otherwise. Temperature readings were taken from a thermoelement that was dipped into the sample solutions. Acid and base strength was adjusted with HCl in the range of 0.1 to 0.001 N or KOH in the range of 0.01 to 0.001 N. Values from buffered solutions quoted in this paper were obtained by extrapolation to zero buffer concentration and thus refer to wholly aqueous solutions. All solutions were adjusted to ionic strength I = 0.1 M by the addition of NaCl. Kinetic data determined by different persons using different experimental setups differed by up to 20%, much more than the standard error of sample means determined by a single person in a series of experiments (cf., e.g., the first two entries of Table 1).

#### Spectrophotometric titration of phenol

A 0.3 mM solution of phenol in water (3 mL) containing 0.010 M NH<sub>4</sub>Cl and 0.09 M NaCl was titrated with 30  $\mu$ L portions of 0.1 N NaOH in a quartz cell which was left untouched in the thermostatted (25 ± 0.1°C) sample holder of a Perkin–Elmer Lambda 9 UV spectrophotometer. The UV spectra were recorded and digitized (250–310 nm, 120 absorbance readings per spectrum, 16 spectra per titration) after each addition and the acid concentration was measured

with a calibrated (35) Metrohm 6.0236.100 micro glass electrode using a digital Metrohm pH meter 654. The spectra were analyzed using the program SPECFIT of Zuberbühler and co-workers (36). The original spectra were reproduced with a standard error of <0.002 absorbance units using the two dominant eigenvectors of the factor analysis. The loading coefficients fitted well to a titration curve (standard errors of single runs were <0.001 pK units). Three independent runs gave an average dissociation quotient of phenol,  $pK_{a,c} = 9.84 \pm 0.02$  (ionic strength I = 0.1 M). Using activity coefficients for I = 0.1 M ( $\gamma_{H^+} = 0.83$  and  $\gamma_1 = 0.76$  (7)), the thermodynamic acidity constant of phenol is estimated as  $pK_a^{\circ} = 10.04 \pm 0.03$ . This is about 0.05 units higher than the literature values commonly quoted (37).

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# References

- P. Haspra, A. Sutter, and J. Wirz. Angew. Chem. Int. Ed. Engl. 18, 617 (1979).
- (a) J.R. Keefe and A.J. Kresge. In The chemistry of enols. Edited by Z. Rappoport. Wiley, New York. 1990. Chap. 7;
   (b) J. Wirz. Pure Appl. Chem. In press; (c) J. Wirz. Chem. unserer Zeit, 32, 311 (1998).
- M. Capponi, I. Gut, and J. Wirz. Angew. Chem. Int. Ed. Engl. 25, 344 (1986).
- 4. M. Demuth, P. Ritterskamp, E. Weigt, and K. Schaffner. J. Am. Chem. Soc. 108, 4149 (1986).
- 5. R.G. Bates. *In* Determination of pH. 2nd ed. *Edited by* P. de Mayo. Wiley, New York. 1973.
- J. Derkosch and W. Kaltenegger. Monatsh. Chem. 88, 778 (1957); K.L. Cook and A.J. Waring. J. Chem. Soc. 529 (1973);
   G. Quinkert, G. Dürner, E. Kleiner, E. Haupt, and D. Leinfritz. Angew. Chem. 91, 584 (1979).
- 7. A.J. Kresge and Y. Chiang. J. Am. Chem. Soc. **89**, 4411 (1967), and refs. therein.
- 8. A.J. Kresge. Acc. Chem. Res. 8, 354 (1975).
- 9. J.R. Keefe and A.J. Kresge. Can. J. Chem. 74, 2481 (1996).
- Y. Chiang, A.J. Kresge, B. Hellrung, P. Schünemann, and J. Wirz. Helv. Chim. Acta, 80, 1106 (1997).
- C.G. Swain, E.C. Stivers, J.F. Reuwer, Jr., and L.J. Schaad. J. Am. Chem. Soc. 80, 5885 (1958).
- A. Streitwieser, Jr., R.H. Jagow, R.C. Fahey, and S. Suzuki. J. Am. Chem. Soc. **80**, 2326 (1958); E.A. Halevi. Prog. Phys. Org. Chem. **1**, 109 (1963); S. Seltzer. J. Am. Chem. Soc. **83**, 2625 (1961).

- 13. J. Thiele. Liebigs Ann. Chem. 306, 87 (1899); 306, 129 (1899).
- 14. A. Lapworth. J. Chem. Soc. 1265 (1901).
- O.S. Tee, N.R. Iyengar, and M. Paventi. J. Org. Chem. 48, 759 (1983);
   O.S. Tee and N.R. Iyengar. J. Am. Chem. Soc. 107, 455 (1985);
   J. Org. Chem. 51, 2585 (1986).
- J.W. Meyer and G.S. Hammond. J. Am. Chem. Soc. 94, 2219 (1972).
- C.E. Kalmus and D.M. Hercules. J. Am. Chem. Soc. 96, 449 (1974); T. Arai, S. Tobita, H. Shizuka. J. Am. Chem. Soc. 117, 3968 (1995).
- 18. S.M. Beck and L.E. Brus. J. Am. Chem. Soc. 104, 1805 (1982).
- R. Bausch, H.-P Schuchmann, C. von Sonntag, R. Benn, and H. Dreeskamp. J. Chem. Soc. Chem. Commun. 418 (1976).
- V.V. Ershov and A.A. Volod'kin. Izv. Akad. Nauk. SSSR Otd. Khim. Nauk. 730 (1962); T. Matsuura and K. Ogura. J. Am. Chem. Soc. 89, 3846 (1967).
- M.-C. Lasne, J.-P. Ripoll, and J.-M. Denis. Tetrahedron Lett.
   463 (1980); V.P. Vitullo. J. Org. Chem. 35, 3975 (1970).
- 22. M.E. Kopach, W.G. Hipple, and W.D. Harman. J. Am. Chem. Soc. **114**, 1736 (1992).
- 23. J.B. Conant and G.B. Kistiakowsky. Chem. Rev. 20, 181 (1937).
- 24. M.J. Cook, A.R. Katritzky, P. Linda, and R.D. Tack. Tetrahedron Lett. 49, 5019 (1972).
- S.W. Benson. Thermochemical kinetics. 2nd ed. J. Wiley, New York. 1976.
- C.S. Shiner, P.E. Vorndam, and S.R. Kass. J. Am. Chem. Soc. 108, 5699 (1986).
- 27. E.D. Laganis and D.M. Lemal. J. Am. Chem. Soc. **102**, 6633 (1980).
- C.K. Ingold, C.G. Raisin, and C.L. Wilson. J. Chem. Soc. 1637 (1936).
- A.J. Kresge, Y. Chiang, G.W. Koeppl, and R.A. More O'Ferrall. J. Am. Chem. Soc. 99, 2245 (1977).
- P. Pruszynski, Y. Chiang, A.J. Kresge, N.P. Schepp, and P.A. Walsh. J. Phys. Chem. **90**, 3760 (1986).
- Y. Chiang, A.J. Kresge, J.A. Santabella, and J. Wirz. J. Am. Chem. Soc. 110, 5506 (1988).
- M. Tashiro, A. Iwasaki, and G. Fukata. J. Org. Chem. 43, 196 (1978).
- 33. C.A. Grob and A. Weiss. Helv. Chim. Acta, 43, 1390 (1960).
- C. Weitemeyer. Dissertation. Universität Göttingen, Germany. 1976.
- 35. H. Sigel, A.D. Zuberbühler, and O. Yamauchi. Anal. Chim. Acta, **255**, 63 (1991).
- H. Gampp, M. Maeder, C.J. Meyer, and A.D. Zuberbühler. Talanta, 32, 95 (1985); 32, 257 (1985).
- H.M. Walborsky, R.M. Brownell, and E.C. Mayo. J. Am. Chem. Soc. **70**, 2493 (1948); A.J. Biggs. Trans. Fararay Soc. **52**, 35 (1956).
- H.S. Harned and R.W. Ehlers. J. Am. Chem. Soc. 55, 652 (1933).
- 39. R.G. Bates and H.B. Hetzer. J. Phys. Chem. 65, 667 (1961).