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Generation of Simple Enols in Solution

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Since the subject of simple enols was reviewed by Hart in 1979,[1] notable advances have been made by Rappoport[2] and by Kresge[3] and their co-workers. We have also carried out investigation in this field,[4-10] and the purpose of this Account is to describe the progress that we have made.

As the following quotations illustrate, many textbooks of organic chemistry tell their readers that vinyl alcohol and other simple enols are very unstable species:

> "But all attempts to prepare vinyl alcohol result—like hydration of acetylene—in formation of acetaldehyde."[11]
>
> "Vinyl alcohol is an unstable compound that rearranges spontaneously to acetaldehyde."[12]
>
> "Since long before the nature of tautomerization was understood, chemists have been fascinated with the challenge of isolating the simplest of the enols, vinyl alcohol; to date this feat has not been accomplished. The equilibrium heavily favors the aldehyde."[13]

In the spring of 1979 it occurred independently to Hart[1] and to one of us[4] that perhaps simple enols were not so unstable as generally thought and that by the use of the right techniques it might be possible to generate them in solution or even isolate them. In our own work we initially concentrated on vinyl alcohol, and the design of our first experiments was based on some earlier work of Lienhard and Wang.[14] These workers concluded that the rate constants for the H_3O^+-catalyzed ketonization of 1-hydroxycyclohexene and for the hydrolysis of 1-methoxycyclohexene are approximately the same. If this also applied to the ketonization of vinyl alcohol and the hydrolysis of methyl vinyl ether, then k_{H^+} for the former reaction should only be about 1 M^{-1} s^{-1} at 25 °C.[15] This suggested to us that if a precursor could be found that generated vinyl alcohol with a rate constant several powers of 10 greater than this, it should be possible to obtain a metastable solution of the latter. In fact, it is now known[7,9] that k_{H^+} for the ketonization

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[1] Hart, H. *Chem. Rev.* **1979**, *79*, 515.

[2] See: Nadler, E. B.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 2112 and references cited therein.

[3] (a) See: Kresge, A. J. *CHEMTECH* **1986**, 250. (b) Chiang, Y.; Hojatti, M.; Keefe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *100*, 4000 and references cited therein. (c) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 6314.

[4] Capon, B.; Rycroft, D. S.; Watson, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 724.

[5] Capon, B.; Rycroft, D. S.; Watson, T. W.; Zucco, C. *J. Am. Chem. Soc.* **1981**, *103*, 1761.

[6] Capon, B.; Siddhanta, A. K. *Tetrahedron Lett.* **1982**, *23*, 3199.

[7] Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567.

[8] Capon, B.; Siddhanta, A. K. *J. Org. Chem.* **1984**, *49*, 255.

[9] Capon, B.; Siddhanta, A. K.; Zucco, C. *J. Org. Chem.* **1985**, *50*, 3580.

[10] Capon, B.; Kwok, F. C. *Tetrahedron Lett.* **1986**, *27*, 3275.

[11] Morrison, R. T.; Boyd, R. W. *Organic Chemistry*, 5th ed.; Allyn and Bacon: Boston, 1987; p 426.

[12] Solomons, T. W. G. *Organic Chemistry*, 2nd ed.; Wiley: New York, 1980; p 336.

[13] Allinger, N. L.; Cava, M. P.; De Jongh, D. C.; Johnson, C. R.; LeBel, A. N.; Stevens, C. L. *Organic Chemistry*, 2nd ed.; Worth Publishers: New York, 1976; p 174.

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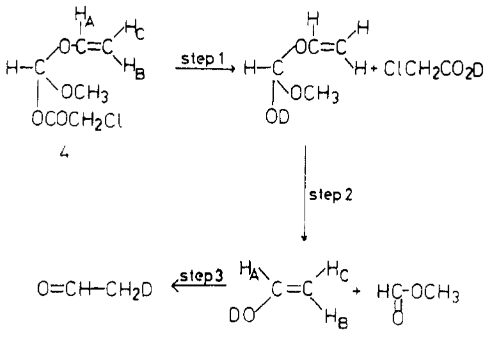
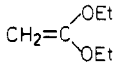
Scheme I



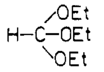
of enols in aqueous solution is 10–10^2 times greater than that for the hydrolysis of the corresponding enol ethers but nevertheless as described below, vinyl alcohol and some other simple enols are still sufficiently unreactive for this argument to apply.

Generation of Simple Enols in Solution

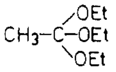
An examination of previous work[16] showed that the hydronium ion catalyzed hydration of ketene acetals (e.g., 1) frequently has rate constants ca. 10^6 M^{-1} s^{-1} and


$CH_2{=}C(OEt)_2$

1


$H{-}C(OEt)_3$

2


$CH_3{-}C(OEt)_3$

3

that the hydronium ion catalyzed hydrolyses of ortho esters (e.g., 2 and 3) frequently have rate constants 10^3–10^4 M^{-1} s^{-1} at 25 °C. A ketene acetal or ortho ester might therefore be a suitable precursor for the generation of vinyl alcohol in solution.

The first precursor to be chosen was therefore methoxy(vinyloxy)methyl chloroacetate (4), a particularly reactive orthoformate derivative. It was thought that this ester might be hydrolyzed in D_2O as shown in Scheme I to give O-deuteriated vinyl alcohol. If in this sequence of reactions steps 1 and 2 were faster than the conversion of O-deuteriated vinyl alcohol into deuteriated acetaldehyde (step 3), then a solution of O-deuteriated vinyl alcohol would be obtained. This is in fact what happens. In CD_3CN at −20 °C the signals of the vinyl group of 4 are approximately a first-order ABC system with $\delta_A = 6.53$, $\delta_B = 4.58$, and $\delta_C = 4.32$ and $J_{AB} = 14.7$, $J_{AC} = 4.9$, and $J_{BC} = 1.7$ Hz. On addition of D_2O (10% (v/v)), the spectrum of 4 slowly disappears and after about 45 min at −20 °C is replaced by the spectra of chloroacetic acid, methyl formate, and a new species with a vinyl group whose ^1H NMR spectrum is again approximately a first-order ABC system with $\delta_A = 6.45$, $\delta_B = 4.18$, and $\delta_C = 3.82$ and $J_{AB} = 14.2$, $J_{AC} = 6.4$ Hz, and $J_{BC} = 1$ Hz. Thus in this new species the signal of the α-proton (H_A) has almost the same chemical shift as that of the precursor 4 but the signals of the β-protons (H_B and H_C) are moved upfield by 0.4–0.5 ppm. The new species was stable in this acidic solution at −20 °C for several hours but if sodium deuterioxide was added or if the temperature was raised to +20 °C, it was rapidly converted into CH_2DCHO.

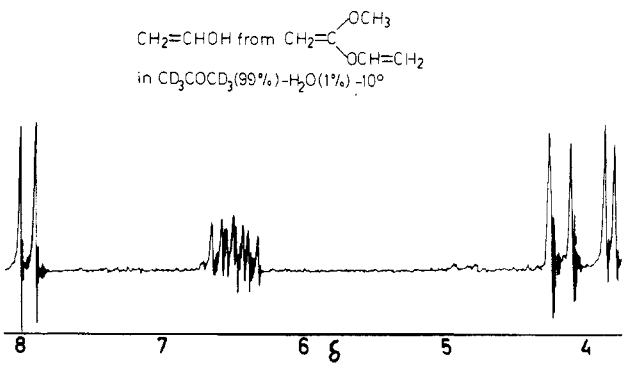
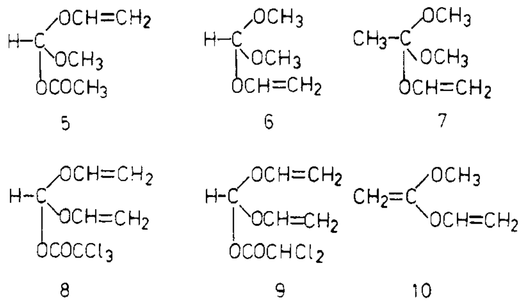


Figure 1. ^1H NMR spectrum of vinyl alcohol under conditions of slow exchange.

Chart I



The same species could be generated from six other precursors (5–10; Chart I). The best of these are 7 and 10, which may be regarded as vinyl alcohol with a very labile ortho ester (7) or ketene acetal (10) protecting group. These can be removed under very mild acidic conditions (see also ref 3b), and proof that the new vinylic species is in fact vinyl alcohol was obtained when 10 was allowed to react in CD_3COCD_3 (99% (v/v)) and H_2O (1% (v/v)) which contained 10^{-4} M HCl. Under these conditions the spectrum shown in Figure 1 was obtained. This spectrum of *O*–H vinyl alcohol differs from that of *O*–D vinyl alcohol in that now there is a signal of the OH group at $\delta = 7.97$ and the signal of the α-proton of the vinyl group is a doublet quartet. The coupling between the OH and α-CH is 9.98 Hz. Working with a solvent that contains a little more water enables the transformation from fast to slow exchange to be observed by changing the temperature (cf. Figure 2).

This method provides a good, and possibly the best, way of preparing solutions of vinyl alcohol. The precursors 7 and 10 are made quite easily (eq 1 and 2; Scheme II), and with a little care it is possible to convert them into vinyl alcohol without any detectable amounts of acetaldehyde being present. Attempts to isolate vinyl alcohol from such solutions and to achieve the goal set by Allinger et al.[13] have, however, so far been unsuccessful. The purest sample that has been obtained up to now was isolated by low-temperature trap-to-trap distillation of a solution of vinyl alcohol prepared from 10 in slightly aqueous acetone and was approximately 70 mol % pure (^1H NMR). The major impurities were acetone and methyl acetate.[17]

The use of ortho ester of ketene acetal precursors to generate simple enols is of fairly general application and

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(14) Lienhard, G. E.; Wang, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 1146.

(15) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228.

(16) Kankaanpera, A.; Tuominen, H. *Suom. Kemistil. B* **1967**, *40*, 271.

(17) Zucco, C., unpublished observations.

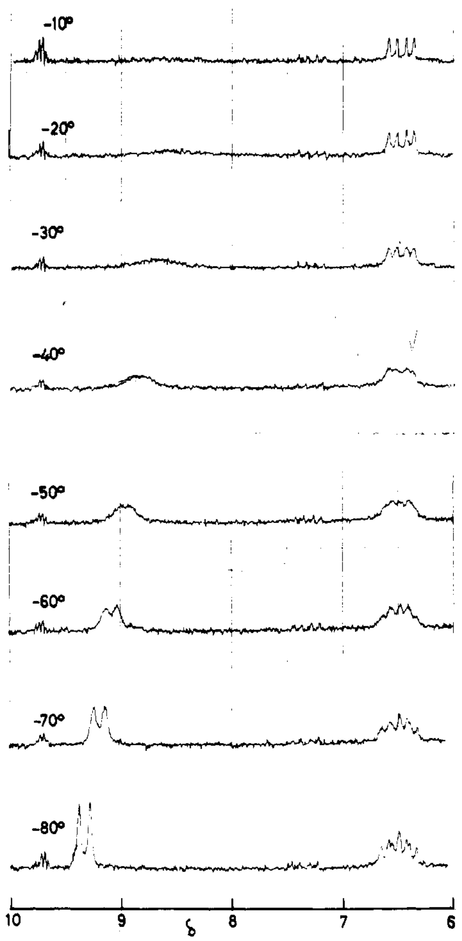
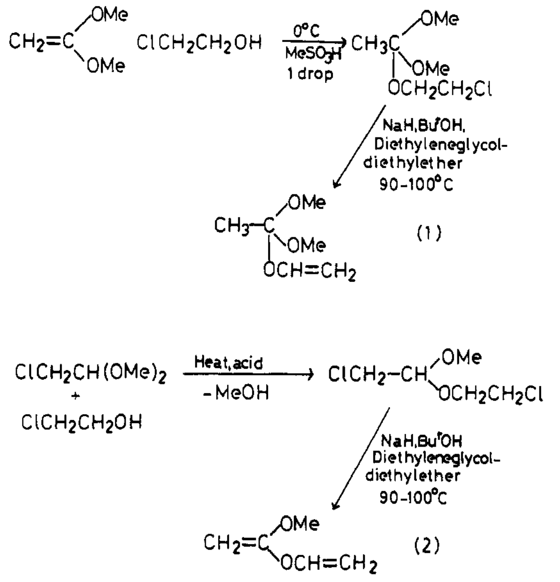


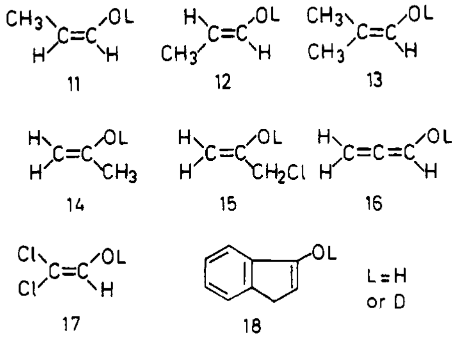
Figure 2. Temperature variation of the OH and C_α-H signals of the ^1H NMR spectrum of vinyl alcohol in CD_3COCD_3 (94.5%)-H_2O (5.5%). Note the presence of small amounts of acetaldehyde (δ = 9.71) and vinyl acetate (δ = 7.27).

Scheme II

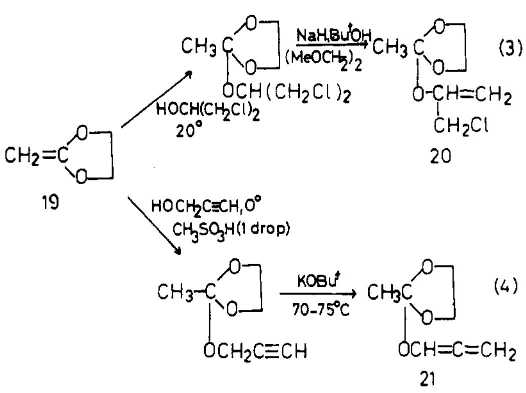


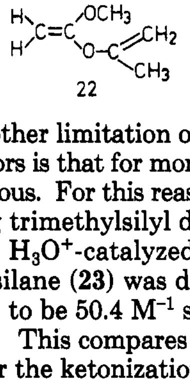
has been used to generate enols **11**–**18** (Chart II). In addition to acyclic orthoacetates, cyclic orthoacetates such as **20** and **21** can be used. These esters have the advantage of being more reactive than their acyclic analogues.[18] They are prepared very easily[9] by adding a chloro or β,γ-unsaturated alcohol to 2-methylene-1,3-dioxolane (**19**) followed by elimination of HCl or migration of a double bond (see eq 3 and 4, Scheme III). This class of precursor could probably be used for the generation of other enols. With all of the enols studied except the acetone enol **14**, the precursor can be converted to the enol without detectable (by ^1H NMR) amounts of the keto form. To generate acetone enol **14** the best precursor is **22**, but even this reacts too slowly in CD_3COCD_3–D_2O (8:2 (v/v)) to form 100% **14** before some of the latter is converted into [$^2H_1$]acetone.

Chart II



Scheme III





22

$(CH_3)_3SiOCH=CH_2$

23

The other limitation of ketene acetal and ortho ester precursors is that for more complex enols their synthesis is laborious. For this reason we examined the possibility of using trimethylsilyl derivatives. The rate constant for the H_3O^+-catalyzed hydrolysis of (vinyloxy)trimethylsilane (**23**) was determined by Tidwell and coworkers to be 50.4 M^{-1} s^{-1} in 50% H_2O-acetonitrile at 25 °C.[19] This compares with a value of 45.9 M^{-1} s^{-1} for $k_{H_3O^+}$ for the ketonization of vinyl alcohol in H_2O at 25 °C.[7] These data suggest that it is unlikely that **23** would be a suitable precursor for vinyl alcohol, and in our hands this has proved to be so. However, we have used trimethylsilyl ethers to generate a variety of more stable enols such as the heterocyclic enols **24**–**27**,[20,21] the homocyclic enols **28**–**32**,[21] 2-methylprop-1-en-1-ol (**13**),[22] (*E*)- and (*Z*)-1-hydroxybuta-1,3-diene (**33** and **34**),[22] and enols **35**, **36**, and **37** (Chart III), in which the double

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[18] Chiang, Y.; Kresge, A. J.; Salmonaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494.

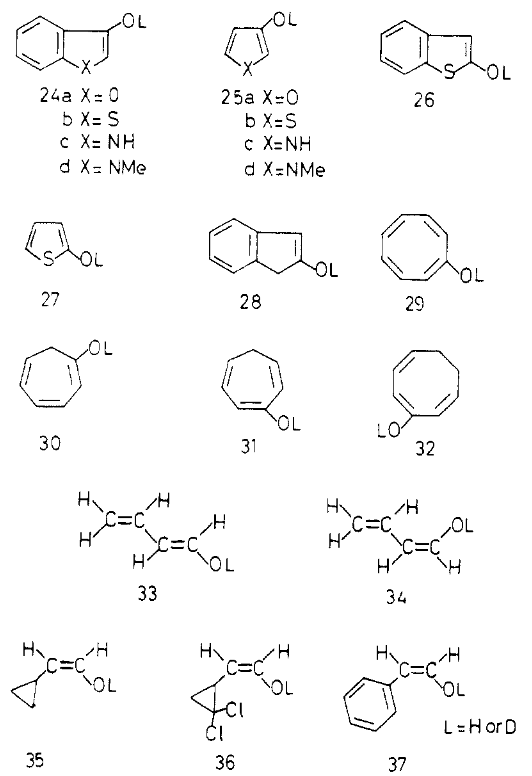
[19] Novice, M. H.; Seikaly, H. R.; Seiz, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 5835.

[20] Kwok, F. C. Ph.D. Thesis, University of Hong Kong, 1987.

[21] Capon, B.; Guo, B. Z.; Kwok, F. C.; Wu, Z. P. *Pure Appl. Chem.* **1987**, *59*, 1577.

[22] Guo, B. Z., unpublished observations.

Chart III

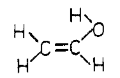


bond is conjugated with a cyclopropane ring or a phenyl group.[22]

In a typical experiment[10,20] 3-((trimethylsilyl)oxy)benzofuran was allowed to hydrolyze at 30 °C in a mixture of acetone-d_6 and D_2O (9:1 (v/v)) that contained DCl (5×10^{-4} M). Removal of the trimethylsilyl group could be followed by the disappearance of the signal at $\delta = 0.27$ (s) and formation of the signal at $\delta = 0.05$ due to trimethylsilanol. There was very little change in the rest of the spectrum except that the singlet of H-2 moved upfield from $\delta = 7.45$ to $\delta = 7.3$. The 3-hydroxybenzofuran was stable for several hours under these conditions but on addition of more acid, the spectrum changed rapidly to that of 2-deuteriobenzofuranone. This method, with slight variations, was used for the other enols listed above.

Stereochemistry of Enols

As described above the HO–C_αH coupling constant for vinyl alcohol is 9.98 Hz. This value decreases slightly with increasing temperature in the range −80 to +40 °C. It was thought that, by analogy to what is found with HC–CH bonds, this coupling constant should be related to the dihedral angle between the OH and C_αH bonds. Two planar conformations are possible for vinyl alcohol, s-cis (**38**) and s-trans (**39**), for which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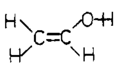
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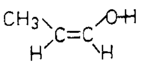
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the dihedral angles are 180° and 0°, respectively. There are also an infinite number of nonplanar gauche conformations possible. When a methyl group is introduced cis to the hydroxy group of vinyl alcohol as in (*Z*)-prop-1-en-1-ol (**11**, L = H) and 2-methylprop-1-en-1-ol (**13**, L = H), $J(\mathrm{OH{-}C_\alpha H}) < 6$ Hz and increases with increasing temperature. With (*E*)-prop-1-enol (**12**, L = H), however, this coupling constant is >9 Hz. These results are interpreted as indicating that for vinyl alcohol and **12**, which have hydrogen cis to the hydroxyl, the predominant conformation is s-cis but with enols **11** and **13**, which have a methyl group cis to the hydroxyl, the predominant conformation is s-trans. As the temperature is raised, the higher energy conformation becomes more highly populated so the coupling constants of vinyl alcohol and **12** decrease whereas those of **11** and **13** increase.[8] The long-range coupling constant between the OH and the trans β-CH, which for vinyl alcohol is 0.4 Hz and for (*Z*)-prop-1-en-1-ol is 0.95 Hz, also supports this conclusion. In the s-trans conformation (**40**) proposed for the latter, there is a W relationship between the OH and the trans C_β-H, which is the most favorable for long-range allylic coupling and hence should lead to a larger coupling constant.

These conclusions are in agreement with MO calculations of Bouma and Radom, which showed the s-cis conformation of vinyl alcohol to be 2.2 kcal mol^{-1} more stable than the s-trans conformation and which indicated "no evidence" for a nonplanar conformation.[23]

Table I
Equilibrium Constants for Enolization in Water at 25 °C

equilibrium	K_{enol}(E/K)	ref
1. acetaldehyde ⇌ vinyl alcohol[a]	2.7×10^{-7} or 3.6×10^{-7}	7
2. acetone ⇌ 2-hydroxypropene	6.0×10^{-9}	26[b]
3. isobutyraldehyde ⇌ 1-hydroxy-2-methylpropene	1.37×10^{-4}	3c[c]
4. acetophenone ⇌ 1-hydroxystyrene	1.25×10^{-8}	27[b]
5. 1-indanone ⇌ 3-indenol	1.85×10^{-8}	20
6. 2-indanone ⇌ 2-indenol	8.19×10^{-5}	20
7. cyclohepta-3,5-dien-1-one ⇌ 1-hydroxycycloheptatriene	1.19×10^{-3}	22

[a] 15 °C. The different values are derived from different literature values for the rate constant for the enolization of acetaldehyde (see ref 7). [b] The enol was generated photochemically. [c] The enol was generated by protonation of the enolate ion.

Thermodynamic Stability of Enols

As discussed by Toullec,[24] many of the earlier measurements of equilibrium constants for enol formation, K_{enol}(E/K), based on halogen titration, are too high, although the estimate ($K_{enol} = 10^{-8}$) made by Gutsche and Pasto on the basis of bond energy considerations is approximately correct.[25] The generation of simple enols as described above allows their ketonization rate constants to be determined, and as it is usually possible to determine the rate constants for enolization of the keto form by halogen trapping or deuterium exchange, the equilibrium constants can be determined as the ratio of the rate constants of the forward and backward reactions (see Table I).

When the carbon–carbon double bond of the enol is conjugated with a benzene ring but the carbon–oxygen double bond of the keto form is not, as expected, the enol form is stabilized (compare Table I, entry 6, with Table I, entry 5). Conjugation with additional car-

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(23) Bouma, W. J.; Radom, L. *J. Mol. Struct.* **1978**, *43*, 267.

(24) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 43.

(25) Gutsche, C. D.; Pasto, D. J. *Fundamentals of Organic Chemistry*; Prentice-Hall: Englewood Cliffs, NJ, 1975; p 253.

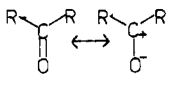
(26) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460.

(27) Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392.

Table II
Equilibrium Constants for the Enolization of Some Heterocyclic Compounds in Water at 25 °C

equilibrium	K_{enol}(E/K)
1. 3-ketobenzofuran $\rightleftharpoons$ 3-hydroxybenzofuran	8.70×10^{-4}
2. 3-ketobenzothiophene $\rightleftharpoons$ 3-hydroxybenzothiophene	6.7
3. 3-ketoindole $\rightleftharpoons$ 3-hydroxyindole	0.086
4. 3-keto-1-methylindole $\rightleftharpoons$ 3-hydroxy-1-methylindole	0.303
5. 3-ketofuran $\rightleftharpoons$ 3-hydroxyfuran	$<10^{-2}$
6. 3-ketothiophene $\rightleftharpoons$ 3-hydroxythiophene	2.96
7. 3-ketopyrrole $\rightleftharpoons$ 3-hydroxypyrrole	0.13
8. 3-keto-1-methylpyrrole $\rightleftharpoons$ 3-hydroxy-1-methylpyrrole	0.18

bon–carbon double bonds also stabilizes the enol form, although whether any of the high stability of 1-hydroxycycloheptatriene can be ascribed to homoaromaticity is not clear. The introduction of β-methyl groups (see Table I, entries 1 and 3) also stabilizes the enol. On the other hand, the introduction of an α-methyl or α-phenyl substituent, to give the enol of a ketone, causes a decrease in K_{enol} (see Table I, entries 1, 2, and 4). This result presumably arises from a stabilization of the keto form, as an α-methyl or α-phenyl substituent should stabilize the mesomeric zwitterionic structure (see 41 ↔ 42).


41 42

The heterocyclic enols **24** are all more stable than their homocyclic analogue 3-indenol (cf. Table I, entry 5, with Table II, entries 1–4). Even 3-hydroxybenzofuran is much more stable than 3-indenol despite the low aromaticity of the five-membered ring of benzofuran.[28] When the heterocyclic ring is more aromatic, as with pyrrole, thiophene, and their benzo derivatives, the 3-hydroxy tautomers are sufficiently stable for there to be detectable amounts of them present at equilibrium.

Heterocyclic enols with the hydroxy group in the 2-position could only be generated for the thiophene and benzothiophene series (**27**, **26**). These are formally enols of thioesters and while the enolic form is stabilized by the aromaticity of the heterocyclic ring, the keto form is stabilized by the thioester resonance.[29] The result is that 2-hydroxybenzothiophene, with $K_{\text{enol}} = 2.29 \times 10^{-5}$ in 90% CH_3CN–10% H_2O (v/v) (25 °C), is much less stable than 3-hydroxybenzothiophene, for which $K_{\text{enol}} = 0.31$, measured under the same conditions, and is only slightly more stable than its homocyclic analogue 2-hydroxyindene, for which $K_{\text{enol}} = 3.42 \times 10^{-6}$.

Kinetic Stability of Simple Enols

The pH–rate profile for the ketonization of vinyl alcohol is a U-shaped curve with H_3O^+-, HO^--, and H_2O-catalyzed reactions. In the pH range 3.5–5.0, the H_2O-catalyzed reaction predominates and the rate of ketonization is almost constant, with $k = (1.5–2.0) \times 10^{-2}$ s^{-1} at 15 °C. This corresponds to a half-life of about 35–45 s. At pHs lower than 3.5 and higher than 5.0, the rate increases as the H_3O^+- and HO^--catalyzed reactions become more important.[7] The rate constants for these reactions and those for the ketonization of a number of other enols measured by ourselves and by Kresge and co-workers are summarized in Tables III–V.

Table III
Rate Constants for the Ketonization of Simple Enols in Water (I = 1.0 M) at 15 °C

	k_{H^+}/ (M^{-1} s^{-1})	k_{HO^-}/ (M^{-1} s^{-1})	k_{H_2O}/s^{-1}
1. vinyl alcohol	20.2	$1.5 \times 10^{7\,a}$	1.38×10^{-2}
2. (Z)-propenol	2.80	5.03×10^4	
3. 2-methylprop-1-en-1-ol	0.370	1.38×10^3	
4. 3-chloro-2-hydroxypropene	6.18	4.74×10^7	6.0×10^{-2}
5. hydroxypropadiene	5.67	1.11×10^9	7.61×10^{-3}

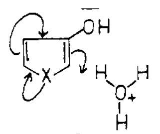
[a] A value of 1.99×10^6 M^{-1} s^{-1} for k_{HO^-} can be calculated for the results given in ref 3b (I = 0.1 M, 25 °C).

As might be predicted from their expected effects on the stability of cationic and anionic transition states, an α-methyl group causes a large rate enhancement of the hydronium ion catalyzed ketonization but has only a small effect on the hydroxide ion catalyzed ketonization (cf. Table IV, entry 2, with Table IV, entry 1, and Table III, entry 1), whereas a β-methyl substituent has a much larger rate-retarding effect on the HO^--catalyzed ketonization than on the H_3O^+-catalyzed ketonization (cf. Table III, entries 2 and 3, with Table III, entry 1). β-Methyl substituents also cause a decrease in the rate of the H_2O-catalyzed reaction so that the half-life of (Z)-propenol at the minimum of the pH–rate profile (pH 3.5–6) at 15 °C is approximately 10 min and that of 2-methylprop-1-en-1-ol is approximately 1 h (pH 3–5.5).

The introduction of a chloro substituent into the methyl group of 2-hydroxypropene has a large rate-decreasing effect on the H_3O^+-catalyzed ketonization but only a small effect on the HO^--catalyzed ketonization (cf. Table IV, entry 2, with Table III, entry 4). On the other hand, the HO^--catalyzed ketonization of hydroxypropadiene is much faster than that of vinyl alcohol (see Table III), which can be explained on the basis of the vinyl anion character of the transition state of the former reaction.[8]

Groups that are conjugated with the carbon–carbon double bond of the enol but not with the carbon–oxygen double bond of the keto tautomer of course stabilize the enol kinetically. This is illustrated by entries 6–10 of Table IV.

The monocyclic heterocyclic enols (**25**) undergo H_3O^+-catalyzed ketonization faster than their benzo analogues (**24**) (see Table V), which can be explained by a mesomeric effect as symbolized by **43**, which is


43

particularly effective when X = NH or NMe. 3-Hydroxybenzofuran and 3-hydroxybenzothiophene undergo hydroxide ion catalyzed ketonization much faster than the 3-hydroxyindoles. This result can be explained partly as arising from the smaller pK_a's of the two former compounds (see Table V), which result in a higher concentration of the anion, which is presumably the reactive species.

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(28) Dewar, M. J. S.; Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron* **1970**, *26*, 4505.

(29) The delocalization energies of simple thioesters have been estimated to be ca. 11 kcal mol^{-1}. Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004.

Table IV
Rate Constants for the Ketonization of Simple Enols in Water (I = 1.0 M) at 25 °C

	$k_{H^+}/(M^{-1}\ s^{-1})$	$k_{HO^-}/(M^{-1}\ s^{-1})$	k_{H_2O}/s^{-1}	ref
1. vinyl alcohol	45.9			7
2. 2-hydroxypropene[a]	4.7×10^3[b]	3.43×10^7		26
3. 1-hydroxystyrene[a]	1250	2.07×10^7	1.9	27
4. 2-hydroxyindene	3.48		5.5×10^{-2}	20
5. 3-hydroxyindene	903[c]			20
6. (Z)-1-hydroxybuta-1,3-diene[c]	9.55×10^{-2}	1.28×10^5	3.99×10^{-3}	22
7. (E)-1-hydroxybuta-1,3-diene[c]	0.53	1.14×10^5	3.03×10^{-3}	22
8. (Z)-2-cyclopropylvinyl alcohol	1.25	4.48×10^4	2.54×10^{-3}	22
9. (Z)-2-(2,2-dichlorocyclopropyl)vinyl alcohol	0.36	1.79×10^6	6.29×10^{-3}	22
10. (Z)-2-hydroxystyrene	0.16	2.59×10^5	6.7×10^{-3}	22

[a] I = 0.1 M. [b] Estimated from k_{H^+} for the enolization of acetone, 2.8×10^{-5} M^{-1} s^{-1} (Albery, W. J.; Gelles, J. S. *J. Chem. Soc., Faraday Trans.* **1982**, *78*, 1569) and $K_{enol} = 6 \times 10^{-9}$ (ref 26). The value agrees well with a recent direct measurement, 5.38×10^3 M^{-1} s^{-1} (ref 3b). [c] Extrapolated from values in acetonitrile–water mixtures. [d] To yield 2-butenal and 3-butenal.

Table V
Rate Constants for the Ketonization of Heterocyclic Enols in Water (I = 1.0 M) at 25.0 °C[a]

	$k_{H^+}/(M^{-1}\ s^{-1})$	$10^{-5}k_{HO^-}/(M^{-1}\ s^{-1})$	$10^3k_{H_2O}/s^{-1}$	pK_a
1. 3-hydroxybenzofuran	0.592	4.05	6.41	9.16
2. 3-hydroxybenzothiophene	0.579	1.14	5.59	8.86
3. 3-hydroxyindole	3.43	0.00994	1.05	10.46
4. 3-hydroxy-1-methylindole	5.82	0.134	1.00	10.76
5. 3-hydroxyfuran	50.1	27.9	8.60	
6. 3-hydroxythiophene	5.83	0.187	2.21	
7. 3-hydroxypyrrole	2.49×10^4	0.346	17.0	
8. 3-hydroxy-1-methylpyrrole	1.17×10^4	0.154	8.87	

[a] References 10, 20, and 21.

2-Hydroxythiophene (k_{H^+} = 11.5 M^{-1} s^{-1}) undergoes acid-catalyzed ketonization faster than 3-hydroxythiophene (k_{H^+} = 1.78) in 50% CH_3CN–50% H_2O (v/v) at 25 °C, and 2-hydroxybenzothiophene (k_{H^+} = 12.4 M^{-1} s^{-1}) undergoes acid-catalyzed ketonization faster than 3-hydroxybenzothiophene (k_{H^+} = 0.314) in 90% CD_3CN–10% H_2O (v/v) at 25 °C. The thermodynamic instability of these 2-hydroxy heterocyclic compounds (see above), which are formally enols at the carboxylic acid level of oxidation, is therefore paralleled by kinetic instability. 2-Hydroxybenzothiophene, which has its hydroxyl group attached to the five-membered aromatic ring, is also kinetically less stable than its homocyclic analogue 2-hydroxyindene (k_{H^+} = 2.79 M^{-1} s^{-1} in 90% CH_3CN–10% H_2O). This is in complete contrast to what is found in the 3-hydroxy series.

Conclusion

The results described in this Account show that many simple enols are species that, if generated in the right way, can be investigated by the standard spectroscopic techniques of organic chemistry. They, like the tetrahedral intermediates of O,O-acyl-transfer reactions,[30] were once hypothetical species, but now the door is open for a full and detailed investigation of their properties.

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[30] See: Capon, B.; Ghosh, A. K.; Grieve, D. McL. A. *Acc. Chem. Res.* **1981**, *14*, 306. Capon, B.; Dosunmu, M. I.; Sanchez, M. de N. de M. *Adv. Phys. Org. Chem.* **1985**, *21*, 37. McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983**, *16*, 394.