trated to *ca.* 5 ml on a rotary evaporator and the residue was extracted with two 5-ml portions of ethyl acetate. The combined ethyl acetate fractions were concentrated and the residue was purified by preparative tlc, affording 2.4 mg of crude **18b**, which was recrystallized twice from ethyl acetate–hexane: white needles, mp 113.5–114.5° (undepressed by admixture with authentic (−)-PGE_1), $[\alpha]D$ −46.9° (*c* 0.064, THF). Hydrolysis of **19a** by the same method gave **19b** (*ca.* 0.3 mg, oil).

Acknowledgments. We thank Dr. Francisco S. Alvarez, Mr. Douglas Wren, and Mr. Anthony Prince for generous supplies of the enone **14a**, and reference samples of (±)-PGE_1, 15-epi-(±)-PGE_1, and (±)15α- and 15β-desoxyprostaglandins, and Dr. John W. Young for assistance with the enzymatic hydrolysis.

Thermodynamically Unstable Enols. 2-Methyl-2-penten-3-ols from 4-Isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane

Erich Alfred Schmidt and H. M. R. Hoffmann*

Contribution from William Ramsay and Ralph Forster Laboratories, University College, London, England. *Received March 15, 1972*

Abstract: By treating 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (**1**) with acidic compounds ranging from *tert*-butyl alcohol to acetic acid, a series of simple aliphatic enols has been generated in high concentrations (0.45 to >1 *M*). The enols so obtained proved to be kinetically surprisingly stable and their formation as well as rearrangement into the corresponding ketones was followed by nmr over periods of 15 min up to 20 days at room temperature. On contact with D_2O all enols could be converted smoothly into the deuterioenols which, in general, were more stable than the ordinary enols, an exception being the dideuterioxy derivative **6-D**, the lability of which was comparable to that of **6**. The lifetime of the enols could be extended by using polar aprotic solvents such as dimethylformamide and, in particular, dimethyl sulfoxide. The facile generation and successful stabilization of the enols are attributed to (i) the reactivity of the heterocycle **1**, which contains a preformed ammonium enolate system, (ii) the use of mild acids including methanol which liberates the enol in a slow reaction such that acidity is never allowed to build up, not even locally, the reaction being homogeneous throughout, and (iii) the nature of the solvent.

We have shown recently that 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (**1**) is a highly reactive heterocycle,[1] which on treatment with catalytic amounts of benzoic acid gave a simple aliphatic enol, namely 2,4-dimethyl-1,3-pentadien-3-ol (**2**). Depending on the experimental conditions the enol **2** could be observed for periods up to 10 days at room temperature before it had rearranged irreversibly into the isomeric ketone **3**.[2]

The question remained whether the enol **2** owed its metastable character merely to the mild and carefully controlled conditions of its genesis or whether the conjugation of two double bonds, worth about 3.5 kcal/mol,[3] also came into play. Accordingly, we sought to generate a nonconjugated enol and it occurred to us that the reaction of heterocycle **1** with suitably weak acids other than benzoic acid[2] might allow the transient formation of such an enol.

Results

Reaction of 1 with Alcohols. Heterocycle **1**, either neat or as a 1.1 *M* solution in dimethylformamide (DMF) or CCl_4, remained unchanged at room temperature, provided it had been purified rigorously and stored in the absence of traces of acid, moisture, oxygen, and ultraviolet light. However, on contact with alcohols, water, carboxylic acids, and their deuterated analogs **1** broke up readily and a variety of enols could be generated and observed spectroscopically (Scheme I). For example, after *ca.* 2 molar equiv (100% excess) of methanol had been added to a 1.1 *M* solution of **1** in spectrograde CCl_4 at 27°, the 100-MHz nmr spectrum in Figure 1a could be scanned after a few minutes. When the same reaction was carried out with less methanol (1.25 molar equiv), the enol **4** had reached its maximum concentration (>0.8 *M*) after *ca.* 30 min; in addition to the enol **4** *ca.* 15% of the dienol **2** was obtained in these conditions. An even greater amount of pentadienol **2** (*ca.* 25%) was formed when using an equimolar quantity of methanol (*cf.* Figure 1b).

(1) (a) H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, *J. Amer. Chem. Soc.*, **94**, 3201 (1972); (b) E. A. Schmidt, Ph.D. Thesis, to be submitted in 1972.

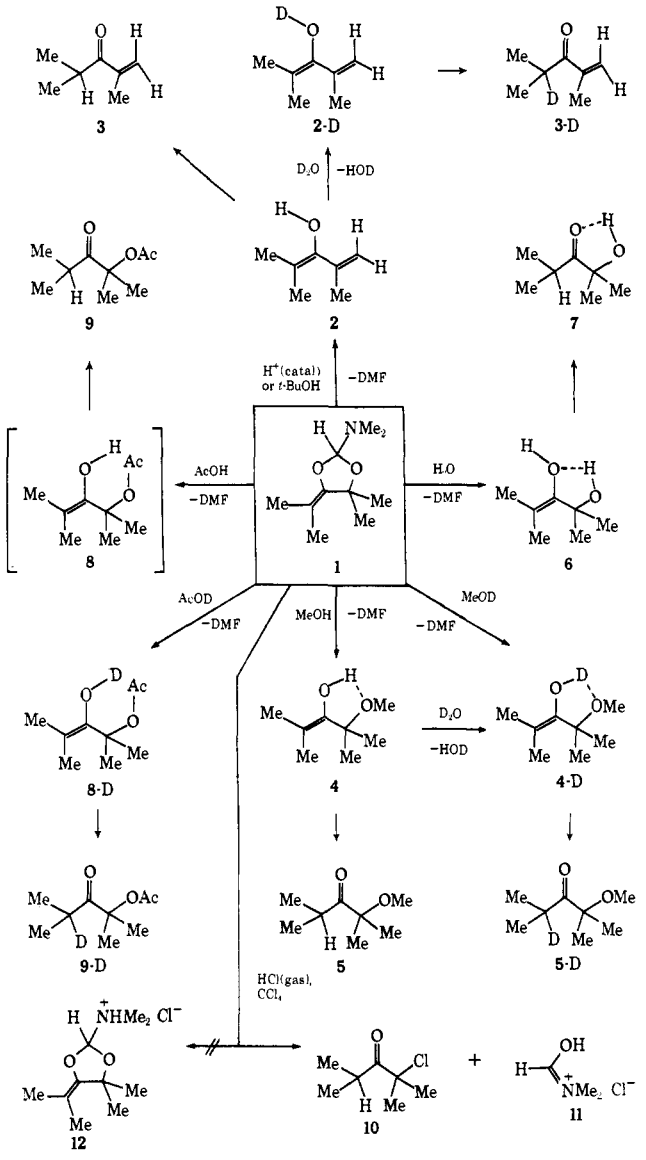
(2) H. M. R. Hoffmann and E. A. Schmidt, *J. Amer. Chem. Soc.*, **94**, 1373 (1972).

(3) Calculated from the heat of hydrogenation of 1-butene (30.3 kcal/mol) and that of 1,3-butadiene (57.1 kcal/mol): see J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1964.

(4) Enols **4**, **4-D**, and **6** have been formulated with weak intramolecular hydrogen bonds in solvent CCl_4. Ideally, such a formulation should be supported by high dilution ir data. However, such measurements have proved uninformative, since, *e.g.*, the α-methoxyenol **4** is accompanied by either pentadienol **2** or methanol (*cf.* below). Furthermore, dimethylformamide is also present in at least equimolar quantity and competes as a hydrogen bond acceptor. In any event it seems clear that intramolecular hydrogen bonding cannot be important in DMSO[5] and pure DMF solutions. We thank a referee for comments on this question.

(5) For recent references see, *e.g.*, O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); F. A. L. Anet, L. M. Sweeting, T. A. Whitney, and D. J. Cram, *Tetrahedron Lett.*, 2617 (1968); W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 90, 6250 (1968); G. Satzinger, *Tetrahedron*, 27, 3739 (1971).

Scheme I. 2-Methyl-2-penten-3-ols from 4-Isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (**1**)[4]



Both enol **4** and pentadienol **2** were found to coexist and to rearrange simultaneously into the corresponding ketones **5** and **3**, respectively. Interestingly, the enol **4** was kinetically more stable; whereas the dienol **2** was transformed into **3** within 5 min at 37°, rearrangement of **4** took longer in several experiments and was complete after *ca.* 10–15 min. Furthermore, the formation of **4** from the enol precursor **1** was the fastest reaction; only after **1** had been consumed was the rate of ketonization accelerated (*cf.* also Figure 1a).

When the heterocycle **1** was allowed to react with a 1.25 *M* amount of *tert*-butyl alcohol instead of methanol, elimination leading to pentadienol **2** was quantitative, no α-*tert*-butoxy ketone being formed. Finally, 2,4-dimethyl-1,3-pentadien-3-ol (**2**) was generated from **1** in dimethyl sulfoxide (B. D. H. laboratory reagent containing traces of moisture or acid). In these conditions the enol **2** turned out to be remarkably stable; even after 8 days the dimethyl sulfoxide solution contained still 0.1 *M* enol.

On briefly shaking a solution of enol **2** or **4** in CCl_4 with a slight excess of D_2O, the deuterioenols **2**-D and **4**-D were formed, as far as we could observe, instantaneously. Independently, **4**-D could be generated from **1** on contact with *O*-deuteriomethanol, the nondeuterated pentadienol being formed as a by-product (*ca.* 5%). It is noteworthy that the rearrangement of the deuterioenol **4**-D into the deuterio ketone required about 20 days! The *O*-deuteriopentadienol **2**-D was again found to be less stable (*cf.* **4** *vs.* **2**), the rearrangement into **3**-D requiring 11 days.

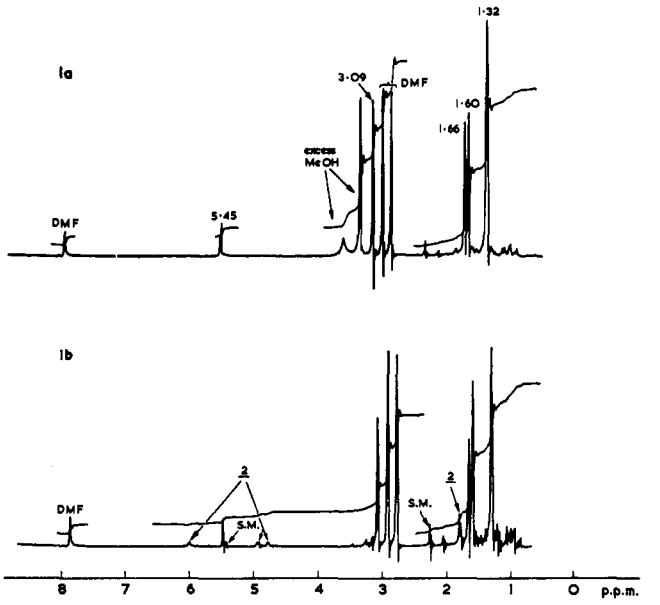


Figure 1. (a) Formation of the α-methoxyenol **4** from **1** and a 2 molar equiv of methanol. (b) Formation of **4** and some pentadienol **2** from **1** and equimolar methanol.

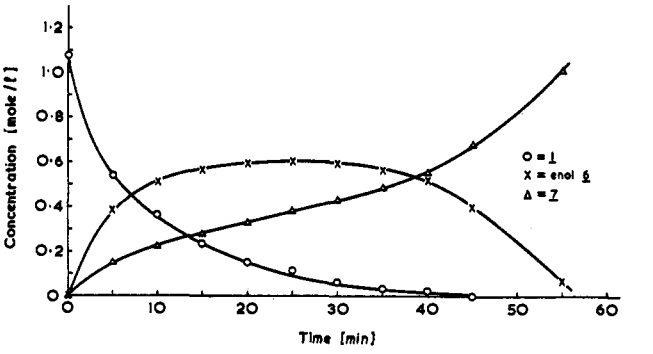


Figure 2. Rise and fall of enol **6** in CCl_4–H_2O.

Reaction of 1 with Water. On treatment of a 1.1 *M* solution of **1** in spectrograde CCl_4, with a 25% excess of water, the simultaneous formation of 2,4-dimethyl-3-pentene-2,3-diol (**6**) and of 2-hydroxy-2,4-dimethyl-3-pentanone (**7**) could be followed by nmr. The sample was shaken briefly before each scan and from 11 consecutive nmr spectra recorded over a period of 60 min, the time-dependent concentration profile of reactants and products could be derived (Figure 2). The reaction started off very fast, *ca.* 50% of **1** being broken up after 5 min at 37°, the ratio of enol **6**-ketone **7** being 7:3. After 25 min the ratio of enol–ketone had dropped to 6:4, but the enol had reached its maximum concentration of 0.6 *M*. The formation of ketone **7** was complete after 60 min. As a by-product *ca.* 5% pentadienol **2** could be detected, which concurrent with the rearrangement described was transformed into **3**.

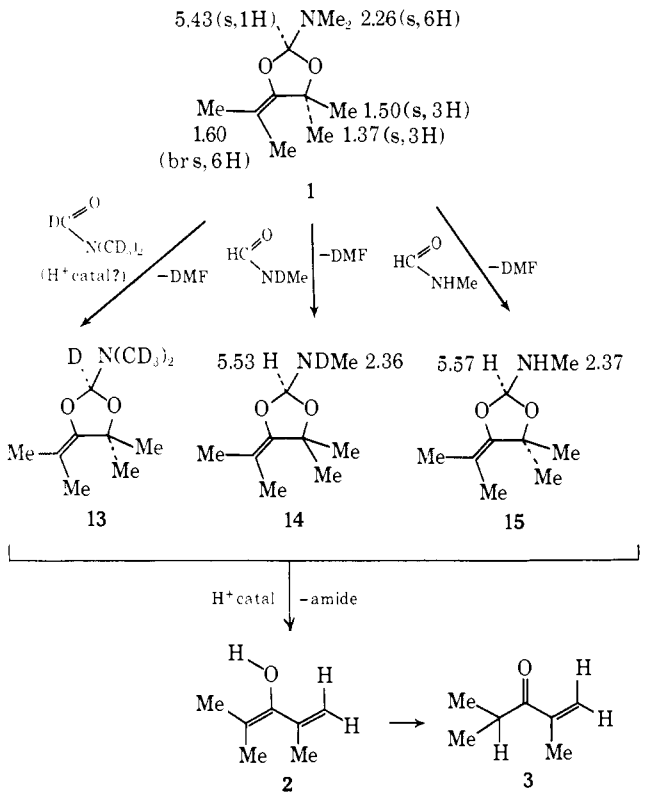
The reaction of **1** and D_2O afforded the dideuterated enol **6**-D, the lifetime of which (*ca.* 30 min) and maximum concentration (*ca.* 0.61 *M* after 20 min) at 37° turned out to be similar to that of the nondeuterated analog **6**; *ca.* 15% pentadienol **2** was also formed in this reaction.

Reaction with Acetic Acid. The formation of 2-acetoxy-2,4-dimethyl-3-penten-3-ol (**8**) could no longer be followed by nmr in our conditions (1.1 *M* precursor **1**, 1.25 *M* equiv of acetic acid, CCl_4 solvent, 37°). Instead, the α-acetoxy ketone **9** built up right away. However, it proved possible to generate and observe the deuterioenol **8**-D from a 1.1 *M* solution of **1** in spectrograde CCl_4 with a 1.25 molar equiv of *O*-deuterioacetic acid.

Although both deuterioenol **8**-D and ketone **9**-D were formed simultaneously, the nmr spectrum of deuterioenol **8**-D could clearly be derived from the change of five consecutive spectra during the reaction. The maximum concentration of **8**-D (0.45 *M*) was reached after 10 min, the ratio of enol **8**-D–ketone **9**-D being *ca.* 5:7; simultaneously, *ca.* 15% pentadienol **2** was formed which rearranged into **3**. The reaction was over after *ca.* 20 min. Finally, gaseous HCl and **1** in CCl_4 afforded the α-chloro ketone **10** and dimethylformamide hydrochloride (**11**) in a clean reaction.

Amide Exchange. On contact with formamides such as perdeuteriodimethylformamide (DDMF), *N*-deuterio-*N*-methylformamide, and even *N*-methylformamide, heterocycle **1** was found to exchange dimethylformamide more rapidly than to break up to the dienol **2**; after release of a corresponding amount of unlabeled dimethylformamide, the heterocycles **13**, **14**, and **15** were identified spectroscopically (Scheme II). Exchange was favored over elimination at low temperatures, especially below 0°. For instance, after maintaining a 1.1 *M* solution of unlabeled heterocycle **1** in perdeuteriodimethylformamide at −15° for 18 days, a 0.8 *M* solution of the d_7 derivative of **13** was obtained. When using *N*-deuterio-*N*-methylformamide and methylformamide itself, the exchange was not so clean, the amide being less nucleophilic and the N–H proton sufficiently acidic ($pK_a \sim 16$) to initiate a relatively fast E1 elimination. Nevertheless, amide exchange was clearly favored during the first half of the reaction, and the concentration of **14** and **15** had reached 0.3 *M* (~30% reaction) before any dienol **2** became visible in the nmr spectrum. Eventually, all the newly formed 1,3-dioxolanes furnished the dienol **2** with release of the corresponding formamide.

Scheme II. Exchange of Amide in **1**



Discussion

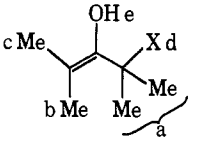
Clearly, the rate of ring opening of heterocycle **1** depends on the acidity of the reagent. Thus **1** is completely stable in the presence of an anhydrous base, such as 2,6-lutidine, and in neutral conditions but breaks up in *tert*-butyl alcohol ($pK_a = 19$), which reacts less readily than methanol ($pK_a = 16$), which in turn reacts more slowly than water ($pK_a \sim 16$).

With acetic acid ($pK_a \sim 5$) at room temperature in CCl_4 solvent, the corresponding enol **8** could no longer be observed in the nmr spectrum. However, the corresponding deuterated 4-acetoxy-2,4-dimethyl-2-penten-3-ol (**8**-D) could clearly be detected and an nmr spectrum was recorded (*cf.* Table I).

All the reactions studied were stoichiometrically simple in that 1 mol of dimethylformamide was expelled per mole of enol formed. For example, the intensity of the two singlets of dimethylformamide can be seen to be almost the same as that of the methoxy protons of the enol **4** (*cf.* Figure 1a); *i.e.*, the conversion of the precursor **1** into enol is strikingly clean and nearly quantitative. The only other peaks discernible are those due to a very small amount of precursor **1** and a trace of pentadienol **2** and of acetone, formed from **1** by reaction with a trace of oxygen (which is difficult to exclude completely). Note also that the enolic proton of **4** at δ 5.45 ppm, that of the pentadienol at 6 ppm, and the hydroxylic proton of methanol appear as three distinct peaks (*cf.* Figure 1a and 1b); *i.e.*, proton exchange is not fast on the nmr time scale. It should be mentioned explicitly that in no instance did we observe the formation of any dimethylamine; even the reaction of **1** with anhydrous HCl in CCl_4 gave a clean conversion into α-chloro ketone **10** and dimethylformamide hydrochloride (**11**) (Scheme I), no dimethylamine hydrochloride or precipitation of **12** being discernible. To summarize, dimethylformamide is an excellent leaving group in **1** and can be liberated under mild conditions which account for the feasibility of forming and observing our enols.

A probable intermediate in the decay of **1** is the delocalized ammonium cation **16**, which can be formed by protonation of the electron-rich oxygen and which can be visualized to collapse to the dienol **2** *via* an E1 reaction and/or the enol **18** in an SN1 process (Scheme III). Not unexpectedly, the competition of **2** and **18** depends on the concentration of nucleophile; for example, the formation of **4** (**18**, R = Me) is complete in the presence of 2 molar equiv of methanol (*cf.* Figure 1a), whereas **2** is discernible (*ca.* 15%) when using 1.25

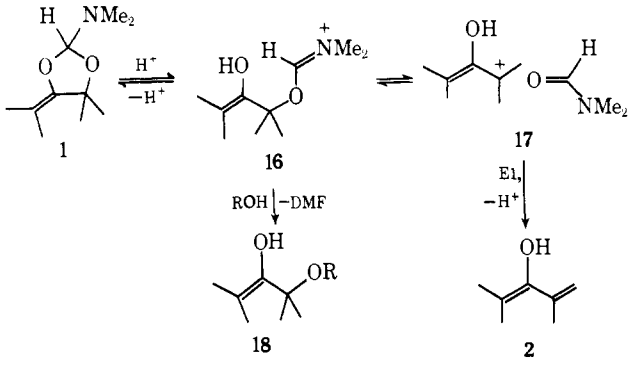
Table I. Chemical Shifts ($\delta_{TMS}^{CCl_4}$) and Maximum Concentrations (c_{max}) of Enols



	c_{max}, mol/l.	a	b	c	d	e	Rearr ketone[a]
4, X = OMe	0.85	1.32 (s, 6 H)	1.60 (s, 3 H)	1.66 (s, 3 H)	3.09 (s, 3 H)	5.45 (s, 1 H)	**5**
4-D, X = OMe	1.0	1.31 (s, 6 H)	1.57 (s, 3 H)	1.66 (s, 3 H)	3.04 (s, 3 H)		**5**-D
6, X = OH	0.60	1.43 (s, 6 H)	1.58 (s, 3 H)	1.60 (s, 3 H)	4.00 (br s, 1 H)	6.25 (br s, 1 H)	**7**
6-D, X = OD	0.61	1.42 (s, 6 H)	1.60 (s, 3 H)	1.62 (s, 3 H)			**7**-D
8-D, X = OAc	0.45	1.52 (s, 6 H)	1.61 (s, 3 H)	1.65 (s, 3 H)	1.93 (s, 3 H)		**9**-D

[a] *Cf.* also Scheme I.

Scheme III. Possible Intermediates in the Formation of Enols **2** and **18** from Heterocycle **1**



molar equiv of methanol and is formed in 25% yield with equimolar methanol (Figure 1b). If elimination is the desired pathway, it can be induced to the exclusion of substitution with, *e.g.*, catalytic amounts of benzoic acid in CCl_4[2] or with 1.25 *M* or less *tert*-butyl alcohol.

That exchange of the dimethylformamide moiety in **1** with other formamides is facile and a faster reaction than elimination to the dienol **2** (*cf.* Scheme III) attests to the high reactivity of the heterocycle **1** and suggests the intermediacy of at least two ions, *i.e.*, presumably **16** and a second one higher up on the potential energy surface. Amide exchange and formation of **18** could proceed starting with the ammonium ion **16**, while **17**, which involves a greater degree of carbon–oxygen bond fission, will be more short-lived and seems likely to collapse to the olefin **2**. It is pertinent that attempts to trap an allyl cation such as **17** by cycloaddition to furan or cyclopentadiene[6] were not successful in the present instance; with 3.0 molar equiv of conjugated diene at temperatures ranging from −5 to 37° and in solvents as different as CCl_4 and dimethylformamide, the dienol **2** was formed exclusively.

Concerning reaction velocities it is clear that the rate of formation of the enols must be higher than the subsequent conversion into the ketone; otherwise the enol could not build up and go through a maximum, as is illustrated in Figure 2 (which resembles the situation

(6) H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, *J. Amer. Chem. Soc.*, **94**, 3940 (1972).

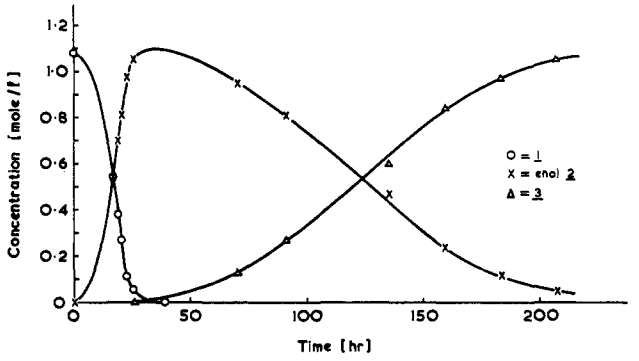


Figure 3. Formation and decline of 2,4-dimethyl-1,3-pentadien-3-ol (**2**) in dimethyl sulfoxide at 25°.

familar from, *e.g.*, radioactive decay) or in Figure 3. In point of fact, Figures 1a and 3 demonstrate an extreme case in that the enol precursor **1** has been consumed almost completely, while rearrangement into the ketone has not yet begun. Obviously, the rate of rearrangement of the enol into the ketone depends on several factors including temperature, absolute concentration of enol, and the solvent. Of these perhaps the most important one is the nature of the solvent. For example, the rate of formation of pentadienol **2** from **1** is approximately constant, *i.e.*, between 15–30 hr until the maximum concentration of **2** is reached, no matter whether the reaction is carried out in CCl_4, DMF, or DMSO. However, the decay of **2** into **3** sets in very steeply in CCl_4 (*cf.* reaction of **1** and equimolar methanol), is more drawn out in dimethylformamide (*ca.* 60 hr), and tails off in dimethyl sulfoxide (Figure 3); note that the concentration of enol **2** is still 0.1 *M* after 8 days. In the light of previous work on, *e.g.*, nmr spectra of alcohols in dialkyl sulfoxides,[5] the pronounced stabilization of the enol **2** in dimethyl sulfoxide is not completely unexpected.

Of the various simple aliphatic enols identified, the most stable one was 4-methoxy-2,4-dimethyl-2-penten-3-ol (**4**). Actually, **4** proved to be kinetically more stable than the pentadienol **2** by a factor of *ca.* 3:1. Since both enols are fully alkylated and hydrogen bonding to dimethylformamide (which is present in the CCl_4 solution) should affect each enol alike, it would appear

that enol **4** is stabilized further by *internal* hydrogen bonding,[4] and in any case more so than is enol **2** by π-electron delocalization.

Kinetic stability of the enols is not only reflected in the lifetime, but also in the maximum concentration which in the case of enol **4** amounted to 1 mol/l., *i.e.*, 140 g of enol per liter of solution! The maximum concentration of the other enols is less but still appreciable (*cf.* Table I and Figure 3), especially so when compared with the concentrations used in ordinary kinetic work, say 0.01–0.1 *M*.

Generally, the deuterioenols were considerably more stable than the corresponding ordinary enols, a notable exception being the dideuterioxy derivative **6-D**, the lability of which was comparable to that of **6**. Conceivably, in this instance hydrogen bonding[4] according to the formulation in Scheme I weakens the enolic O–H bond and hence stabilizes the enolate ion and facilitates ketonization. In any event it seems unlikely that ketonization proceeds *via* a concerted 1,3-hydrogen shift which would have to be antarafacial and is not readily accessible on steric grounds.[7] Clearly, all the enols described here are structurally very similar, yet differ widely in stability, which appears to be controlled largely by the availability of protons. Furthermore, since the enolization of a carbonyl compound is subject to general acid and base catalysis,[8] the postulated stepwise path for the ketonization of the enol is also demanded by microscopic reversibility.

It should be mentioned that the attempted conversion of the enols into enol ethers with diazomethane was not successful, the enols being not sufficiently acidic. Likewise, conversion into a trimethylsilyl ether using trimethylsilyl chloride and pyridine failed, and ketonization was actually accelerated, presumably owing to catalysis by pyridine hydrochloride formed.

Conclusions

The facile generation and successful stabilization of the enols in high concentrations can be attributed to several, very simple reasons. Obviously, the enol precursor **1** is highly reactive as demonstrated, *e.g.*, by exchange of dimethylformamide which occurs at a temperature as low as $-15°$. Put another way, dimethylformamide is a very good leaving group and, moreover, an ammonium enolate system is already preformed in the heterocycle **1**.

The conditions for generating the enol are very mild and some of the enols are formed very slowly, *i.e.*, over a period of 15–45 hr. By using weak acids such as alcohols in stoichiometric amounts, the acidity of the reaction medium is never allowed to build up beyond a certain limit, which is solely determined by the acidity of the added reagent and by that of the enol itself. Furthermore, the reaction is homogeneous throughout so that acidity cannot even build up *locally*. Finally, polar aprotic solvents such as dimethylformamide and, in particular, dimethyl sulfoxide provide a further striking stabilization of the enols. These circumstances, when taken together, ensure kinetic control throughout the reactions of the heterocycle **1** with weak acids, and one might hope now to be able to observe other, even more sensitive enols.[9]

Experimental Section

Nmr spectra were recorded on a Varian T-60 spectrometer and that of **4** on a Varian HA 100-MHz instrument. Ir spectra were scanned on a Unicam SP 200 spectrometer and mass spectra were recorded on an AEI MS9 instrument.

Preparation and Purification of 4-Isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (1).[1] 2,4-Dimethyl-2,4-dibromo-3-pentanone was debrominated with a highly active zinc–copper couple in dimethylformamide (DMF) at $-10°$. The product was extracted from the DMF mother liquor with isopentane as described previously. The extract contained *ca.* 25% dimethylformamide which was removed by stirring the isopentane solution under thoroughly dried and deoxygenated nitrogen in a Dry Ice–acetone bath at $-78°$ for 3 hr. In this manner virtually all dimethylformamide was frozen out and deposited on the walls of the vessel. The resulting **1** was remarkably pure (>95%) (*cf.* also Figure 1a and 1b).

Dimethylformamide Exchange in 1. Heterocycle **1** (100 mg, 0.54 mmol) was dissolved in heptadeuteriodimethylformamide (0.5 ml) in an nmr tube and kept in the freezing box of the refrigerator at $-15°$. The exchange was monitored by nmr, heptadeuteriodimethylformamide being slowly incorporated and a corresponding amount of unlabeled DMF being released. After 200 hr *ca.* 75% of **1** had been converted into the d_7 derivative **13** (0.8 *M*). The amount of **13** formed was calculated from the decrease of both the 6-proton singlet of the dimethylamino group and the 1-proton singlet of the C-2 proton in **1** relative to the retained peaks of the remaining methyl protons. Nmr of **13**: δ_{TMS} 1.37 (s, 3 H), 1.50 (s, 3 H), 1.60 (br s, 6 H).[10] On acid catalysis **13** was converted into the pentadienol **2**.

2-Methyl-2-penten-3-ols from 1. Heterocycle **1** (100 mg, 0.54 mmol) was dissolved in spectrograde CCl_4 (0.5 ml) in an nmr tube. The reactant (MeOH, MeOD, H_2O, D_2O, AcOD) (0.68 mmol) was added with shaking and the reaction was monitored by recording consecutive nmr spectra throughout the reaction. In the case of the heterogeneous reaction (H_2O, D_2O) the sample was shaken briefly before each scan.

The maximum concentration of the enols **4** and **4-D** was determined by integrating the 6 H singlet (*cf.* Table I, second column), the corresponding 6 H singlet in the ketones **5** and **5-D**, and the 6 H dimethylamino singlet in the starting material **1**. The amount of pentadienol **2** formed was taken into account accordingly. All the peaks chosen were sharp, intense, and did not overlap with other peaks (see, *e.g.*, Figure 1). Enols **6**, **6-D**, and **8-D** gave fleeting nmr spectra, which could not be integrated; here the peak heights were used rather than peak areas in order to determine concentrations. Since all peaks were well resolved, it is clear that any error is small and within the limits of integration accuracy ($\pm 10\%$).

The α-substituted ketones **5**, **5-D**, **7**, **7-D**, **9**, and **9-D** (*cf.* Table I) were isolated and identified by nmr, ir,[11] and mass spectroscopy.

2-Methoxy-2,4-dimethyl-3-pentanone (5):[11] nmr $\delta_{TMS}^{CCl_4}$ 1.02 (d, 6 H), 1.23 (s, 6 H), 2.9–3.5 (sept, 1 H),[12] 3.18 (s, 3 H); mass spectrum *m/e* 144.1150, calcd for $C_8H_{16}O_2$ 144.1144.

4-Deuterio-2-methoxy-2,4-dimethyl-3-pentanone (5-D): nmr $\delta_{TMS}^{CCl_4}$ 1.02 (br s, 6 H), 1.23 (s, 6 H), 3.18 (s, 3 H); mass spectrum *m/e* 145.1198, calcd for $C_8H_{15}DO_2$ 145.1213.

2-Hydroxy-2,4-dimethyl-3-pentanone (7): nmr $\delta_{TMS}^{CCl_4}$ 1.06 (d,

(7) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(8) E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt & Co., New York, N. Y., 1959; C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969.

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(10) The two olefinic methyl signals in both **1** and **13** collapse to a slightly broadish singlet in polar solvents such as DMF, DMF-d_7, MeCN, and DMSO but appear as two distinct 3 H singlets in CCl_4 and C_6H_6.[1]

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(12) Partly obscured by the 3 H methoxy singlet at δ 3.18 ppm.

6 H), 1.30 (s, 6 H), 3.16 (sept, 1 H), 3.62 (br s, 1 H); mass spectrum *m/e* 130.0982, calcd for $C_7H_{14}O_2$ 130.0993.

4-Deuterio-2-deuteroxy-2,4-dimethyl-3-pentanone (7-D): nmr $\delta_{TMS}^{CCl_4}$ 1.07 (br s, 6 H), 1.30 (s, 6 H); mass spectrum *m/e* 132.1101, calcd for $C_7H_{12}D_2O_2$ 132.1103.

2-Acetoxy-2,4-dimethyl-3-pentanone (9): nmr $\delta_{TMS}^{CCl_4}$ 1.03 (d, 6 H, J = 7 Hz), 1.45 (s, 6 H), 2.00 (s, 3 H), 2.93 (sept, 1 H); mass spectrum *m/e* 172.1098, calcd for $C_9H_{16}O_3$ 172.1099.

2-Acetoxy-4-deuterio-2,4-dimethyl-3-pentanone (9-D): nmr $\delta_{TMS}^{CCl_4}$ 1.02 (br s, 6 H), 1.46 (s, 6 H), 2.03 (s, 3 H); mass spectrum *m/e* 173.1154, calcd for $C_9H_{15}DO_3$ 173.1162.

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Solvent Effects in Organic Chemistry. XV. Thermodynamics of Solution for Nonelectrolytes in Aqueous Acid and Salt Solutions[1,2]

Edward M. Arnett,* John J. Burke, John V. Carter, and Charles F. Douty

Contribution from the Department of Chemistry, University of Pittsburgh and Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213. *Received November 19, 1971*

Abstract: Partial molar heats of solution ($\Delta\bar{H}_s$) at 25° are reported for a variety of organic compounds of widely differing basicity in aqueous sulfuric acid solutions ranging from dilute to highly concentrated. Comparisons are made of the heats of transfer from weak to strongly acid solutions for a variety of quaternary ammonium salts, strongly basic amines, weak oxygen bases, and several nonelectrolytes which are not protonated by even the most acidic media. There is very little difference between the behavior of salts and nonbasic nonelectrolytes, both of which show only minor changes in $\Delta\bar{H}_s$ across the range of acid solutions. In contrast, basic molecules undergo large changes in $\Delta\bar{H}_s$ as the strength of acid increases from dilute to concentrated, the size of the change being proportional to the pK_a of the base. This is consistent with the correlations between pK_a and heats of ionization in strong acids, which we have reported previously. The large enthalpy changes (*e.g.*, 20 kcal/mol) for the transfer of strongly basic solutes from dilute to concentrated acids are directly attributable to the heat of transfer of sulfuric acid used for protonation from the weakest to the strongest solution. The use of enthalpimetric titration for the determination of pK_a of weak bases appears to fail in aqueous sulfuric acid and to be of dubious value in sulfuric–acetic acid. The enthalpy data in sulfuric acid are compared in a few cases with some obtained in aqueous phosphoric acid. The effect of varying acid concentration on the heat of solution is combined with comparable changes in free energy of solution (from distribution experiments) to generate $\delta\Delta\bar{G}_s$, $\delta\Delta\bar{H}_s$, and $T\delta\Delta\bar{S}_s$ for transfer from water across the whole spectrum of aqueous sulfuric acid solutions for anilinium ion, *N,N*-dimethylanilinium ion (both relative to tetraethylammonium ion), benzonitrile, nitrobenzene, tetrahydrofuran, acetone, and acetophenone. These data provide the first complete thermodynamic analysis for the behavior of solutes in this system. In highly aqueous solutions the normal compensation of $\delta\Delta\bar{H}_s$ and $T\delta\Delta\bar{S}_s$ which we have found in other aqueous binaries is seen. In solutions stronger than *ca.* 30% H_2SO_4, entropies of transfer for all of the above solutes remain nearly constant so that increasingly negative trends in free energy and enthalpy parallel each other. For comparison, heats of solution of several solutes are measured in a number of aqueous salt solutions and complete thermodynamic analyses of $\delta\Delta\bar{G}_s$, $\delta\Delta\bar{H}_s$, and $T\delta\Delta\bar{S}_s$ are given (again these analyses appear to be novel). No general pattern is found, but in the majority of cases free-energy changes are enthalpy controlled. Some discussion is presented of extrathermodynamic relationships between free energies and enthalpies of solution and also of linear enthalpy correlations. This leads to estimates of the acid strengths of HSO_3F (H_0 = −14) and "magic acid," HSO_3F–SbF_5 (H_0 = −18, H_R = −36).

The study of the kinetics and equilibria of acid–base interactions in aqueous acid is of fundamental importance since acid-catalyzed reactions are probably the largest mechanistic class in organic chemistry and aqueous media are the most thoroughly explored systems of solution chemistry. A great deal is known about such processes in dilute aqueous acid (*i.e.*, within the pH range). There are, however, a large number of weak Brønsted bases whose proton transfer equilibria must be studied in much more acidic media. By far the majority of these latter cases have been investigated using aqueous sulfuric acid solutions. Sulfuric acid is a natural choice for such studies since it offers a wide range of acidities, is an excellent ionizing solvent, and is relatively cheap and easy to handle.

An understanding of the kinetics of acid-catalyzed reactions in these solutions is directly dependent upon a knowledge of the acid–base equilibria between the Brønsted base substrates and their conjugate acids in the reactant media. Therefore, any information regarding the thermodynamic behavior of such solutes in aqueous sulfuric acid solutions is relevant to the general problems of equilibrium and kinetic processes in these systems.

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(2) The majority of the results presented here are taken from the doctoral theses of C. F. D. (1965) and J. J. B. (1966).