Intermediates in the Paal–Knorr Synthesis of Furans

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New experimental evidence for the mechanism of the Paal–Knorr reaction involving the acid-catalyzed cyclization of a 1,4-diketone to form a furan is reported. In aqueous or alcoholic solutions containing hydrochloric acid and in chloroform containing boron trifluoride-etherate *d,l*- and *meso*-3,4-diethyl-2,5-hexanediones (**2r** and **2m**) cyclize at unequal rates; the stereochemical configuration of the unchanged dione is preserved during the reaction. This disagrees with the commonly accepted mechanism involving the ring closure of the rapidly formed monoenol (**11b**) followed by loss of water. A pathway involving the rapid protonation of one of the carbonyls followed by the electrophilic attack on the protonated carbonyl by the enol being formed at the other carbonyl group (**10c**) is proposed to account for the difference in reaction rates between the diastereomers of 3,4-disubstituted 2,5-hexanediones (**1–3**). The following results also seem to support the intermediacy of **10c**. The presence of two isopropyl groups in 3,4-diisopropyl-2,5-hexanedione (**3**) considerably reduces the rate of cyclization. The catalytic constants k_{H^+} for the cyclization of **2r** and **2m** are larger than the constants for enolization of methyl ketones. The diastereomers of 2,3-dimethyl- and 2,3-diethyl-1,4-diphenyl-1,4-butanediones (**4** and **5**), which could enolize only toward the center of the molecule, also react at different rates. The *d,l* and meso dideuterio analogs (d_2-**4r** and d_2-**4m**) exhibit a primary isotope effect during cyclization. The order of cyclization of 1,4-diphenyl-1,4-butanedione (**6**) and its analogs (**7-9**) reveals that the presence of electron-donating groups facilitate the reaction.

Introduction

The furan ring can be found in many natural products, and several derivatives of furan have industrial applications.[1] One of the most important methods for the preparation of furans is the acid-catalyzed cyclization of 1,4-dicarbonyl compounds. The only limitation of this reaction, known as the Paal–Knorr synthesis, has been the availability of suitably substituted starting diones. In recent years many excellent methods for the preparation of 1,4-diones[2,3] have been developed, improving the synthetic utility of the Paal–Knorr condensation. Although the reaction has been known for more than a century, very little is known about the mechanism of the reaction. Cyclization of the monoenol is often stated, with little supporting evidence, as the pathway for the reaction.[4–6]

Recently, the *d,l* and meso diastereomers of 2,3-disubstituted 1,4-diketones were utilized to study the stereochemical aspects of the Paal–Knorr synthesis of pyrroles from 1,4-diones and primary amines.[7,8] It was shown that the higher reactivity of the racemic mixture over the meso isomer in water and other solvents under basic, neutral, or mildly acidic conditions was incompatible with the previously proposed mechanism involving cyclization of an enamine intermediate.[9] Furthermore, it could be demonstrated that the cyclization of the hemiaminal in the rate-determining step was consistent with all the observations reported for the reaction.[8] The same methodology has been applied to elucidate the mechanism of furan synthesis, and the results are contained in this paper.

Results

A. Cyclization of 3,4-Disubstituted 2,5-Hexanediones. When the rates of pyrrole formation of *d,l* (**1r**) and meso (**1m**) isomers of 3,4-dimethyl-2,5-hexanedione with methylamine was studied in 0.1 N HCl,[8] the expected pentamethylpyrrole was not detected. The product of cyclization was found to be 2,3,4,5-tetramethylfuran (**15a**). In addition, the rates of formation of furan from these two diastereomers were not equal, as was the case with the synthesis of pyrroles in nonacidic solutions. The dependence of the rate of furan formation on the stereochemistry of the dione was confirmed with the *d,l* (**2r** and **3r**) and meso (**2m** and **3m**) isomers of 3,4-diethyl- and 3,4-diisopropyl-2,5-hexanediones.

The rate of cyclization of a pure diastereomer of **1** or **2** in aqueous solutions was determined by measuring the production of furan (**15**) spectrophotometrically (Table 1). In nonaqueous solvents GC analyses yielded the relative concentrations of the dione and the furan, and revealed the extent, if any, of isomerization of the uncyclized dione (Table 2). The order of the reaction was found to be one with respect to the dione. The rate was also dependent on the acid concentration. At each concentration of acid catalyst the reaction was found to satisfy a first order rate equation. The dependence of rate on acid strength was demonstrated by measuring the rates of furan

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Table 1. The Rates of Acid-Catalyzed Cyclization of the Diketones 1 and 2 in Water

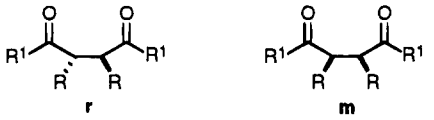
entry	dione[a]	$[H^+]$ M	$k \times 10^6$, s^{-1}
1	**1r**	0.50	57.25 ± 1.02
2	**1m**	0.50	64.93 ± 1.00
3	**2r**	0.50	73.82 ± 0.81
4	**2m**	0.50	14.11 ± 0.25
5	**2r**	0.97	160. 32 ± 0.91
6	**2m**	0.97	32.68 ± 0.35
7	**2r**	0.5 ($D^+ - D_2O$)	170.53 ± 1.60
8	**2m**	0.5 ($D^+ - D_2O$)	36.70 ± 0.67

[a] The initial concentration of **1** (or **2**) was 1 mM.

Table 2. The Rates of Cyclization of the Aliphatic Diketones in Nonaqueous Solvent

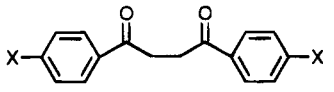
entry	dione	reaction condition[a]	$k \times 10^4$, s^{-1}
1	**1r**	E	9.423 ± 0.37
2	**1m**	E	18.88 ± 1.15
3	**2r**	E	21.10 ± 1.70
4	**2m**	E	10.19 ± 0.34
5	**2r**	BF_3	21.36 ± 0.56
6	**2m**	BF_3	9.330 ± 0.41
7	**2r**	B	–[b]
8	**3r**	B	5.189 ± 0.54
9	**3m**	B	0.843 ± 0.06

[a] The initial concentration of the diketone was 100 mM. E, stirring in 5 mM HCl-ethanol at 23.5 °C; BF_3, stirring in $CHCl_3$ containing 100 mM BF_3–OEt_2 at 23.5 °C; B, refluxing in benzene containing 0.5 mM *p*-TsOH. [b] The rate of reaction was too rapid to measure accurately.



r **m**

	R^1	R
1	CH_3	CH_3
2	CH_3	C_2H_5
3	CH_3	$CH(CH_3)_2$
4	C_6H_5	CH_3
5	C_6H_5	C_2H_5



6, X = H
7, X = CH_3
8, X = OCH_3
9, X = NO_2

generation of **2r** and **2m** in water containing different concentrations of HCl. In the range 0.188 to 0.969 N HCl the plot of rate constant k_{H^+} against $[H^+]$ was linear (Figure 1).

In the Paal–Knorr synthesis of pyrroles, irrespective of the structure of the starting dione, the racemic pair always reacted with the primary amine faster than the symmetric isomer. Surprisingly the meso isomer of 3,4-dimethyl-2,5-hexanedione (**1m**) was found to cyclize to furan **15a** faster than the racemic mixture **1r**. However, the order of reactivity was reversed when the substituents at the 3- and 4-positions of hexanedione were ethyl groups.

B. Cyclization of 1,4-Diphenyl-1,4-butanedione and Its Derivatives. Initial work with aliphatic diones was next extended to the diastereomers of the aromatic diketones 2,3-dimethyl- and 2,3-diethyl-1,4-diphenyl-1,4-butanediones (**4** and **5**). The cyclization of these diones

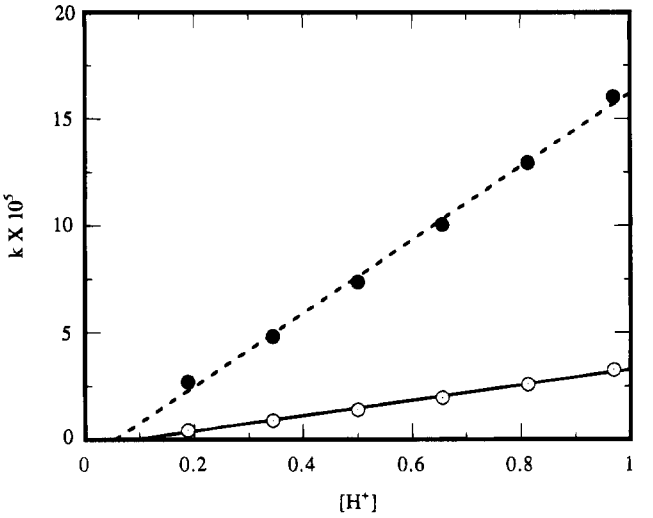


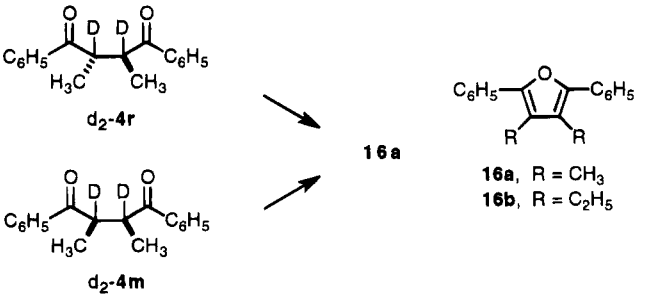
Figure 1. Dependence of the observed rate of formation of furan from 3,4-diethyl-2,5-hexanedione on the stoichiometric concentration of HCl; (●) **2r**, and (○) **2m**.

Table 3. The Rates of Furan Formation from 2,3-Dimethyl- and 2,3-Diethyl-1,4-diphenyl-1,4-butanediones[a]

entry	dione	dione concentration	$k \times 10^6$, s^{-1}
1	**4r**	10	14.65 ± 0.41
2	**4m**	10	32.46 ± 0.90
3	d_2-**4r**	10	1.83 ± 0.042
4	d_2-**4m**	10	4.97 ± 0.034
5	**4r**	20	13.14 ± 0.44
6	**4m**	20	28.32 ± 0.58
7	**5r**	20	5.62 ± 0.12
8	**5m**	20	2.16 ± 0.061

[a] The dione was stirred in 1:1 MeOH–$CHCl_3$ containing 4 mM HCl.

to 3,4-dimethyl-2,5-diphenylfuran (**16a**) or 3,4-diethyl-



d_2-**4r**

d_2-**4m**

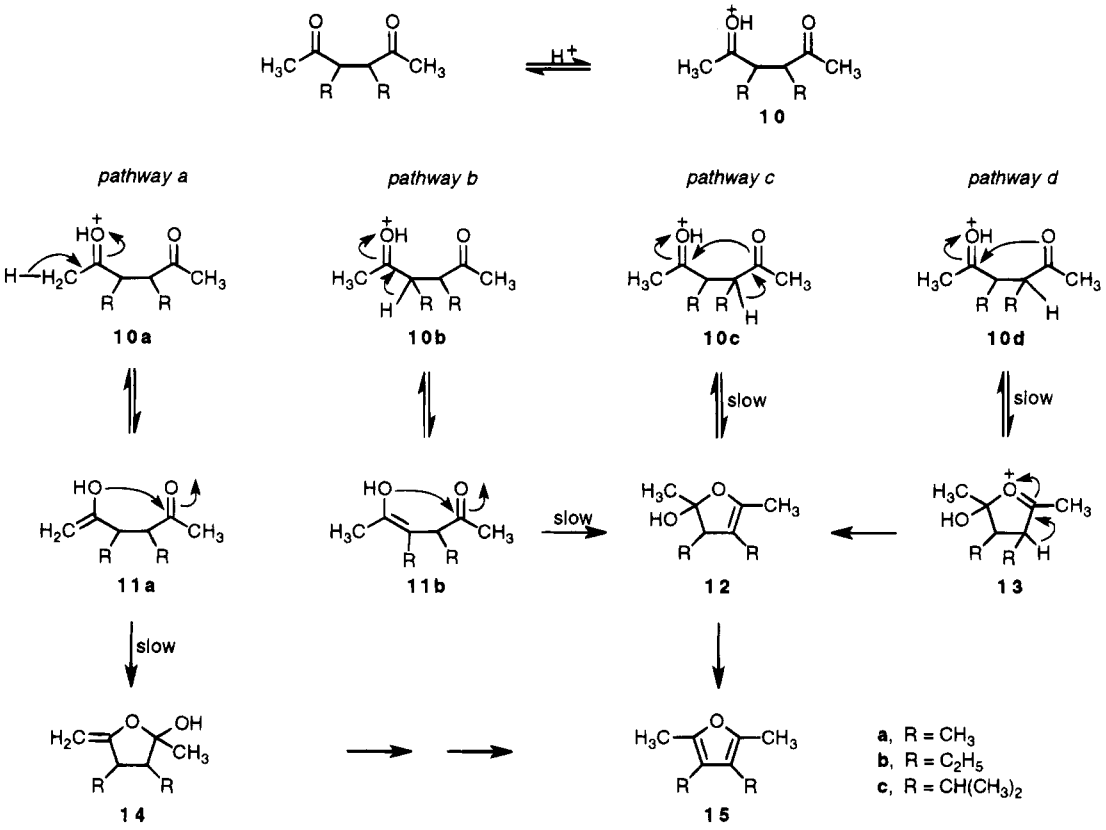
16a

16a, R = CH_3
16b, R = C_2H_5

2,5-diphenylfuran (**16b**) was carried out in a mixture of methanol and $CHCl_3$ catalyzed by HCl. As in the case of aliphatic diones **1** and **2**, *meso*-2,3-dimethyl-1,4-diphenyl-1,4-butanedione (**4m**) cyclized more rapidly than the *d,l* isomer **4r** while the racemic mixture **5r** of 2,3-diethyl-1,4-diphenyl-1,4-butanedione formed furan at a faster rate (Table 3). Under the conditions of the reaction the isomer purity of the starting diastereomer was preserved. The plot of the pseudo first order rate constant with respect to hydrochloric acid concentration was linear; the slope was 3.440×10^{-3} M^{-1} s^{-1} for **4r** and 6.537×10^{-3} M^{-1} s^{-1} for **4m**.

Each of the two carbons between the carbonyl functions loses a hydrogen atom during the reaction. In order to determine whether the C–H bond cleavage occurred before or after the rate-limiting step, racemic and symmetrical isomers of 2,3-dideuterio-2,3-dimethyl-1,4-diphe-

Scheme 1



nyl-1,4-butanediones (d_2-**4r** and d_2-**4m**) were prepared by deuterium exchange under basic conditions. The rate constants for HCl-catalyzed cyclization of d_2-**4r** and d_2-**4m** were compared with those for **4r** and **4m** measured at identical conditions (Table 3). Deuterium labeling was found to lower the rate of cyclization by a factor of 7.99 for **4r** and by a factor of 6.53 for **4m**. This compares well with the most recent value of 7.9 + 0.8 reported[10] for the primary isotope effect for the acid-catalyzed C–H bond cleavage during enolization of acetone. In addition, unchanged d_2-**4r** and d_2-**4m** retained their labels, suggesting that under these conditions cyclization took place more rapidly than enolization.

The relationship between the electron density at the carbonyl function and the reaction rate was studied with 1,4-diphenyl-1,4-butanedione (**6**) and its dimethyl (**7**), dimethoxy (**8**) and dinitro (**9**) derivatives. The rates of furan formation for **9** was very slow in methanol containing HCl at room temperature. Refluxing in benzene containing a catalytic amount of *p*-TsOH[11,12] was found to bring about the ring closure of **6** and its derivatives. The reaction proceeded with fewer side products under these conditions than under other commonly used conditions involving anhydrous $ZnCl_2$ and acetic anhydride[13] or heating with polyphosphoric acid.[14] The order of cyclization was found to be **7** > **8** > **6** >> **9** (Table 4) which was identical to the order for enolization of the corresponding acetophenones.[15–17]

Table 4. The Effect of Para Substitution on the Rate of Cyclization of 1,4-Diphenyl-1,4-butanediones[a]

entry	dione (substituent)	product	$k \times 10^6$, s^{-1}
1	**6** (H)	**18a**	1.246 ± 0.019
2	**7** (CH_3)	**18b**	2.647 ± 0.026
3	**8** (OCH_3)	**18c**	1.615 ± 0.066
4	**9** (NO_2)	**18d**	0.01203 ± 0.00098

[a] The diketone (100 mM) was refluxed in benzene containing 1 mM *p*-TsOH.

The presence of isopropyl groups at the 3- and 4-positions of **3** caused considerable steric hindrance during ring closure. The reaction was very slow in ethanol containing HCl. In refluxing benzene, **3r** and **3m** were found to undergo ring closure at measurable rates. The racemic mixture **3r** formed furan **15c** much faster than the other diastereomer, and isomerization was not detected.

Discussion

Possible steps in the Paal–Knorr reaction of substituted hexanediones leading to furans are shown in Scheme 1. The first step most likely is the rapid and reversible addition of a proton to one of the carbonyls to give **10** and is kinetically inseparable from the subsequent steps.[18]

The positively charged **10** can go through one of four possible pathways. Pathway b involves enolization of the protonated dione **10b** to the monoenol **11b** followed by attack of the enol on the carbonyl group. This is the

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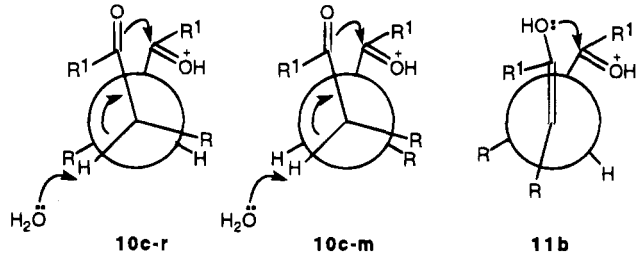
generally accepted mechanism[4-6] and the slowest step could either be the enolization of **10b** or the ring closure to dihydrofuran **12**. One variation of this pathway is that the enol intermediate can have the structure **11a** with a methylene group (pathway a). Enolization and cyclization could occur simultaneously (**10c**) leading to **12** (pathway c).[19,20] Dehydration of the dihydro intermediate **12** (or **14**) to the product **15** can be expected to be rapid and irreversible due to aromatization.

The last pathway (d) is similar to the rate-determining oxygen protonation mechanism described for the enolization of ketones.[18] The electrophilic attack of one carbonyl oxygen on the other protonated carbonyl to give an oxonium intermediate (**13**) is followed by rapid proton removal from **13**. If loss of hydrogen occurs after the rate limiting step deuterium substitution at the 3- and 4-positions of 3,4-dimethyl-2,5-hexanedione (**1**) may be expected to cause only a slight variation in the rate of cyclization. Treatment of **1** with D_2O under basic conditions resulted in many side reactions and deuterio analogs could not be obtained. However, deuterium substitution was successful with 2,3-dimethyl-1,4-diphenyl-1,4-butanedione, as was the separation of the diastereomers d_2-**4r** and d_2-**4m**. The presence of larger deuterium atoms may also be expected to retard the reaction rate through the eclipsing effect (see later). During pyrrole formation the difference in reactivity attributable to such an effect was found to be very small.[8] The large decrease in reaction rates (7.99 and 6.53) observed during the cyclization of d_2-**4r** and d_2-**4m** compared to **4r** and **4m** suggests that the difference in reactivity is due to a primary isotope effect, requiring that the carbon-hydrogen bond be broken during or before the rate limiting step. This does not support pathway d.

The unequal rates of cyclization of the diastereomers of 3,4-dialkyl-2,5-hexanediones **1**–**3** in aqueous solutions or in organic solvents are in apparent discord with the slow cyclization of the monoenol **11b**. Since **11b** is common to both the *d,l* and meso isomers, they would be expected to react at the same rate. However, the rates for the two diastereomers are not equal, although the faster reacting isomer is not always the same. In addition, starting with a pure diastereomer, if enolization of **10b** is occurring at a faster rate than cyclization of the resulting monoenol **11b**, conversion of a part of the unchanged dione to the other diastereomer can be anticipated during the reaction. Again, in water and alcohol under mildly acidic conditions, isomerization does not compete with ring closure. Both of these observations are incompatible with cyclization of the monoenol **11b** in the rate-determining step.

The results discussed so far are consistent with a rate-limiting step involving either the enolization of the protonated dione to form **11b**[18] or the cyclization of **10c**. Enolization is brought about by the removal of the hydrogen α to the protonated carbonyl group. In cyclization of **10c** the hydrogen next to the nonprotonated carbonyl function is eliminated leading to the electrophilic attack of the developing enol on the protonated carbonyl. The rate of acid-catalyzed enolization is known to be not very sensitive to the structure of the ketone.[18] Hence, the large differences in reactivity between diethyl (**2**) and diisopropyl (**3**) derivatives of 2,5-hexanedione or the differences between the two diastereomers **3r** and **3m** of 3,4-diisopropyl-2,5-hexanedione could not be explained by their different rates of enolization. The concerted cyclization to form **12** (pathway c) seems to explain the kinetic results better than pathways b and d and will be considered in some detail.

The difference in reactivities between the diastereomers of a γ-diketone can be easily explained by looking at the Newman projections across C-3 and C-4 atoms of the protonated dione **10c**. The most probable conformation during ring closure is represented. The approach of a base (such as water) to remove a proton from the carbon atom adjacent to the carbonyl group is less hindered for the meso isomer (**10c–m**) than the racemic mixture (**10c–r**) which has the alkyl group in the proximity of the ionizing proton. On the other hand, the alkyl groups at the 3- and 4-positions are brought into an unfavorable eclipsed orientation during the cyclization of the meso isomer.[8] When R is a methyl group, the eclipsing effect is apparently less important than the facile access of the base, and the meso isomers of 3,4-dimethyl-2,5-hexanedione (**1m**) and 2,3-dimethyl-1,4-diphenyl-1,4-butanedione (**4m**) undergo ring closure faster than their racemic counterparts.



As the substituents become larger, the advantage gained by the meso isomer may be overshadowed by the eclipsing effect of the substituents. Increased steric hindrance could lead to a decrease in the overall rate of reaction. As the substituents become bulkier, the meso isomer is expected to undergo ring closure less readily than the *d,l* mixture. This is shown by the meso isomers of diethyl (**2**) and diisopropyl (**3**) derivatives of hexanedione. The ratios of the rates of reaction of the diastereomers ($k_{d,l}/k_{meso}$) for **2** and **3** are 2.1 and 6.2, respectively. These values are much smaller than those observed for these diones during pyrrole formation.[7] While the *d,l* diastereomer **2r** cyclized in $CHCl_3$ containing BF_3-OEt_2 only twice as rapidly as the meso isomer **2m**, the rates of pyrrole formation for these diastereomers with isobutylamine in chloroform differed by a factor of 57. This is also reflected in the activation energies for the cyclization of **2r** (16.18 + 0.13 kcal/mol) and **2m** (17.69 + 0.14 kcal/mol) in water. These values determined in the temperature range 16–39 °C differ only by 1.51 kcal/mol compared to the difference of 4.25 kcal/mol for pyrrole formation in the same temperature range. The smaller difference in reactivities between the diastereomers is probably due to the fact that, unlike the pyrrole ring, the furan oxygen is devoid of any substitution. The developing five membered ring may be able to assume a puckered half-chair conformation to reduce the strain caused by eclipsing of the substituents at the 3- and 4-positions.

Cyclization of the enol **11b** in the rate-limiting step, on the other hand, cannot explain the dependence of dione reactivity on the size of the R group. Enolization

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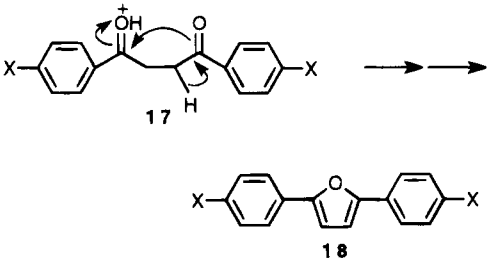
toward the methyl group to give **11a** followed by slow cyclization could also explain the stereochemical aspects of cyclization of the substituted hexanediones **1–3**. This pathway is also in agreement with the observation that the preferred orientation of acid-catalyzed enolization of 3-methyl- and 3-ethyl-2-pentanones is through proton removal at the methyl group.[21] However, the inequality in the rate of furan formation between the diastereomers is also observed with 1,4-diphenyl-1,4-butanediones **4** and **5** that can form a double bond only toward the other carbonyl group. On this basis, product formation through pathway a does not appear likely.

The catalytic constants (k_{cat}) for the acid-catalyzed cyclization of *d,l*- (**2r**) and *meso*-3,4-diethyl-2,5-hexanediones (**2m**) were determined from the first order rate constants at different H^+ concentrations (Figure 1) to be 17.12×10^{-5} and 3.604×10^{-5} M^{-1} s^{-1}, respectively. The k_{cat} for enolization of acetone in HCl solutions has been reported to be 2.56×10^{-5} M^{-1} s^{-1} at 25 °C[10] and the constants for other methyl ketones are in the same range.[21] A similar value for the enolization of **2** can be anticipated and it will be smaller than the catalytic constants for cyclization. This suggests that enolization occurs at a slower rate than the furan formation, discounting pathway a which requires the formation of **11a** be faster than its cyclization to **14**. It also explains why, under the conditions studied, isomerization of diastereomers of diones **1–5** and loss of deuterium labels from d_2-**4r** and d_2-**4m**, that are consequences of enolization toward the middle of the molecule, are not observed during furan formation.

The rates of cyclization of **2r** and **2m** to 3,4-diethyl-2,5-dimethylfuran (**15b**) were also determined in D_2O containing DCl to study the solvent isotope effect. The reaction proceeded more rapidly in D_2O than in H_2O. This suggests that protonation occurs prior to the rate-determining step.[22,23] The solvent isotope effect for the enolization of acetone has been determined by iodination in sulfuric acid solution (1.64[24]) or in perchloric acid solution (1.53[25]). Furan formation was found to be more positively influenced by D_2O than enolization of acetone or acetaldehyde. The rate of furan formation was improved by the deuterated solvent by a factor of 2.3 for **2r** and by 2.6 for **2m**.

Furan formation from 1,4-diphenyl-1,4-butanedione (**6**), and dimethyl (**7**), dimethoxy (**8**), and dinitro derivatives (**9**) were compared (Table 4) to understand the effect of electron density at the carbonyl function on the rate of the reaction. Substitution at the para positions was chosen so that the effect of the substituents would be electronic and not steric. The ratio of the rate constants for sulfuric acid-catalyzed enolization of acetophenone and its derivatives with methyl, methoxy, and nitro groups at the 4-position has been reported to be 1:1.16:1.17:0.57.[15] Same orders of ratios have been reported for enolization in 10% acetic acid at 60 °C[17] and in water at 25 °C.[16] The effect of substituents on the rates of furan formation from **6** through **9** was similar. Although methyl substitution (**7**) was found to be more effective than methoxy (**8**), both increased the rate of the reaction. The formation of the intermediate undergoing cyclization (**10**) is facilitated by the presence of electron-donating groups. The presence of an electron-withdrawing nitro group, on the other hand, reduced the rate of cyclization by 2 orders of magnitude. Both the initial protonation and the subsequent attack of the developing enol **17** seem to be severely affected by the reduced electron density on the carbonyl groups.



17

18

a, X = H
b, X = CH_3
c, X = OCH_3
d, X = NO_2

Conclusion

In this paper several kinetic experiments have been described which permit a better understanding of the mechanism of the Paal–Knorr synthesis of furans. The key observations are the following: (1) The acid catalyzed ring closure of 1,4-diones exhibits a primary isotope effect and a positive solvent isotope effect. (2) The *d,l* and meso diastereomers of the diones **1–5** form furan at unequal rates; the meso isomer is consumed faster when the substituents at the carbons between the carbonyls are methyls while the *d,l* cyclizes faster when the substituents are larger. (3) Cyclization seems to proceed at a higher rate than enolization, since neither isomerization of the diones **1–5** nor loss of deuterium labels from the dideuterio analogs d_2-**4r** and d_2-**4m** was observed. (4) The formation of furan from 1,4-diphenyl-1,4-butanedione (**6**) is adversely affected by nitro groups at the 4-positions, but facilitated by methoxy groups at those positions. These results are consistent with initial protonation of the dione followed by a rate-determining attack on the protonated carbonyl group by the enol being formed at the other carbonyl group (**10c**).

Experimental Section

General. GC analyses were carried out with a Varian Aerograph 1400 fitted with a 3% OV-101 column (at 20 mL/min flow rate of nitrogen carrier gas) and a flame ionization detector (30 mL/min of hydrogen and 200 mL/min of air). The data from GC were handled by a Hewlett-Packard integrator 3394-A. Single wavelength measurements and wavelength scans were recorded with a Hewlett-Packard spectrophotometer 8452A. NMR and mass spectra were obtained as described before.[8,26] Boiling and melting points were uncorrected. TLC was run on aluminum sheets coated with silica (Merck 60 F), and column chromatography was performed with silica (200–400 mesh) with a positive pressure of argon applied on the column. Hexane and ethyl acetate were mixed in the proportion indicated to obtain the solvent systems. Hydrochloric acid (1 N from Fisher Scientific) was used directly or with appropriate dilution. Deuterium oxide containing DCl (20%) was diluted with D_2O to obtain 1 N DCl. Solutions of

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Table 5. Physical Data for Furans

furan	reaction time, h	yield %	mp or bp/Torr °C	UV maxima[a] λ nm (ε)	mass spectrum	^{1}H NMR signals	^{13}C NMR signals
2,3,4,5-tetramethylfuran (**15a**)[13]	0.5	79	52–54/40	222 (4 040)	124 (M^+), 123 (M − H)	1.82 (s), 2.14 (s)	8.33, 11.28, 114.92, 143.97
3,4-diethyl-2,5-dimethylfuran (**15b**)[13]	1	70	70–72/20	222 (4 250)	152 (M^+), 137 (M − CH_3)	1.07 (t), 2.16 (s), 2.29 (q)	11.40, 15.34, 16.86, 120.78, 144.0
2,5-dimethyl-3,4-bis(1-methylethyl)furan (**15c**)	18	60	20–25/0.2		180 (M^+), 165 (M − CH_3)	1.21 (s), 2.22 (s), 2.81 (m)	13.05, 22.62, 24.28, 124.6, 143.0
3,4-dimethyl-2,5-diphenylfuran (**16a**)[11]	17	80	117–118	318 (28 130)	248 (M^+)	2.22 (s), 7.24 (d), 7.42 (t), 7.70 (t)	9.93, 125.7, 126.6, 128.5
3,4-diethyl-2,5-diphenylfuran (**16b**)[29]	40	72	80–81	318 (26 600)	276 (M^+), 261 (M − CH_3)	1.27 (t), 2.70 (q), 7.25 (d), 7.41 (t), 7.71 (d)	14.90, 17.14, 125.2, 126.6, 128.4
2,5-diphenylfuran (**18a**)[30]	48	70	88–89	324 (32 100)	220 (M^+)	6.72 (s), 7.26 (m), 7.39 (m), 7.74 (m)	107.2, 123.66, 127.3, 128.66, 130.7, 153.27
2,5-bis-(4-methylphenyl)furan (**18b**)[14]	48	75	167–168	328 (37 250)	248 (M^+)	2.36 (s), 6.65 (s), 7.19 and 7.63 (q)	21.25, 106. 4, 123.6, 128.2, 129.3, 137.0, 153. 16
2,5-bis-(4-methoxyphenyl)furan (**18c**)[30]	40	80	194–195	332 (51 500)	280 (M^+), 265 (M − CH_3)	3.84 (s), 6.57 (s), 6.93 and 7.66 (q)	55.3, 105.6, 114.1, 124.0, 125.0, 152. 7, 158. 8
2,5-bis(4-nitrophenyl)furan (**18d**)[30]	50	75	270–272	396 (36 000)	CI (NH_3) 328 (M + NH_4)$^+$. EI 309 (M − 1)$^+$		

[a] The UV spectra of **15a** and **15b** were recorded in 0.5 N HCl while those of others were taken in 95% ethanol.

HCl in methanol and ethanol were prepared by appropriate dilution of concd HCl with methanol or absolute ethanol and used within 1 week. All solutions of HCl (or DCl) were standardized using potassium hydrogen phthalate.

γ-Diketones. The disubstituted hexane-2,5-diones **1**–**3** were prepared and the diastereomers were separated according to the published methods.[7] The diones **6**–**9** were obtained by oxidative coupling of the silyl enol ethers of the corresponding acetophenones.[27,28]

Propiophenone and butyrophenone were oxidized with lead dioxide to obtain **4** and **5**, respectively. The diastereomers were separated by column chromatography (20:1) and the structures were assigned on the basis of ^{13}C NMR spectra.[7,8] The slower moving isomer (bp 144–146 °C/0.15 Torr) of **5** was assigned as ***d,l*-2,3-diethyl-1,4-diphenyl-1,4-butanedione** (**5r**): ^{13}C NMR δ 10.37 (CH_3), 22.13 (CH_2), 46.75 (CH), 128.35, 128.48, 132.74, 137.60 (phenyl ring), 204.17 (carbonyl); MS *m*/*z* 294 (M^+), 148 ($PhCOCH_2CH_2CH_3$), 105 (C_6H_5CO). The other isomer (mp 147–148 °C) providing identical MS was the meso (**5m**): ^{13}C NMR δ 11.70 (CH_3), 25.35 (CH_2), 49.04 (CH), 128.35, 128.72, 133.25, 138.54 (phenyl ring), 204.21 (carbonyl).

2,3-Dideuterio-2,3-dimethyl-1,4-diphenyl-1,4-butanedione (d_2-4). A solution of **4** (1.33 g, 5 mmol) in pyridine (25 mL) was stirred with D_2O (10 mL) and 40% NaOD (50 μL) for 48 h. Pyridine was removed *in vacuo* and the residual solution was extracted with dichloromethane (3 × 30 mL). The extracts were combined and concentrated, and the residue was subjected to one additional deuterium exchange. The diastereomers in the crude product were separated by column chromatography (9:1): d_2-**4r**, 800 mg, mp 87.5–88.5 °C; d_2-**4m**, 150 mg, mp 102.5–103.5 °C; MS of either isomer *m*/*z* 268 (M^+) and 105 (C_6H_5CO).

Furans. All the furans reported here were prepared by the following general procedure.[12] A solution of the diketone (5 mmol, 1 mmol for **9**) in benzene (75 mL) containing *p*-TsOH (19 mg, 0.1 mmol) was refluxed with azeotropic removal of water. After the solvent was removed, furans with alkyl substituents (**15**) were isolated by distillation and others were purified by column chromatography (20:1 for **16a**, **16b**, **18a**, and **18b**, 3:1 for **18c**, and 1:1 for **18d**). The physical and spectral data of the furans are summarized in Table 5.

Kinetics. The rate of cyclization in aqueous solution was followed with a Beckman DU-8 spectrophotometer in the kinetic mode. The temperature of the cuvet holder was electronically controlled by the machine and the actual temperature inside the cuvet was measured with a thermistor probe of YSI thermometer 43TA. The wavelength for monitoring the reaction was 222 nm. In a representative run 3.1 mL of 1.0 N HCl taken in a cuvet was equilibrated at 25 °C in the spectrophotometer, **2r** (100 μL of 32 mM solution in water) was rapidly added and mixed, and the kinetic program was immediately started. Wavelength scan was performed on the reaction solution at the end of the reaction to assure the presence of the product. The first order rate constant was arrived at from the absorbances at various time points.[8] Furthermore, in order to examine the extent of isomerization during the reaction, **2r** (17 mg, 0.1 mmol) was stirred with 1 N HCl (100 mL) for 1 h and extracted with $CHCl_3$ (2 × 20 mL). The extracts were combined and evaporated, and the residue was found by GC to contain only **15b** and **2r**. Similar results were obtained when **2m** was treated with acid for 18 h.

In order to determine the activation energy the rate of cyclization was measured at 4 or 5 °C intervals in the temperature range 16 to 40 °C (±0.25 °C).

Acid-catalyzed cyclization of **1** and **2** in ethanol and that of **3** in benzene were followed by GC. For the cyclization of **1**,

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the oven temperature was kept at 80 °C for 4 min and heated at the rate of 20 °C/min for 4 min. The initial isothermal heating was done at 100 °C and 120 °C for **2** and **3**, respectively. In a typical kinetic run a solution of **2r** (34 mg in 1.0 mL of ethanol) was mixed with 10 mM HCl in ethanol (1.0 mL) and the mixture was stirred in a water bath at 23.5 °C; 1 μL of the reaction mixture was injected every 10 min for 70 min. The concentration of furan calculated from the relative areas under the peaks for **2r** and **15b** led to the first order rate constant (Table 2). In addition, the isomerization of uncyclized **2r** to **2m** was not detected. Cyclization of **2r** (and **2m**) in $CHCl_3$ in the presence of BF_3–OEt_2 was similarly studied by GC. The two reactants (0.2 mmol each) were mixed in 2 mL of $CHCl_3$ to start the reaction.

The generation of furan from **4r**, **4m**, d_2-**4r**, d_2-**4m**, **5r**, and **5m** was carried out in a mixture (1:1) of methanol and $CHCl_3$. A solution of the dione in $CHCl_3$ (5 mL) was stirred with an equal volume of methanol containing HCl. The reaction flask was immersed in a large water bath whose temperature remained at 23.5 + 0.25 °C. At various time points aliquots were removed from the reaction solution and diluted appropriately with ethanol, and the absorbance at 320 nm was measured. Cyclization of **4** (10 mM) was also followed in $CHCl_3$–MeOH containing different concentrations of HCl. The reaction mixtures were checked by TLC (9:1) to confirm the formation of furan and the absence of isomerization. In the case of d_2-**4r** and d_2-**4m** the reaction mixture was purified by column chromatography, and the unreacted starting diones and **16** were analyzed by GC-MS.

The cyclization of 1,4-diones requiring higher temperature to react was followed in the following way. Benzene (9.95 mL) containing 1 mmol of dione **3r** (or **3m**) was refluxed in an oil bath maintained at 80 °C. A solution of *p*-TsOH (50 μL of 100 mM solution in ethanol) was added and samples were removed at various time points. The relative amounts of **3r** (or **3m**) and **15c** were determined by GC. For the cyclization of **6**, **7**, **8**, or **9**, 0.1 mmol of dione was used and twice the amount of *p*-TsOH was added. Aliquots (100 μL) were diluted with ethanol, and the absorbance at the maximum wavelength of **18** was measured to determine the concentration of the product. The first order rate constants were calculated as described before.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of 2,5-dimethyl-3,4-bis(1-methylethyl)furan (**15c**) (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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