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Relative Stabilities of *Endo-Exo* Isomeric Furan Derivatives and the Kinetics of Their Cleavage in Acid Solutions

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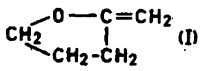
The acid-catalyzed hydrolysis of 2-methylenetetrahydrofuran (I) and its *endo*-cyclic isomer, 2-methyl-4,5-dihydrofuran (II), and that of the unsubstituted *endo* compound, 2,3-dihydrofuran (III), have been kinetically studied in aqueous solutions containing different acid catalysts. It is shown that the reactions exhibit general acid catalysis with a Brønsted α of approximately 0.55. The deuterium solvent isotope effect, k_D/k_H, for the lyonium ion-catalyzed reaction is approximately 0.32. These facts and the influence of structure on the kinetic values suggest that the reactions take place by a mechanism in which a proton transfer from the catalyst is the rate-determining stage.

The value of the standard free energy change, $\Delta G°$, for the isomerization reaction, *exo* → *endo*, is -1.64 ± 0.10 kcal/mole, as determined by infrared measurements on equilibrium mixtures. This free energy change is about the same as the difference between the free energies of activation of the isomers in their hydrolytic cleavage, and thus the kinetic effect of the position of the double bond depends primarily on the energy difference of the initial states of hydrolysis.

The relative stabilities of *endo* and *exo* forms of unsaturated five-membered cyclic systems is discussed in terms of σ-bond energies and nonbonded interactions.

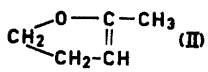
The thermodynamic stabilities of isomeric *endo*- and *exo*-cyclic olefins, 1-methylcyclenes and methylenecyclanes, have been the subject of a number of recent studies.[1–6] In the case of five-membered homocyclic rings, the *endo* form has been found to be more stable than the *exo* form by approximately 4 kcal/mole,[4,5] whereas the stability difference was found to be almost 10 kcal/mole in related five-membered heterocyclic olefins, 4-methyl-1,3-dioxoles and 4-methylene-1,3-dioxolanes.[7] It was also shown that this great difference in stability of the latter compounds had a pronounced influence on the kinetics and mechanisms of their hydrolytic decomposition.

The present paper describes equilibrium and kinetic data for the closely similar five-membered heterocyclic ring system in 2-methylenetetrahydrofuran (I) and 2-methyl-4,5-dihydrofuran (II):



(I)

exo-cyclic



(II)

endo-cyclic

The primary aim of the study was to confirm the conclusions about stabilizing effect of the six p-π ring electrons postulated for 1,3-dioxoles,[7] because this stabilization could not be present in dihydrofurans. As the present compounds, unlike 1,3-dioxolanes and 1,3-dioxoles, are not acetals, and thus a hydrolysis mechanism similar to that of acetals is wholly excluded, a study of their relative stabilities and kinetics of hydrolysis provides direct information on the effect of the position of the double bond on the kinetics of cleavage of *endo*- and *exo*-cyclic vinyl ethers.

EXPERIMENTAL

Preparation of materials. 2-Methylenetetrahydrofuran was prepared from 2-chloromethyltetrahydrofuran and potassium hydroxide according to Paul and Tchelitcheff.[8] The chloromethyltetrahydrofuran used was synthesized by a standard method.[9] The crude 2-methylenetetrahydrofuran was dried and carefully fractionated from potassium hydroxide pellets. It was ascertained by infrared spectroscopy (see below) that the purified compound contained less than 1 % of its *endo*-cyclic isomer, 2-methyl-4,5-dihydrofuran. The following physical constants were recorded for 2-methylenetetrahydrofuran: b.p. 52—54°C/118 torr, n_D^{20} 1.4462.

2-Methyl-4,5-dihydrofuran was also prepared according to the directions of Paul and Tchelitcheff.[8] B.p. 80—82°C/760 torr, n_D^{20} 1.4309, d_4^{20} 0.8960. The purity was controlled by gas chromatography and infrared spectroscopy.

2,3-Dihydrofuran was synthesized according to Paul *et al.*[10] by isomerization of commercial 2,5-dihydrofuran in the presence of potassium *tert.*-butylate at 170°C. B.p. 55.0—55.5°C/760 torr, n_D^{20} 1.4215, d_4^{20} 0.9170. The purity as determined by gas chromatography was over 99.5 %.

Acetone dimethyl acetal, which was needed as a standard substance when measuring the hydronium ion concentrations of a number of buffer solutions, was a commercial product, which was purified by repeated fractional distillation from metallic sodium until no impurities were detected in gas chromatograms. B.p. 79.5°C/740 torr, n_D^{20} 1.3776, d_4^{20} 0.8410.

Kinetic experiments. The hydrolytic decomposition reactions were monitored by following the disappearance of the furan derivative spectrophotometrically, using the same technique as in the previous studies of vinyl ethers.[7,11] The absorbances were measured at about 235 mμ. In the case of acetone dimethyl acetal, the increase of the carbonyl peak at 269 mμ was measured. First-order kinetics was obeyed in all cases.

Excepting the rate of hydrolysis of 2,3-dihydrofuran, which could be studied also in dilute perchloric acid solutions, the rates were usually too fast to be measured in solutions of strong acids, and buffer solutions had to be used. However, the catalytic coefficients of the hydronium ion could be calculated from the results of measurements in a series of buffer mixtures with constant [HA]/[A^-] and constant ionic strength by determining the least-square intercepts of the plots of the first-order rate coefficient against [HA]. This intercept, which was equal to $k_{H_3O^+} \times [H_3O^+]$, allowed a calculation of $k_{H_3O^+}$, if the hydronium ion concentration of the buffer solution was known. The latter was measured using a standard substance, acetone dimethyl acetal, which is known to be subject to specific hydronium ion catalysis, by determining its rate coefficient both in dilute perchloric acid solutions and in the buffer solutions under the same conditions. Table 1 gives the experimental first-order rate coefficients measured for the vinyl ethers in different buffer solutions, and Table 2 the rate coefficients of acetone dimethyl acetal in two buffer solutions. The plots of the first-order rate coefficients of Table 1 against the respective values of [HA] were fairly linear for all the buffer solutions.

Table 1. First-order rate coefficients k of the hydrolysis of a number of furan derivatives in different buffer solutions at 25°C. *A*, $H_2PO_4^-$ and HPO_4^{2-} in a molar ratio of 1 to 1. *B*, $H_2PO_4^-$ and HPO_4^{2-} in a molar ratio of 7 to 3. *C*, HCO_3^- and CO_3^{2-} in a molar ratio of 5 to 1. *D*, HCOOH and $HCOO^-$ in a molar ratio of 5 to 1. The ionic strengths in the buffer solutions were adjusted with sodium chloride. [HA] denotes the concentration of the more acidic component of the buffer system.

Compound	Buffer system	Ionic strength	[HA] mole/l	$10^3\ k$, s^{-1}
2-Methylenetetrahydrofuran	A	0.070	0.001111	5.92
»	»	»	0.00222	10.24
»	»	»	0.00333	14.50
»	B	»	0.001556	9.28
»	»	»	0.00311	15.33
»	»	»	0.00467	21.3
»	C	0.200	0.0303	0.453
»	»	»	0.0606	0.807
»	»	»	0.0909	1.178
2-Methyl-4,5-dihydrofuran	A	0.070	0.001111	1.013
»	»	»	0.00222	1.932
»	»	»	0.00333	2.724
»	B	»	0.001556	1.516
»	»	»	0.00311	2.751
»	»	»	0.00467	3.988
»	C	0.200	0.0303	0.829
»	»	»	0.0606	0.1599
»	»	»	0.0909	0.236
2,3-Dihydrofuran	D	1.000	0.0667	4.078
»	»	»	0.1333	4.986
»	»	»	0.2000	5.86

Table 2. First-order rate coefficients k of the hydrolysis of acetone dimethyl acetal in phosphate buffer solutions (ionic strength 0.070 M) at 20°C and the calculated hydronium ion concentrations. $k_{H_3O^+} = 386 \pm 2\ M^{-1}s^{-1}$, as derived from data for the reaction in perchloric acid solutions under the same conditions.

Buffer system	$10^4\ k$, s^{-1}	$10^7 \times [H_3O^+]$ calc.
A: $[H_2PO_4^-]/[HPO_4^{2-}] = 1/1$	1.010	2.61
B: » = 7/3	2.228	5.77

Endo-exo equilibrium measurements. It was found that 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran were readily interconvertible in acid conditions. In cyclohexane solutions containing *p*-toluenesulfonic acid (about 10^{-4} M), the equilibrium was reached in a few hours at room temperature.

Attempts to analyze the equilibrium mixtures by gas chromatography were unsuccessful, no column packing was found in which the *exo* form was stable. However, the analysis was possible by infrared spectroscopy. The method was based on measurement of the characteristic absorption maxima of both forms, namely at 795 cm^{-1} for 2-methylenetetrahydrofuran and at 720 cm^{-1} for 2-methyl-4,5-dihydrofuran. Standard mixtures of both compounds were prepared by dissolving known amounts in cyclohexane (which does not absorb in this wavelength region), and the heights of the respective infrared

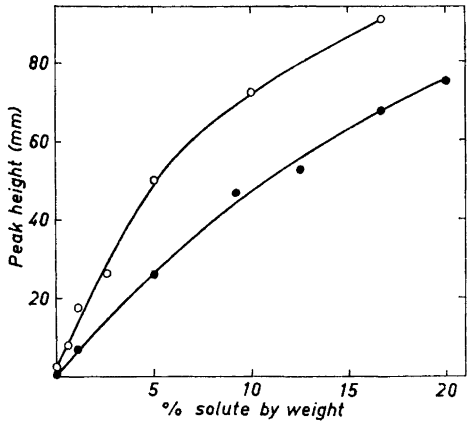


Fig. 1. The heights of the infrared absorption peaks of 2-methylene-tetrahydrofuran (○) at 795 cm^{-1} and 2-methyl-4,5-dihydrofuran (●) at 720 cm^{-1} as functions of weight percentage in cyclohexane solutions. The thickness of the potassium bromide cell was constant (approximately 0.025 mm).

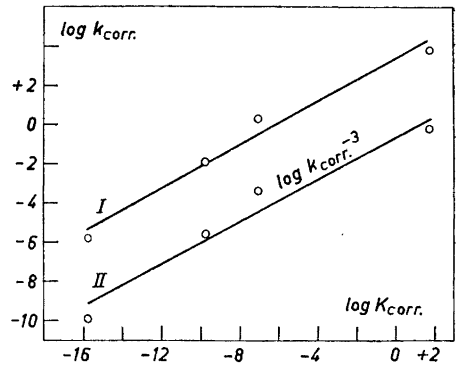


Fig. 2. Brønsted plots for the hydrolysis of 2-methylenetetrahydrofuran (I) and 2-methyl-4,5-dihydrofuran (II) in water at 25°C. The acid dissociation constants $K_{corr.}$ and the rate coefficients $k_{corr.}$ are those obtained by making the appropriate statistical corrections.

peaks were plotted as functions of concentration. Fig. 1 shows the calibration curves obtained in this way which were used in the analysis of the equilibrium mixtures. The ground levels, from which the both peak heights were measured, were the absorbances at 570 cm^{-1}.

The infrared measurements were performed on a Perkin-Elmer Grating Infrared Spectrophotometer, Model 337.

RESULTS AND DISCUSSION

The results of the experiments in different buffer solutions indicate that the cleavage of the investigated furan derivatives exhibits general acid catalysis. In Table 3 are given the catalytic coefficients of different acids calculated by the method of least squares from the data of Table 1. For 2-methylene-

Table 3. Catalytic coefficients k_{HA} (in $M^{-1}s^{-1}$) of different acids in the protolytic cleavage of furan derivatives in water at 25°C.

Substrate	k_{HA}				
	H_3O^+	HCOOH	$H_2PO_4^-$	HCO_3^-	H_2O
2-Methylenetetrahydrofuran	6000		3.86	1.20×10^{-2}	1.6×10^{-6}
2-Methyl-4,5-dihydrofuran	590		0.783	2.53×10^{-2}	1.2×10^{-7}
2,3-Dihydrofuran	1.43	1.34×10^{-2}			

tetrahydrofuran and 2-methyl-4,5-dihydrofuran, the values of the catalytic coefficients of the hydronium ion, $k_{H_3O^+}$, were determined from the data for the reactions in phosphate buffers as described in the experimental part, whereas it was possible to measure the corresponding values for 2,3-dihydrofuran in dilute (about 10^{-2} M) perchloric acid solution. The catalytic coefficients of the solvent water were determined from data for the reactions in bicarbonate-carbonate buffer solutions similarly as in the earlier studies of vinyl ethers.[11]

Fig. 2 shows the Brønsted plots for 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran based on the values determined for the different catalyzing acids. The least-square slopes of the plots, the Brønsted α values, are 0.55 ± 0.06 and 0.55 ± 0.09 for 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran, respectively. Thus the sensitivity of the reactions to the acid strength of the catalyst is very similar to that of open-chain vinyl ethers.[11]

Table 4 contains values of the catalytic coefficient of the lyonium ion for the hydrolysis of 2,3-dihydrofuran in heavy water, along with the respective values in light water. The deuterium solvent isotope effect, $k_D/k_H = 0.32$ at 25°C, is comparable with that for open-chain vinyl ethers: 0.41 for 2-chloroethyl vinyl ether, and 0.34 for ethyl vinyl ether.[12] Thus all of the data obtained are well accounted for if it is assumed that the hydrolysis mechanism with a rate-determining proton transfer [11,12] is also applicable to the cleavage of the investigated furan derivatives.

The value of A_H/A_D calculated from the values of Table 4 seems to be abnormally low, *viz.* 0.12. In proton transfer reactions, this generally points to the presence of proton tunneling.[13] Although this pertains to the primary deuterium isotope effect, in which a proton or deuteron is transferred in the rate-determining stage, it is not certain whether similar arguments apply to the gross isotope effects when going from H_2O to D_2O. In this case, the values of k_D/k_H involve, in addition to the primary effect of the proton which is being transferred, also the equilibrium constant of the isotopic disproportionation in the hydronium ion as well as the isotopic fractionation factor relating to the two additional hydrogens that are not transferred in the formation of the transition state.[11] A determination of the pre-exponential factor of the equilibrium constant φ_1 (for notations, see Ref. 11) should allow more definite

Table 4. Deuterium solvent isotope effect in the lyonium ion-catalyzed hydrolysis of 2,3-dihydrofuran in water.

			15°C	25°C	35°C	45°C
$k_{H_3O^+}$	(in H_2O)	$M^{-1}s^{-1}$	0.605	1.429	3.17	6.35
$k_{D_3O^+}$	(in D_2O)	»	0.1717	0.458	1.073	2.53

$E_H = 14.3$ kcal/mole, $\log A_H = 10.64$, $\Delta S_H^{\ddagger} = -11.3$ e.u.
$E_D = 16.2$ » $\log A_D = 11.55$, $\Delta S_D^{\ddagger} = -7.6$ e.u.

conclusions about the possible occurrence of proton tunneling, but suitable methods are still lacking.

The actual magnitudes of the rate coefficients of the hydronium ion-catalyzed reaction (Table 3) are comparable with those of the open-chain analogs. 2,3-Dihydrofuran (1.43 $M^{-1}s^{-1}$) hydrolyzes at almost the same rate as ethyl vinyl ether[11] (1.87 $M^{-1}s^{-1}$). Introduction of an α-methyl group increased the rates of aliphatic vinyl ethers by a factor of several hundreds, and similarly, 2-methyl-4,5-dihydrofuran hydrolyzes about 400 times faster than 2,3-dihydrofuran. The observation that 2-methylenetetrahydrofuran hydrolyzes about ten times faster than its *endo*-cyclic isomer, 2-methyl-4,5-dihydrofuran, is discussed in detail below.

The equilibrium measurements in cyclohexane solutions (see experimental part) gave the following equilibrium concentrations of the *endo-exo* isomer pairs and the standard errors at 25°C:

2-Methylenetetrahydrofuran	5.9 ± 1.0 %
2-Methyl-4,5-dihydrofuran	94.1 ± 1.0 %

The standard free energy change, $\Delta G°$, for the isomerization, *exo*-cyclic → *endo*-cyclic, is thus −1.64 ± 0.10 kcal/mole. From the values of Table 3 for the hydronium ion-catalyzed reaction one can calculate for the difference between the standard free energies of activation, $\Delta G_0^{\ddagger}$ (*exo*) − $\Delta G_0^{\ddagger}$ (*endo*), a value of −1.37 kcal/mole with an estimated accuracy of 0.15 kcal/mole. The latter difference applies also to the reactions catalyzed by the other acids because the Brønsted α values are practically the same for both compounds. The difference in the hydrolysis rates is in this case primarily accounted for by the difference in the stabilities of the initial states, the transition states being at almost the same free energy levels, as illustrated in Fig. 3.

It is interesting to note that the free energy difference between the investigated *endo*- and *exo*-cyclic furan derivatives is only 1.6 kcal/mole, whereas in the case of the corresponding homocyclic compounds, 1-methylcyclopentene and methylenecyclopentane, the respective difference is 4.1 kcal/mole.[4,5] An explanation for this is given below in terms of the changes in hybridization of the carbon atoms and the conformational energy differences involved in the *exo-endo* isomerization reactions.

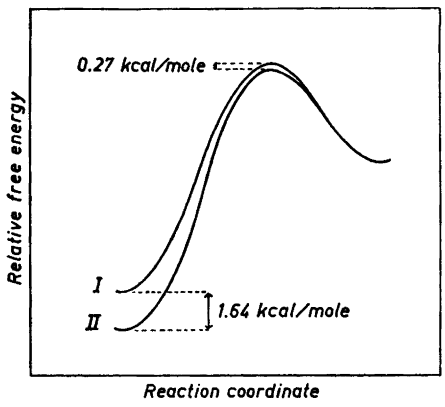
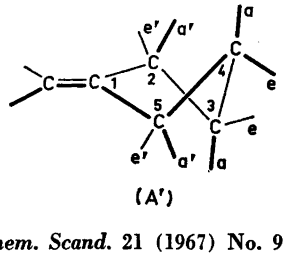


Fig. 3. Free energy profiles for the hydrolyses of 2-methylenetetrahydrofuran (I) and its *endo* isomer, 2-methyl-4,5-dihydrofuran (II).

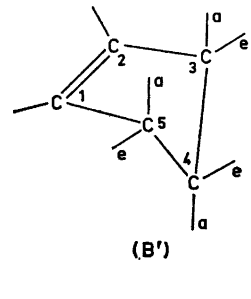
Let us first consider the isomerization of methylenecyclopentane to 1-methylcyclopentene:

Apart from stereochemical changes, the isomerization is accompanied by changes in the hybrid states of some of the carbon atoms, which alter the respective bond energies. The latter energies have been recently discussed by Dewar and Schmeising,[14] and their data may be applied to the present case. We are using here these bond energy values merely as empirical, without committing ourselves to any specific interpretation of these energies. The net change from (A) to (B) is to replace one sp^3—sp^3 carbon-carbon bond by a sp^3—sp^2 bond, and one hydrogen-to-sp^2-carbon and two hydrogen-to-sp^3-carbon (secondary) bonds by three hydrogen-to-sp^3-carbon (primary) bonds. According to the corresponding bond energy values,[14] the calculated enthalpy difference for the net process is −2.9 kcal/mole, which is about 1 kcal/mole less than the experimental value −3.9 kcal/mole.[4] Although the carbon-hydrogen bond energy values of Dewar and Schmeising empirically account for the mutual nonbonded interactions of the carbon-hydrogen bonds, these apply only to systems in which a state of minimum interaction is attained by a staggering of these bonds, as in aliphatic systems. Complete staggering is, however, not possible in a five-membered ring as in the compounds studied here, and in view of this circumstance the agreement between the observed and calculated energy differences is satisfactory. At this point it is interesting to note that the observed enthalpy difference, −2.4 kcal/mole, [2] in the corresponding six-membered compounds, methylenecyclohexane and 1-methylcyclohexane, differs but slightly from the value calculated above from the σ-bond energy differences.

In the corresponding furan derivatives, 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran, the situation is quite similar to that in the five-membered olefins discussed above so far as the changes in the hybrid states of the carbon atoms and their effects on the respective σ-bond energies are concerned. This implies that the smaller energy difference of the *exo* and *endo* forms in comparison with those of the cyclic olefins must be derived from conformational factors, *i.e.*, from the differences in nonbonded interactions. The conformation of the cyclopentane ring in methylenecyclopentane is the



(A')



(B')

"half chair" (A') with the sp^2-carbon located on the axis of symmetry,[15] and it is most probable that also 2-methylenetetrahydrofuran assumes the same conformation. The only possible conformation for isomeric 1-methylcyclopentene and 2-methyl-4,5-dihydrofuran is an "envelope" form (B'), as implied by the unsaturated *endo* ring bond and by the minimization of the C—H eclipsing strains. In the envelope form of 1-methylcyclopentene (B') the 5-carbon-hydrogen bonds are staggered with the 4-carbon-hydrogen bonds and therefore the replacement of the 5-methylene group by an oxygen atom does not significantly affect the conformational energy differences. A different situation prevails in the half-chair form of methylenecyclopentane (A'), in which the 5-hydrogens cannot be staggered with the 4-hydrogens. The resulting eclipsing strain is completely eliminated when the 5-methylene group is replaced by oxygen. The net result is that methylenecyclopentane will be on a higher energy level relative to that of 1-methylcyclopentene as compared with the corresponding furan derivatives, 2-methylenetetrahydrofuran and 2-methyl-4,5-dihydrofuran. The nonbonded interactions between the CH-bonds of the methylene group and those on the 5-carbon atom of methylenecyclopentane, being absent in 2-methylenetetrahydrofuran would have an effect in the same direction, although the contribution of this energy difference is probably less significant.

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