

The Stereochemistry of the 2,5-Dialkyl Derivatives of 1,3-Dioxolone-(4) and the Kinetics of Their Neutral Hydrolysis

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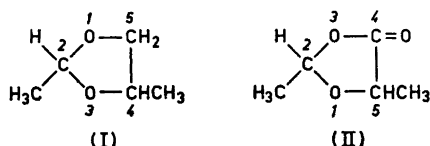
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Several 2,5-dialkyl derivatives of 1,3-dioxolone-(4) have been synthesized by a condensation reaction from aldehydes and α -hydroxy-acids. It has been established that at ordinary temperatures the *cis* and *trans* forms of these compounds undergo rearrangement so readily that the pure isomers cannot be isolated, but equilibrium mixtures are obtained which contain 60–69 moles per hundred of the *cis* isomers. The structural assignments were made on the basis of kinetics and equilibrium data.

The 2,5-dialkyl dioxolones hydrolyzed readily in water and the individual rate coefficients of the two different isomers were in each case determined from the overall rate by a method developed earlier. It was found that the relative rates of the pairs of isomers are almost independent of the 2-alkyl substituent present; *e.g.*, for 2-alkyl-5-methyl-1,3-dioxolones k_{cis}/k_{trans} is 4 to 5 when the alkyl group is methyl, ethyl, propyl or *sec.*-propyl. On the contrary, a change in the 5-alkyl group alters significantly the relative rates of the isomers. Thus k_{cis}/k_{trans} is approximately 20 for 5-ethyl-substituted dioxolones.

The mechanisms of the hydrolysis and isomerization reactions have been discussed in terms of the possible stereochemical conformations of the isomers.

The *cis* and *trans* forms of 2,4-dimethyl-1,3-dioxolane (I) and 2,5-dimethyl-1,3-dioxolone-(4) and the kinetics of their hydrolysis reactions were discussed in connection with earlier studies of 5-membered cyclic acetals and acetal-esters.¹⁻³ Although (I) underwent hydrolysis and the *cis-trans* interconversion only in acidic media, whereas (II) exhibited these reactions also under neutral or alkaline conditions, both compounds were found to display



certain structural features that were quite similar and suggested that the reaction mechanisms were closely related. The present study was undertaken in order to obtain more extensive experimental information about the influence of different alkyl substituents on the kinetics of the isomeric forms of the derivatives of (II) and on the stereochemical factors involved.

EXPERIMENTAL

Materials. The general method used to prepare the 2,5-dialkyl derivatives of 1,3-dioxolone-(4) was to boil under reflux for several hours a mixture of α -hydroxy-acid, aldehyde (in 50 % excess to the acid) and benzene (about 500 ml per mole of the acid) in an azeotropic distillation assembly in the presence of *p*-toluenesulfonic acid (0.05 M) as catalyst. After the water initially present in the reactants and that formed in the reaction had been removed, the mixture was neutralized and dried with anhydrous potassium carbonate and the excess aldehyde and benzene distilled off under reduced pressure. The crude 2,5-dialkyldioxolone thus obtained was then carefully distilled 2–3 times under reduced pressure in a Todd precision fractionation assembly.

Similar to 2,5-dimethyldioxolone,³ the distillates did not exhibit any tendency to separate into two different products having different boiling points, *i.e.*, the *cis* and *trans* forms, but boiled at approximately constant temperatures. Moreover, the preparations behaved in gas chromatography like single compounds giving single symmetrical peaks with no shoulders. On the contrary, the kinetic analyses showed that the preparations were equilibrium mixtures of the two isomers. As the boiling points of closely related compounds, the *cis* and *trans* isomers of 2,4-dimethyldioxolane,^{1,2} differ by 3° and the both isomers give distinct peaks in gas chromatography, the conclusion can be drawn that in the case of the dioxolones a ready interconversion of the two isomers is taking place. In fractional distillation and in gas chromatography, it is the lower-boiling isomer that is preferably removed from the equilibrium mixture, and in the remaining solution the equilibrium is continuously attained due to the facile interconversion reaction. Thus the compounds behave like single compounds with no isomeric forms during their purification and gas-chromatographic analysis.

Table 1. Physical constants for 2,5-dialkyl derivatives of 1,3-dioxolone-(4).

	B.p. (°C)/pressure (torr)	d_4^{20}	n_D^{20}	$[R]_D$ obs.	$[R]_D$ calc.
2,5-Dimethyldioxolone	91/42	1.0778 ^a	1.4070 ^a	26.51	26.32
2-Methyl-5-ethyldioxolone	84/38	1.0512	1.4155	31.03	31.16
2-Ethyl-5-methyldioxolone	83/39	1.0508	1.4164	31.16	31.16
2,5-Diethyldioxolone	92/30	1.0253	1.4221	35.73	35.80
2-Propyl-5-methyldioxolone	98/34	1.0231	1.4207	35.72	35.80
2- <i>sec.</i> -Propyl-5-methyldioxolone	88.5/30	1.0210	1.4191	35.67	35.78

^a at 25°C

In Table 1 are given physical constants for the compounds synthesized by the method described above. The total yields varied from 60 to 80 % calculated from the amounts of the α -hydroxy-acids used, but only the distillates of highest purity were employed in the kinetic experiments. The purities of these preparations were in each case also controlled by gas-chromatographic analyses. The values calculated for mole refractions were based on the atom and group refractivities given by Vogel.⁴

Table 2. Hydrolysis of the equilibrium mixture of the *cis* and *trans* isomers of 2-methyl-5-ethyl-1,3-dioxolone-(4) in water at 17.00°C. $\Delta = \xi_{\text{calc}} - \xi_{\text{obs}}$, k_t = the apparent rate coefficient calculated from the ordinary first-order rate equation.

t (in min)	ξ_{obs}	ξ_{calc}	$10^6 \times k_t$ (in s ⁻¹)	
5	0.054	0.053	185	
9	0.094	0.093	183	
13	0.132	0.130	181	$k_1 = 2.65 \times 10^{-4} \text{ s}^{-1}$
18	0.174	0.174	177	$k_1 = 1.53 \times 10^{-5} \text{ s}^{-1}$
23	0.219	0.214	180	
29	0.260	0.259	173	
34	0.294	0.293	171	$\frac{\Sigma \Delta^2}{n-1} = 1.5 \times 10^{-6}$
40	0.332	0.330	168	
48	0.378	0.376	165	
58.5	0.412	0.427	151	
70	0.477	0.475	154	
85	0.529	0.526	148	
98	0.564	0.563	141	
110.5	0.590	0.592	135	
129	0.625	0.626	127	
152	0.660	0.659	118	
175	0.683	0.683	109	
253	0.736	0.732	88	
325	0.755	0.757	72	
415	0.777	0.779	58	
590	0.814	0.812	46	
750	0.840	0.838	41	
835	0.848	0.850	38	

Kinetic measurements. The experimental method used to follow the hydrolysis of 2,5-dialkyldioxolones was that described in detail in connection with the earlier study of 2,5-dimethyldioxolones.³ This method was based on the observation that the hydrolysis reactions of all single dioxolones obey strictly the first-order rate law and thus the rate law for a mixture of two dioxolones, like that present in a mixture of the *cis* and *trans* forms of a 2,5-dialkyldioxolone, can be written

$$\xi = \alpha[1 - \exp(-k_1 t)] + (1 - \alpha)[1 - \exp(-k_2 t)] \quad (1)$$

In this equation, ξ is the fraction of the initially added dioxolone that is hydrolyzed during time t , α and $(1 - \alpha)$ are the mole fractions of the components initially present, and k_1 and k_2 their first-order rate coefficients, respectively. An accurate determination of the constants α , k_1 , and k_2 from the experimental values of ξ requires, first, that α and $(1 - \alpha)$ are of comparable magnitude and, second, that the rate coefficients k_1 and k_2 are substantially different. Fortunately, both of these requirements were satisfied in the reactions studied. The suppression of systematic errors to a minimum was effected as described earlier.³ The numerical calculation of the parameters of eqn. (1) was made on a Wegematic-1000 computer. Table 2 shows the data for a typical run.

RESULTS AND DISCUSSION

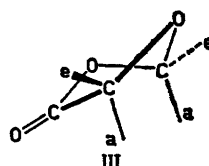
The equilibrium ratio of the isomers. Table 3 shows the equilibrium compositions of the isomer mixtures studied in the present work including the earlier data on 2,5-dimethyldioxolone.³ It is seen that there are but slight variations in the equilibrium molar ratio of the isomers. The average value of this ratio corresponds to a free-energy difference ($\Delta G = G_{\text{Form II}} - G_{\text{Form I}}$)

of about + 360 cal/mole, which is of the same magnitude as that between the isomers of 2,4-dimethyldioxolone.^{1,2} In the case of the latter compounds, the *cis* structure was suggested for the more stable form, primarily on the basis of kinetic results.

Table 3. The compositions of the equilibrium mixtures of the geometric isomers of 2,5-dialkyldioxolones at 25°C. Isomer I = the faster-hydrolyzing isomer for which the *cis* structure is proposed.

	% Isomer I	% Isomer II
2,5-Dimethyldioxolone	69	31
2-Methyl-5-ethyldioxolone	67	33
2-Ethyl-5-methyldioxolone	68	32
2,5-Diethyldioxolone	62	38
2-Propyl-5-methyldioxolone	60	40
2- <i>sec.</i> -Propyl-5-methyldioxolone	64	36

The small differences between the stabilities of the isomers of 2,5-dialkyldioxolones presumably originate from the non-planarity of the dioxolone ring, in a similar fashion as those between the dimethyl derivatives of cyclopentane.⁵ For the latter compounds an "envelope form" of the ring has been suggested.⁵ The preferable model for the dioxolone ring is that confirmed for cyclopentanone and methylenecyclopentane,^{6,7} *viz.* a "half-chair" form with the doubly-bonded carbon atom located on the average plane of the ring. This conformation is exaggerated in sketch (III), from which it is seen that the



(III)

Half-chair form of the dioxolone ring

atoms or groups attached to 2- and 5-carbon atoms may assume either equatorial (*e*) or axial (*a*) positions. In the *cis* forms of 2,5-dialkyldioxolones the bond-eclipsing involving the two alkyl groups will be negligible when they are placed in equatorial positions. In the *trans* isomers, however, one of the alkyl groups must be located in the less favorable axial position and hence they may be expected to be slightly less stable. This suggests that the isomers denoted by "Isomer I" in Table 3 are the *cis* forms, which is also supported by the kinetic data (*vide infra*).

Kinetics and mechanism of hydrolysis. The rate coefficients measured at different temperatures for the neutral hydrolysis of 2,5-dialkyldioxolones are collected in Table 4, Table 5 giving derived kinetic quantities. The energies and entropies of activation were calculated from the plots of $\log k$ against $1/T$. In all cases the individual rate coefficients k_1 and k_2 conformed to the Arrhenius equation.

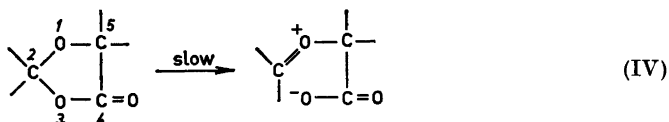
Table 4. The first-order rate coefficients for the hydrolysis of the *cis* and *trans* isomers of 2,5-dialkyldioxolones in water at different temperatures.

	°C	$10^4 \times k$ (in s^{-1})	
		Isomer I	Isomer II
2,5-Dimethyldioxolone	15	1.97	0.523
»	25	5.80	1.51
»	35	15.7	4.25
2-Methyl-5-ethyldioxolone	17	2.65	0.153
»	25	6.34	0.403
»	35	17.5	1.24
2-Ethyl-5-methyldioxolone	25	6.31	1.25
»	35	18.4	3.83
2,5-Diethyldioxolone	17	3.22	0.142
»	25	7.39	0.364
»	35	19.3	1.04
2-Propyl-5-methyldioxolone	25	9.02	1.92
2- <i>sec.</i> -Propyl-5-methyldioxolone	17	1.48	0.264
»	25	3.86	0.790
»	35	10.4	2.01

Table 5. Energies and entropies of activation and the relative rate coefficients at 25°C for the hydrolysis of the isomers of 2,5-dialkyldioxolones.

	E (in kcal)		ΔS^* E.U.		k_I / k_{II} at 25°C
	Isomer I	Isomer II	Isomer I	Isomer II	
2,5-Dimethyldioxolone	18.76	18.92	-12.4	-14.5	3.8
2-Methyl-5-ethyldioxolone	18.62	20.62	-12.7	-11.5	15.7
2-Ethyl-5-methyldioxolone	19.56	20.73	-9.5	-9.3	5.0
2,5-Diethyldioxolone	17.65	19.69	-15.7	-14.8	20.3
2-Propyl-5-methyldioxolone	—	—	—	—	4.7
2- <i>sec.</i> -Propyl-5-methyldioxolone	19.21	20.04	-11.5	-12.1	4.9

In connection with the earlier studies of the neutral hydrolysis of 2-methyl- and 2,2-dimethyl-substituted dioxolones^{3,8} it was suggested that the rate-determining stage of these reactions involves a heterolytic ring opening at the 2-carbon-3-oxygen bond leading to a mesomeric intermediate, which then



reacts rapidly with the solvent. This conclusion was reached by comparisons with the kinetic data relating to the corresponding acetals, the derivatives of 1,3-dioxolane, and by arguments based on the actual magnitudes of the rate coefficients and derived kinetic quantities. A number of additional observations

can be made from the present results which conform to this mechanism and the *cis* structures proposed for "Isomers I".

An interesting fact is that, although "Isomers I" are thermodynamically slightly more stable than "Isomers II", the former are hydrolyzed 4 to 20 times faster than the latter. This difference in the rates must be due to stereochemical factors influencing the transition states because for a given pair of isomers the polar influences of the substituent alkyl groups must be quite similar. The presence of stereochemical factors is also clearly illustrated by the observation that the nature of the 5-alkyl group influences differently on the rates of hydrolysis of the isomers. Thus, *e.g.*, "Isomer II" of 2-methyl-5-ethyldioxolone hydrolyzes at 25°C about 4 times slower than the corresponding isomer of 2-methyl-5-methyldioxolone (Table 4), whereas in the case of "Isomers I" the situation is reversed, the isomer of the former compound hydrolyzing slightly more rapidly than that of the latter. As a replacement of a 5-methyl group by a 5-ethyl group effects a similar change in the polar factors involved, the different behavior of the isomers must arise from different steric influences on the transition states. It is also seen from Table 4 that, in contrast to 5-alkyl substituents, a change in the 2-alkyl group has almost a similar effect on the hydrolysis rates of the two isomers.

The above facts are readily understood in terms of mechanism (IV), if the faster-hydrolyzing isomers are assigned the *cis* structures. In the transition state of reaction (IV) the 2-carbon-1-oxygen bond will assume a partial double bond character and hence the adjoining bonds will be bent to a certain degree toward a coplanar position. The bond-eclipsing of hydrogens and alkyl groups will be in a minimum when the 2-alkyl group is in, or assumes, an equatorial position and the less bulky 2-hydrogen atom is that which is axially bent toward the inside of the ring. This is in conformity to the observation that the nature of the 2-alkyl group has little if no steric influence on the relative hydrolysis rates of the pairs of isomers. Additionally it may be seen that if there is a 5-alkyl group on the same side of the ring as the 2-hydrogen atom, which is the situation in case of a *trans* form, the bond-oppositions will make the transition state less stable than the probably insignificant hydrogen-hydrogen eclipsing present in the *cis* isomers, and this difference will increase with the bulkiness of the 5-alkyl group. This is in good harmony with the observation that the *cis* isomers of 2-alkyl-5-methyldioxolones hydrolyze faster than the *trans* isomers by a factor of 4 to 5, and that the value of this factor increases to 16—20 when going to 2-alkyl-5-ethyldioxolones (Table 5).

The close resemblance of the above mechanism to that generally accepted for the acid-catalyzed hydrolysis of acetals^{9,10} also implies that the polar influences of the substituent groups on the rates of both reactions should be very similar. Unfortunately, in the reaction under study the situation is complicated by the steric factors arising from the ring structure of the reacting molecules and it thus seems difficult to draw any definite conclusions as to the individual contribution of polar effects. However, one particular case in which this is possible can be foreseen.

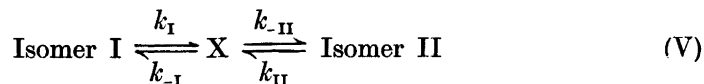
Let us vary the 2-alkyl group, *i.e.*, [the aldehyde component of the dioxolone, keeping the 5-alkyl group unchanged. In the case of the *cis* isomers both alkyl groups will be able to assume equatorial positions, and in the trans-

tion states the bond-eclipsing of the two axial hydrogens cannot be significant. Thus it may be concluded that the steric requirements for the hydrolysis of the *cis* forms of dioxolones derived from different aldehydes should be substantially the same, and the variations in their rates of hydrolysis could be solely attributed to changes in the polar character of the 2-alkyl group.

The influence of the structure of the carbonyl component on the rates of hydrolysis of aliphatic acetals and ketals has been extensively investigated by Kreevoy and Taft.¹⁰ As the steric factors could be neglected in this case, the observed changes in the rate could be quantitatively interpreted in terms of the polar substituent constants and the hyperconjugative effect of the α -hydrogens. For instance, the relative rates of the acetals $\text{RCH}(\text{OEt})_2$ in 50 % aqueous dioxane were: 1, 1.08, and 0.66 for $\text{R} =$ methyl, ethyl and *sec.*-propyl, respectively. These relative values may be compared with those of the "Isomers I" of 2-R-5-methyldioxolones, which for the same alkyl groups are at 25° C: 1, 1.09 and 0.67, respectively. Of course, it is a fortunate coincidence that these two sets of values are practically the same, which in terms of the Taft equation only means that the polar reaction constants for these two reactions in the two different media happen to be virtually the same. The important fact is that the structural effects are quite similar and influence in the same directions, which on the basis of the above discussion is in excellent agreement with the *cis* structures of "Isomers I".

The interconversion of the isomers. The mutual transformation of the *cis* and *trans* forms of dialkyldioxolones necessarily involves a cleavage of one of the ring bonds and an attendant inversion of configuration at a carbon atom which contains an alkyl group. There are hardly any other relatively easy routes for this except a rupture of the 2-carbon-3-oxygen bond in a similar fashion as in the hydrolysis reaction (IV). Differing from the latter, in which the intermediate reacts further rapidly with the solvent, it undergoes the reversal of reaction (IV). It is readily noted that this ring closure, owing to the partial double-bond character of 2-carbon-1-oxygen bond of the intermediate, may take place in either of two ways, for one or the other of the oxygen atoms attached to the 4-carbon atom may approach the 2-carbon atom from two opposite directions leading to the different isomers.

The reaction scheme suggested above for the isomeric interconversion can be simply formulated as follows:



Here X is the reaction intermediate, k_I and k_{II} are the rate coefficients for the slow reaction steps, the ring openings in the isomers I and II, and k_{-I} and k_{-II} are the rate coefficients for the respective reverse reactions. The equilibrium constant K of reaction (V) can be expressed in terms of the individual rate coefficients as follows:

$$K = \frac{[\text{Isomer II}]}{[\text{Isomer I}]} = \frac{k_I}{k_{II}} \times \frac{k_{-II}}{k_{-I}} \quad (2)$$

in which, owing to the relative instability of the intermediate, k_{-I} and k_{-II} must be very large in comparison to k_I and k_{II} . The relative magnitudes of these constants can be roughly estimated from the known value of the equilibrium constant K , which is approximately 0.5 in different cases (Table 3), and from the relative rates of hydrolysis of the two isomers. Although the reaction media in the hydrolysis and isomerization reactions are quite different, it should be noted that the rate coefficients k_I and k_{II} of the isomerization refer to reactions similar to those of the rate-determining stages of the hydrolyses of the isomers I and II, respectively. Moreover, it may be concluded that the ratio of these coefficients cannot depend significantly on the medium. If k_I° and k_{II}° are the values of these constants in some standard solvent in which the activity coefficients are unity by definition, we obtain

$$k_I = k_I^\circ \times \frac{f_I}{f_I^*} ; k_{II} = k_{II}^\circ \times \frac{f_{II}}{f_{II}^*} \quad (3)$$

in which the f 's and f^* 's are the activity coefficients of the parent compounds and their respective critical complexes in an arbitrary medium. Because the substrate molecules are very similar here, differing only by their geometric configurations, their activity coefficients should vary with the medium quite similarly, and the same applies to the respective values of the critical complexes. Hence the value of k_I/k_{II} in any medium cannot be very different from its value in water.

The significance of the k_I/k_{II} ratio may be rationalized by considering the experimental values of this quantity measured in water solution, which for 5-methyl-substituted compounds are 4 to 5, and for 5-ethyl-substituted compounds 16 to 20 (Table 5). From eqn. (2), and from the known values of K it is found that the ratio k_{-II}/k_{-I} is approximately 0.1 for 5-methyl and 0.02 for 5-ethyl compounds, respectively. Thus the relative rates of the ring closures are very susceptible to the nature of the 5-alkyl group, in accordance with the stereochemical factors discussed above.

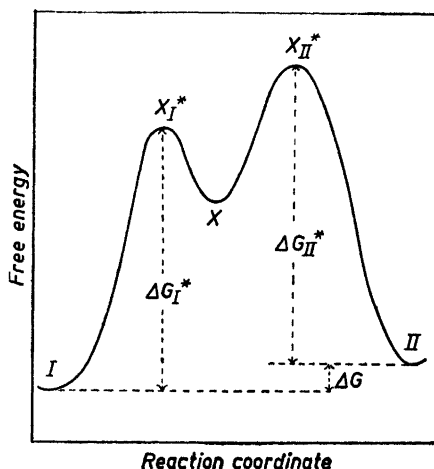


Fig. 1. The free-energy profile showing the relative stabilities of the isomers of 2,5-dialkyldioxolones and the relative rates of the reaction stages involved in their interconversion. X is the reaction intermediate, X_I^* and X_{II}^* are the critical complexes.

Fig. 1 shows, on an arbitrary scale, a free-energy profile for the mechanism suggested for the interconversion of dioxolones. As found experimentally the relative stabilities of the isomers, ΔG , are almost independent of the alkyl groups present. Although the rates themselves are dependent on the nature of the 2-alkyl group, this group does not, however, have any material influence on the relative rates of the two isomers, *i.e.*, the relative heights of the two barriers in Fig. 1 remain substantially the same with different 2-alkyl groups. On the contrary, a change in the 5-alkyl group has a pronounced effect on the relative heights of the barriers depending on the circumstance that in the transition state derived from the *trans* form the bond-oppositions involving the unfavorably placed axial alkyl group become much stronger than in the parent compound.

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