

Studies on Cyclic Anhydrides

IV.* Rate Constants for the Hydrolysis of Some Cyclic Anhydrides Exhibiting Ring Strain

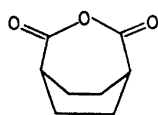
L. EBERSON and L. LANDSTRÖM

*Division of Organic Chemistry 1, Chemical Center, University of Lund,
P.O. Box 740, S-220 07 Lund 7, Sweden*

Hydrolytic rate constants have been measured for a number of cyclic anhydrides exhibiting different kinds of ring strain, *i.e.*, conformational, angle, and torsional strain. In all cases the strained anhydrides are hydrolyzed at significantly higher rates than unstrained model compounds. It is concluded that succinic anhydride has an anomalously high reactivity (relative to glutaric anhydride) due to conformational strain and that the high rate of hydrolysis of maleic anhydride is due to angle strain.

Previous studies on the effect of structural changes on the uncatalyzed hydrolysis of carboxylic anhydrides have revealed some unusual features which are not very well understood. Firstly, the Brown-Brewster-Shechter rule,¹ which predicts higher reactivity for an *exo* double bond in a six-membered ring as compared to an analogous one in a five-membered ring, is not valid for cyclic anhydrides – in contrast to other types of carboxylic acid derivatives.^{2,3} The fact that succinic and glutaric anhydride hydrolyze at almost identical rates was rationalized by Bruice and Pandit³ in terms of a rate-determining attack by the nucleophile, the transition state having the attacked carbonyl group in an essentially *sp*²-hybridized state. Secondly, studies by Hall⁴ demonstrated that a bicyclic anhydride (*1*) possessing ground-state strain, as evidenced by its ability to polymerize spontaneously, was hydrolyzed at a rate comparable to that of anhydride *2*, unstrained by the same criterion. Thus ring strain does not seem to affect the hydrolysis rate, a fact which was again taken to indicate that the transition state must be close to reactants in structure. However, Bruice and Bradbury⁵ in a later study suggested that the hydroxide ion catalyzed and spontaneous hydrolysis of 3-alkyl- and 3,3-dialkylglutaric anhydrides was best interpreted in terms of a transition

* Part III, see Ref. 19.



(1)



(2)

state possessing appreciable sp^3 character at the attacked carbonyl site. This view appears to be commonly accepted now.⁶ Thirdly, the effect of alkyl substituents on the hydrolysis of succinic anhydrides is anomalous. Although the series of acyclic anhydrides below shows the rate behavior to the expected from a consideration of polar and steric effects and benzoic anhydrides behave

R in (RCO) ₂ O	Me	Et	Pr	<i>i</i> -Pr	<i>t</i> -Bu
Relative rate ⁷ at 20°	1	0.59	0.35	0.21	0.030

normally in a Hammett plot,⁸ the successive introduction of methyl groups in succinic anhydride increases the hydrolysis rate in all cases except in the tetramethyl derivative.^{9,10} This trend is contrary to predictions based on the operation of the normal steric and polar effects.

It was earlier suggested by one of us¹⁰ that attempts to explain these and other small rate variations in anhydride solvolysis might be rather meaningless because measurements have been conducted too close to the isokinetic temperature, but this was refuted by Bruice and Bradbury⁵ on the basis of Petersen's criticism¹¹ of the whole concept of isokinetic relationships. Since also Exner's treatment¹² of the isokinetic relationship¹³ suggests that our previous conclusion was overly pessimistic,¹⁰ we have extended our kinetic studies to include a number of additional cyclic and bicyclic anhydrides, chosen to provide information with respect to the problems outlined above.

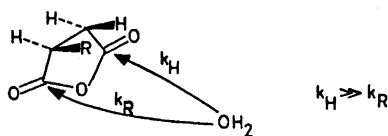
Table 1. Kinetic data for hydrolysis of methyl- and ethylsubstituted succinic anhydrides in aqueous solution at 20.0° and pH 5.20.

Succinic anhydride	Compound No.	k min ⁻¹	k^a corrected	k_{rel}^b
Unsubstituted	3	0.109 ^c	0.027	1.00
Me	4	0.151 ^c	0.050	1.85
2,2-Me ₂	5	0.122 ^c	0.061	2.26
<i>meso</i> -2,3-Me ₂	6	0.247 ^c	0.124	4.54
<i>dl</i> -2,3-Me ₂	7	0.168 ^c	0.084	3.10
Me ₃	8	0.134 ^c	0.134	4.95
Me ₄	9	0.0101 ^c	0.0025	0.092
Et	10	0.102 ^d	0.034	1.25
2,2-Et ₂	11	0.0226 ^d	0.0113	0.042
<i>meso</i> -2,3-Et ₂	12	0.0722 ^d	0.0361	1.33
<i>dl</i> -2,3-Et ₂	13	0.0414 ^d	0.0207	0.77
Et ₄	14	0.0005 ^e	0.00013	0.005

^a Corrected for symmetry factors (see text). ^b Based on corrected rate constants. ^c Taken from Ref. 10. ^d This work. ^e Estimated from rate data at 60° (Ref. 19).

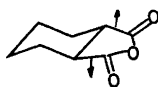
RESULTS

The anomalous trend in the series of methylsuccinic anhydrides appeared in other alkylsuccinic anhydrides also. Table 1 lists the *pseudo*-first-order rate constants for hydrolysis of methyl and ethyl substituted succinic anhydrides (column 3), symmetry-corrected rate constants (column 4), and relative rate constants derived from the corrected values (column 5). Corrections for symmetry were based on the assumption that the rate constant for attack on a carbonyl position on the side where it is flanked by an alkyl group is negligible compared to the rate constant for attack on a carbonyl position flanked by only a hydrogen atom (see below).

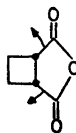


We feel justified in applying this correction from the fact that k_H is roughly 10 times that of k_{CH_3} , and 200 times that of $k_{C_2H_5}$ (see Table 1, anhydrides 3, 9, and 14). It should, however, be stressed that such a correction is only an approximation since the remaining sites available for attack are not equivalent in all cases, especially for the ethyl group which is larger. Thus, the symmetry-corrected rate constant for succinic anhydride will be 0.109/4, for methylsuccinic anhydride 0.151/3, *etc.* Using these corrected rate constants one indeed finds compounds with higher hydrolysis rates than succinic anhydride in the series of ethyl substituted anhydrides also. As expected, steric effects are more pronounced when methyl groups are replaced by ethyl groups, resulting in lower relative rates in the ethyl substituted compounds.

Next we have studied the effect of ring strain on the hydrolytic rates of cyclic anhydrides. Ring strain can be introduced into a cyclic anhydride by annelation of a second carbocyclic ring at the C²-C³ bond of the five-membered anhydride ring (which is assumed to be planar, see below), and by incorporating the six-membered anhydride ring (assumed to exist in a conformation analogous to the cyclohexane chair conformation, see below) in a bicyclic ring system. In this way one applies a constraint which either tends to reduce the planarity of the ring (28) or to increase the angle strain *in the plane* of the ring (25). In *trans*-1,2-cyclohexanedicarboxylic anhydride (28) the torsional force applied at C¹-C² introduces severe strain in the anhydride



28



25

ring due to deviation from planarity, whereas *cis*-1,2-cyclobutanedicarboxylic anhydride (25) is an example of an anhydride ring in which angle strain has been introduced in the ring plane. These principles have been applied to three series of cyclic anhydrides – substituted maleic, succinic, and glutaric anhydrides.

Maleic anhydride hydrolyses at a rate ten times higher than that of succinic anhydride. This has been explained either as a result of ring strain,¹⁴ or as being due to activation of one carbonyl group for nucleophilic attack by electronic relay through the double bond,¹⁵ *i.e.* a conjugation effect.* Table 2 shows rate constants for the hydrolysis of a number of substituted 1-ene-1,2-dicarboxylic anhydrides, chosen to demonstrate that ring strain must be the predominant factor in determining the rate variations observed. As a qualitative measure of ring strain one can assume the strain to be a function of the distance between the carboxyl groups in the hypothetically unstrained molecules of the corresponding dicarboxylic acids,** as measured on molecular models, assuming that a larger distance must be reflected in larger ring strain. In this connection it is interesting to note that 1-cyclobutene-1,2-dicarboxylic acid with a very large distance between the carboxyl groups does not form

Table 2. Kinetic data for hydrolysis of 1-ene-1,2-dicarboxylic anhydrides in aqueous solution at 20.0° and pH 5.20.

Anhydride	Compound No.	k , min ⁻¹	Distance O···O in corresponding diacid ^a
Maleic	15	1.18 ^b	1.68
Methylmaleic	16	0.737 ^b	
Dimethylmaleic	17	0.204 ^c	
1-Cyclopentene-1,2-dicarboxylic	18	1.13 ^b	1.92
Diethylmaleic	19	0.111 ^c	
1-Cyclohexene-1,2-dicarboxylic	20	0.381 ^c	1.44
Diisopropylmaleic	21	0.041 ^d	
2-Norbornene-2,3-dicarboxylic	22	1.19 ^{b,e}	2.11
1-Cycloheptene-1,2-dicarboxylic	23	0.185 ^b	

^a From Ref. 17. ^b This work. ^c From Ref. 27. ^d From Ref. 19. ^e For comparison, *endo*-2,3-norbornedicarboxylic anhydride has a hydrolysis rate constant²⁰ of 0.0181 min⁻¹ at 20°.

a cyclic anhydride at all.¹⁸ Another way of demonstrating the importance of ring strain is to compare structurally related mono- and bicyclic anhydrides. Three such pairs are included in Table 2, the most significant effect being noticeable in the comparison between anhydrides 21 and 22. In both cases

* However, a simple Hückel LCAO–MO calculation¹⁶ shows that the electron density at either carbonyl carbon in succinic anhydride is lower than that at the corresponding positions of maleic anhydride. Hence, from such consideration one would predict that conjugation should make maleic anhydride less reactive than succinic anhydride, all other factors being equal.

** The distance is here taken as the O···O distance, as was done by McCoy¹⁷ in his interpretation of ΔpK values of dicarboxylic acids.

steric and electronic effects are similar; yet the angle-strained tricyclic anhydride reacts roughly 30 times faster. The similarity in hydrolysis rates of maleic anhydride, 18, and 22 in combination with the lower reactivity of the dialkylmaleic anhydrides, shows that the main reason for the high hydrolysis rate of maleic anhydride compared to that of succinic anhydride must be the presence of ring strain in the former.

Similar effects are observed when strain is introduced in the succinic anhydride ring. Table 3 shows the effect of angle strain, in that rate constants for the hydrolysis of a series of cycloalkane-1,2-dicarboxylic anhydrides

Table 3. Kinetic data for hydrolysis of 1,2-cycloalkanedicarboxylic anhydrides in aqueous solution at 20.0° and pH 5.20.

Anhydride	Compound No.	k , min ⁻¹
Succinic	3	0.109 ^a
<i>cis</i> -1,2-Cyclopentanedicarboxylic	24	0.096 ^b
<i>meso</i> -2,3-Dimethylsuccinic	6	0.247 ^a
<i>cis</i> -1,2-Cyclobutanedicarboxylic	25	0.771 ^b
<i>cis</i> -1,2-Cyclopropanedicarboxylic	26	0.449 ^b

^a Ref. 10. ^b This work.

together with rate constants for suitable reference compounds are given. The reference compounds have been chosen to represent cases of similar steric and polar effects. Table 4 lists rate constants for the hydrolysis of some

Table 4. Kinetic data for hydrolysis of twisted 1,2-cycloalkanedicarboxylic anhydrides and certain reference compounds in aqueous solution at 20.0° and pH 5.20.

Anhydride	Compound No.	k , min ⁻¹
<i>cis</i> -1,2-Cyclohexanedicarboxylic	27	0.615
<i>meso</i> -2,3-Diethylsuccinic	12	0.0728
<i>trans</i> -1,2-Cyclohexanedicarboxylic	28	2.33
<i>dl</i> -2,3-Diethylsuccinic	13	0.0414
<i>cis</i> -1,2-Cycloheptanedicarboxylic	29	0.032
<i>trans</i> -1,2-Cycloheptanedicarboxylic	30	0.105

anhydrides in which torsional strain has been introduced, together with suitably substituted reference compounds. In all these cases one can note that the more strained ring has a considerably enhanced rate of hydrolysis, in spite of the fact that steric effects should be smaller in the bicyclic anhydrides.

Table 5. Kinetic data for hydrolysis of six- and seven-membered ring anhydrides in aqueous solution at 20.0° and pH 5.20.

Anhydride	Compound No.	k , min ⁻¹
Glutaric	31	0.113 ^a
<i>meso</i> -2,4-Dimethylglutaric	32	0.0484 ^b
<i>dl</i> -2,4-Dimethylglutaric	33	0.0949 ^b
<i>cis</i> -1,3-Cyclobutanedicarboxylic	34	0.547 ^b
<i>cis</i> -1,3-Cyclopentanedicarboxylic	2	0.200 ^b
<i>cis</i> -1,3-Cyclohexanedicarboxylic	35	0.113 ^b
<i>cis</i> -1,4-Cyclohexanedicarboxylic, monomer	1	0.101 ^b
<i>cis</i> -1,4-Cyclohexanedicarboxylic, polymer	36	0.035 ^b

^a Ref. 10. ^b This work.

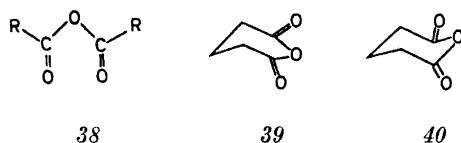
Table 5 gives rate constants for a number of bicyclic anhydrides, in which the glutaric anhydride ring system is incorporated, a few reference compounds, and one representative of the seven-membered ring anhydrides, *I*. This compound has a hydrolysis rate constant almost identical to that of acetic, succinic, and glutaric anhydride. It polymerizes on standing to a polymer which has a hydrolysis rate constant of 0.035 min⁻¹ at 20.0°.

DISCUSSION

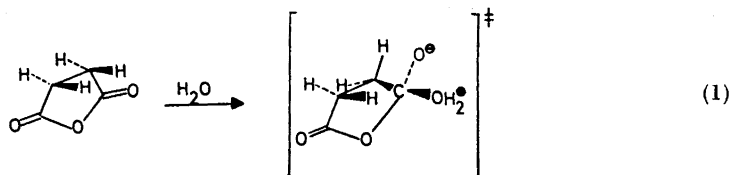
As has already been mentioned in the introduction, aliphatic carboxylic anhydrides behave normally with respect to their hydrolytic rates in that the rate constant decreases regularly as hydrogens on the α carbon are successively substituted for alkyl groups. This limited series of compounds obeys the Taft relationship ($\log k/k_0 = 2.3\sigma^* + 0.54 E_s$) showing that inductive and steric effects of alkyl groups operate in the normal manner; substituted benzoic anhydrides likewise respond normally with respect to the inductive effect of *meta* and *para* substituents⁸ ($\log k/k_0 = 3.19\sigma$). Why is it then that alkyl substituted succinic anhydrides do not follow the predicted pattern?

To answer this problem — a very complex one since rate variations are rather small in the series studied — it is first appropriate to summarize present knowledge about the structure of acyclic and cyclic anhydrides in solution. Acyclic anhydrides have been shown to exist predominantly in the *trans-trans*-conformation 38, analogous to the conformational situation in carboxylic esters and other carboxylic acid derivatives.²¹ Succinic anhydride must necessarily exist in a *cis-cis*-conformation, and it appears to be reasonably well established that the ring is approximately planar.²² Different opinions have been expressed with regard to the structure of glutaric anhydride in solution: Bruce and Bradbury⁵ postulate that it exists in a half-chair conformation (39), whereas Le Fèvre and Sundaram^{22a} favor a chair conformation (40) on the basis of determination of Kerr constants. The latter view will be the favored one in this paper (*vide infra*).

It is now possible to rationalize the trends observed with increasing alkyl substitution in succinic anhydride in the following way. In its ground state succinic anhydride itself must possess considerable conformational strain, since the planar or nearly planar ring structure forces two pairs of C-H bonds to be eclipsed or nearly eclipsed. Moreover, the planarity of the ring causes an unfavorable conformational situation also with respect to the



CH_2-CO bond, in that two C-H bonds are forced out of the favored conformation of this bonding arrangement (which has eclipsing C-H and C=O bonds²³). Following the postulate that the transition state for hydrolysis is very nearly sp^3 hybridized, part of the conformational strain in succinic anhydride will be relieved in the transition state (eqn. 1):



For glutaric anhydride the situation is different, since the chair conformation (40) does not exhibit any conformational strain and hence no change can take place in the transition state in this respect. Therefore, we conclude that the breakdown of the Brown-Brewster-Shechter rule for cyclic anhydrides is due to the fact that succinic anhydride is conformationally strained.

The rate increase due to methyl substitution in the succinic anhydride ring would then be caused by the additional increase in ground state conformational strain relative to that in the transition state due to introduction of eclipsing CH_3-H and CH_3-CH_3 nonbonded interactions. Also, the conformational situation around the CH_2-CO bond in succinic anhydride should be destabilized by substituting one or both hydrogens for methyl groups. This can be inferred from the fact that C-C and C=O bond eclipsing appears to be energetically favored over C-H and C=O bond eclipsing (*e.g.*, by about 1 kcal/mol between the two conformers of isobutyric aldehyde^{23,24}). Therefore, the introduction of alkyl groups in succinic anhydride should lead to an increase in hydrolysis rates, at least in cases where the steric requirements of the alkyl group(s) are not too pronounced. In the series of methyl substituted succinic anhydrides it takes four methyl groups to bring about a rate retardation relative to succinic anhydride, whereas already two of the three diethyl derivatives are hydrolyzed at a slower rate than succinic anhydride because of the greater steric demands of the ethyl group.

In view of the close structural resemblance between cyclic anhydrides and imides, the behavior of these latter compounds should provide a useful test of the above argument. Indeed, succinimide is hydrolyzed *ca.* five times faster than glutarimide in basic solution. This result is consistent with our model, assuming that the unionized imide is the kinetically active species.^{2,25} For *N*-methyloximides the six-membered ring is, however, the more reactive one (albeit only by a factor of 12), in line with the Brown-Brewster-Shechter rule. This may be due to stabilization of the ground state of *N*-methylsuccinimide by the eclipsing of C=O and C-N bonds. The expected rate increase upon substitution by alkyl groups in succinimides is actually observed in the series of methylsubstituted succinamides,²⁶ provided rate constants are corrected for symmetry factors in the same way as done for the succinic anhydrides. The rate increase is small, however, and the reversal of the trend due to steric effects becomes noticeable already for the trimethyl compound.

In the maleic anhydride series it is well established that substitution by alkyl groups leads to stabilization of the anhydride.^{19,27} Dialkylmaleic anhydrides are actually so strongly stabilized that they predominate in the equilibrium with the diacid in aqueous solution, the equilibrium constant, $C_{\text{anhydride}}/C_{\text{diacid}}$, being about 5. This cyclization process has been analyzed in detail¹⁹ and it has been shown that the closer the carboxyl groups of the diacid are to each other the more prone is the diacid to form the anhydride. Hence one would expect that the distance between the carboxyl groups in the diacid would be a qualitative measure of the stability of the ring towards hydrolysis (and other ring opening reactions). Table 2 shows that on the whole this appears to be true, although one has to use O...O distances estimated from molecular models and not directly measure ones. For dialkylmaleic acids no reliable estimate can be made at all; from consideration of the ΔpK values^{17,27} it can, however, be inferred that the O...O distance must be shorter than that in maleic acid. The major reason for the high reactivity of maleic anhydride as compared to succinic anhydride therefore appears to be the presence of ring strain in the former anhydride. Ring strain must be even larger in 18 and 22, but the effect is partly cancelled by the steric effect (compare with 17 and 21, respectively) of the annelated ring systems.

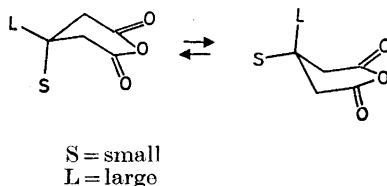
Table 3 shows that ring strain introduced by annelating a small ring increases the hydrolysis rate (25 and 26) as compared to an unstrained compound (24), similarly to the effects observed in substituted maleic anhydrides. Also conformational strain might be of importance here.

By annelating a cyclohexane ring to succinic anhydride a strong twisting force is applied to the anhydride ring, as evidenced by very high hydrolysis rates for compounds 27 and 28 (compare with 12 and 13, respectively). The effect in this case should mainly affect the ground state, since this strain should be partly relieved in the transition state. The cycloheptane ring is much more flexible and does not produce any dramatic effect on annelation to the succinic anhydride ring (29 and 30).

Table 5 shows that incorporation of the six- and seven-membered anhydride ring in bicyclic systems does not lead to any large rate enhancements, except for compound 34. Studies of molecular models indicate that the more flexible 6- and 7-membered anhydride rings should not be as susceptible as the succinic

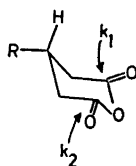
anhydride ring to different types of strain, so these results are the expected ones.

Finally, we wish to make some comments on the treatment used by Bruice and Bradbury⁵ in discussing the conformation of the glutaric anhydride ring (*i.e.* half-chair *vs.* chair conformation). On the assumption that the effect of 3-alkyl substituents on the hydrolysis rate of glutaric anhydride is entirely of steric origin, a Winstein-Holness²⁸ treatment of the conformational equilibrium in eqn. 2 leads to the conclusion that there is no steric hindrance for



the larger substituent being axial in glutaric anhydride. This pertains even to the *t*-butyl substituent, since according to this treatment 3-methyl-3-*t*-butylglutaric anhydride would exist to an extent of 35 % in the conformation with the *t*-butyl group axial. This was taken to indicate that the preferred conformation would be a half-chair, since interactions between an axial 3-alkyl group and the two carbonyl groups would be smaller in this conformation than in a chair conformation.*

We find it difficult to rationalize that the normal, very strong preference for the *t*-butyl group to be in the equatorial position in six-membered rings²⁹ should be so dramatically changed in glutaric anhydride. In fact, molecular models suggest that there must be a strong steric interaction between an axial *t*-butyl group and the carbonyl groups, and also that smaller axial alkyl groups should interfere with the two carbonyl groups, especially in the chair conformation but also in the half-chair. As mentioned above, we favor the chair conformation for glutaric anhydride since there is experimental evidence for this.^{22a} It is then perfectly possible to interpret in a self-consistent manner the hydrolysis rates of 3-alkylglutaric anhydrides on the basis of a conforma-



tional equilibrium in which the conformer with an equatorial 3-alkyl group is the predominant or exclusive one and where the attack can occur from either side of the ring (k_1 and k_2 , see below). It can be shown that k_1 is essentially

* The test of these assumptions made by Bruice and Bradbury⁵ is based on an equation identical to that used for calculating the conformational equilibria and hence not valid.

independent of R, whereas k_2 is influenced by the steric demands of R. The rate constant k_1 is invariably much greater than k_2 , so that all 3-alkyl-substituted glutaric anhydrides hydrolyze at very similar rates (e.g., the rates for hydrolysis of 3-methyl- and 3-*t*-butylglutaric anhydride are almost identical³⁰). Since this analysis of the relative hydrolysis rates provides an economy of rationale and preserves existing concepts regarding the effect of bulky substituents on six-ring conformations, we prefer it to that of Bruice and Bradbury.

EXPERIMENTAL

Materials. Diacids and their corresponding anhydrides were prepared according to well established literature procedures: 2,³¹ 10,³² 11,³³ 12,^{34,35} 13,^{34,35} (final purification was done by preparative GLPC on a 20 % silicon oil DC-30 column at 140°), 18³⁶ (m.p. 45.5–46°), 22,³⁷ 23,³⁸ 24,³⁹ 25,⁴⁰ 26,⁴¹ 27,⁴² 28,⁴² 29,^{38a} 30,⁴³ 32,⁴⁴ 33,³⁴ 34,^{38b,45} 35,⁴⁶ 36,^{4,47} and 37.⁴⁸ Anhydrides 15 and 16 were of commercial quality and purified by recrystallization and distillation, respectively. The purity of the anhydride specimen was checked by GLPC, NMR, and hydrolysis to the corresponding diacid.

Kinetics. The kinetic procedure was identical to that described earlier.¹⁰

Acknowledgements. We thank the *Swedish Natural Science Research Council* and the *Faculty of Mathematics and Sciences* at the University of Lund for generous financial support.

REFERENCES

1. Brown, H. C., Brewster, J. H. and Shechter, H. *J. Am. Chem. Soc.* **76** (1954) 467.
2. Hall, Jr., H. K., Brandt, M. K. and Mason, R. M. *J. Am. Chem. Soc.* **80** (1958) 6420.
3. Bruice, T. C. and Pandit, U. K. *J. Am. Chem. Soc.* **82** (1960) 5858.
4. Hall, Jr., H. K. *J. Org. Chem.* **28** (1963) 2027.
5. Bruice, T. C. and Bradbury, M. C. *J. Am. Chem. Soc.* **87** (1965) 4838.
6. Jencks, W. P. *Catalysis in Chemistry and Enzymology*, McGraw, New York 1969.
7. Values for propionic and butyric anhydride were extrapolated from kinetic data at 0 and 25° (Vles, S. E. *Rec. Trav. Chim.* **52** (1933) 809), that for isobutyric anhydride was determined in this work (0.023 min⁻¹), whereas the rate constant for hydrolysis of pivalic anhydride was obtained from Butler, A. R. and Gold, V. *J. Chem. Soc.* **1962** 976.
8. Berliner, E. and Altschul, L. H. *J. Am. Chem. Soc.* **74** (1952) 4110.
9. Verkade, P. E. *Rec. Trav. Chim.* **40** (1921) 199.
10. Ebersson, L. *Acta Chem. Scand.* **18** (1964) 534.
11. Petersen, R. C. *J. Org. Chem.* **29** (1964) 3133.
12. Exner, O. *Collection Czech. Chem. Commun.* **29** (1964) 1094.
13. For an exhaustive and critical review, see Lumry, R. W. and Rajender, S. *Biopolymers* **9** (1970) 1125.
14. Koskikallio, J. *Ann. Acad. Sci. Fennicae Ser. A II* **57** (1954) 1.
15. Buntton, C. A., Fuller, N. A., Perry, S. G. and Shiner, V. J. *J. Chem. Soc.* **1963** 2918.
16. Ebersson, L. and Sandström, J. *Unpublished results*.
17. McCoy, L. L. *J. Am. Chem. Soc.* **89** (1967) 1673.
18. Wren, J. J. *J. Chem. Soc.* **1956** cf. also Crigee, R. and Zanker, F. *Chem. Ber.* **98** (1965) 3838. Our own synthetic attempts were based on the method published by Duckworth, A. C. (*J. Org. Chem.* **27** (1962) 3146) for the preparation of malonic anhydrides but consistently failed to give any cyclic anhydride.
19. Ebersson, L. and Welinder, H. *J. Am. Chem. Soc.* **93** (1971) 5821.
20. Ebersson, L. and Modler, R. *Unpublished results*.
21. Exner, O. and Jehlicka, V. *Collection Czech. Chem. Commun.* **35** (1970) 1514.
22. a. Le Fèvre, J. W. and Sundaram, A. *J. Chem. Soc.* **1962** 4009; b. Ehrenberg, M. *Acta Cryst.* **19** (1965) 698; c. Erickson, L. E. *J. Am. Chem. Soc.* **87** (1965) 1867.

23. For a summary of the conformational situation in compounds containing C=O bonds, see Ebersson, L. In Patai, S., Ed., *Chemistry of Carboxylic Acids and Esters*, Interscience, London 1969, Chap. 6.
24. Guillory, J. P. and Bartell, L. S. *J. Chem. Phys.* **43** (1965) 654.
25. Edward, J. T. and Terry, K. A. *J. Chem. Soc.* **1957** 3527.
26. Herd, III, A. K., Ebersson, L. and Higuschi, T. *J. Pharm. Sci.* **55** (1966) 162.
27. Ebersson, L. *Acta Chem. Scand.* **18** (1964) 1276.
28. Winstein, S. and Holness, N. J. *J. Am. Chem. Soc.* **77** (1955) 5562.
29. Eliel, E. E. *Accounts Chem. Res.* **3** (1970) 1.
30. Ebersson, L. and Landström, L. *Unpublished results*.
31. a. Birch, S. F., Oldham, W. J. and Johnson, E. A. *J. Chem. Soc.* **1947** 818; b. Pospischill, K. T. *Ber.* **31** (1898) 1952.
32. Cocker, W., Hopkin, L. O., Mabrouk, L., McGormick, J. and McMurry, T. B. H. *J. Chem. Soc.* **1960** 2236.
33. Verkade, H. *Rec. Trav. Chim.* **52** (1933) 953.
34. Ebersson, L. *Acta Chem. Scand.* **13** (1959) 40.
35. Schotte, L. and Rosenberg, A. *Arkiv Kemi* **8** (1956) 565.
36. Sen-Gupta, S. C. and Nath Saha, N. *J. Indian Chem. Soc.* **29** (1952) 331; **17** (1940) 183.
37. Diels, O. and Alder, K. *Ann.* **490** (1931) 239.
38. a. Sicher, J., Sipos, F. and Jonas, J. *Collection Czech. Chem. Commun.* **26** (1961) 262; b. *Neth. Appl.* **6**, 513, 262; *Chem. Abstr.* **65** (1966) 20032h.
39. a. Fuson, R. C. and Cole, W. *J. Am. Chem. Soc.* **60** (1938) 1237; b. Perkin, Jr., W. H. *J. Chem. Soc.* **65** (1894) 588.
40. Buchmann, E. R., Reims, A. O., Skei, T. and Schlatter, M. J. *J. Am. Chem. Soc.* **64** (1942) 2696.
41. McCoy, L. L. *J. Am. Chem. Soc.* **80** (1958) 6568.
42. Bayer, A. *Ann.* **258** (1890) 218.
43. Brannock, K. C., Burpitt, R. D., Gollett, W. T. and Tweatt, J. G. *J. Org. Chem.* **28** (1963) 1464.
44. Ebersson, L. *Acta Chem. Scand.* **12** (1958) 314.
45. Allinger, N. L. and Tuschaus, L. A. *J. Org. Chem.* **30** (1965) 1945.
46. a. Hewgill, F. R., Jeffries, P. R. and McBeth, A. K. *J. Chem. Soc.* **1954** 700; b. Goodwin, W. and Perkin, Jr., W. H. *J. Chem. Soc.* **87** (1905) 849.
47. Smith, H. A., Byrne, F. P. *J. Am. Chem. Soc.* **72** (1950) 4406.
48. Malachowski, R. and Jankiewiczowna, J. *Ber.* **67** (1934) 1783.

Received April 24, 1971.