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A STUDY ON KINETIC C-H-ACIDITY: THE α-EPIMERIZATION OF ß-LACTONES

Johann Mulzer* and Matthias Zippel

Institut für Organische Chemie der Universität
Karlstrasse 23, D-8000 München 2, West-Germany

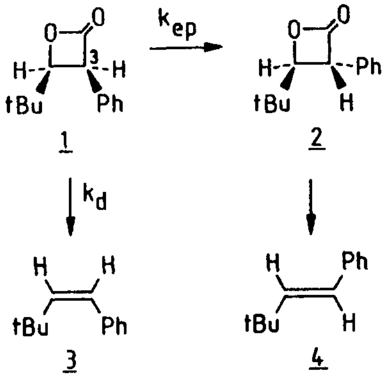
Summary: The rate constants of the α-epimerization of the ß-lactone 1 show a LFE-correlation with the solvent donicity parameters DN or B; additionally, the kinetic CH-acidity of 1 is unusually high.

The enolization of carbonyl compounds has been a subject of intensive investigation for many years[1]. Among the various methods which have been used for studying this reaction kinetically are deuteriation, bromination, racemization and epimerization. Herein we report kinetic data on the α-epimerization[2] of ß-lactones.

Model System and Kinetic Scheme

Cis-4-tert-butyl-3-phenyl-2-oxetanone[3] (1) proved to be a suitable model system (Scheme I).

Scheme I



On heating 1 in various solvents we observed a competition between epimerization (k_{ep}) and decarboxylation[3] (k_d). In CH_3OD, DOAc or pyridine/D_2O 2 was obtained with >95% deuterium at C-3. As the H/D-exchange of 2 is more than 100 times slower than the isomerization 1→2 we conclude that 1 epimerizes via an enolization mechanism involving C-3 and the carbonyl moiety. It was independently shown that under the conditions a re-isomerization of 2 to 1 does not occur; thus Scheme I is composed of first order steps only and k_{ep} may easily be calculated from the two observables k and R (Table I).

Solvent Effects on k_{ep} (Table I).

Linear Free Energy (LFE) correlations of rate constants with empirical solvent parameters are of central importance in the determination of reaction mechanisms[4]. The overwhelming majority of cases can successfully be treated by using Lewis acidity parameters like Y,Z,AN or E_T[4]. By con-

Table I. Solvent Dependence of k_{ep} [a]

Solvent	B	Temp °C	$k^b (sec^{-1})$	R^c	$k_{ep}(100°C) sec^{-1}$
1,2-Dichlorobenzene	28	160	$1.2 \cdot 10^{-4}$	<0.020	$<3.6 \cdot 10^{-8 d}$
Acetic Acid (1)	131	140	$1.0 \cdot 10^{-4}$	0.097	$6.6 \cdot 10^{-7 d}$
Benzonitrile (2)	155	150	$8.0 \cdot 10^{-5}$	0.072	$1.8 \cdot 10^{-7 d}$
Acetophenone (3)	202	140	$2.9 \cdot 10^{-5}$	0.41	$6.0 \cdot 10^{-7 d}$
Benzylalcohol (4)	208	100	$3.8 \cdot 10^{-6}$	1.2	$2.0 \cdot 10^{-6}$
THF (5)	287	140	$6.0 \cdot 10^{-5}$	4.3	$4.2 \cdot 10^{-6 d}$
HMPT (6)	471	50	$1.3 \cdot 10^{-5}$	>50	$3.4 \cdot 10^{-4 d}$
Pyridine (7)	472	100	$6.8 \cdot 10^{-5}$	>50	$6.8 \cdot 10^{-5}$
Triethylamine (8)	650	50	$5.3 \cdot 10^{-4}$	>50	$8.3 \cdot 10^{-3 d}$
20% DABCO in 1,2-Dichlorobenzene		30	$1.3 \cdot 10^{-3}$	>50	$5.1 \cdot 10^{-2 d}$

[a] All kinetic results were obtained by 60-MHz ^{1}H-NMR; [b] $k = \frac{1}{t} \ln \frac{[1]_o}{[1]} = k_{ep} + k_d$, accuracy of k ~ 5%; [c] $R = \frac{k_{ep}}{k_d} = \frac{[2] + [4]}{[3]}$; all Rs are averages of 20 different values determined over the whole reaction period ; [d] extrapolated to 100°C using the activation parameters of k_{ep} in quinoline ($\Delta H^{\ddagger} = 16.1$ kcal mole^{-1}, $\Delta S^{\ddagger} = -35$ eu).

trast, LFE-correlations solely based on Lewis basicity parameters (e.g. B[5] or DN[6]) are extremely scarce in Organic Chemistry. It can be seen from Fig.1 that k_{ep} belongs to this rare category. Only B (and DN[7]) furnish the required linearity (Fig.1a),whereas E_T (and similarly Y,Z and AN) totally fail (Fig.1b). This result, and in particular the enormous increase of k_{ep} with the solvent donicity (a rate difference of $\sim 10^5$ is observed on comparing 1,2-dichlorobenzene and triethylamine) may be interpreted in terms of a nucleophilic attack of one or more solvent molecules on 3-H during the rate determining step of the epimerization. However, this deprotonation process does not lead to the formation of a real solvent separated enolate intermediate. We may draw this conclusion from previous experiments with 5, the lithium enolate of 1/2. 5, which in THF may at least partly exist as a solvent separated ion pair[8], is unstable at temperatures above 0°C and would quickly rearrange into 6 under the epimerization conditions[9]. So we suggest that on the way from 1 to 2 a contact ion pair (7) is passed in which the enolate, 3-H and some solvent molecules (S) are tightly associated. The abovementioned deuterium exchange clearly indicates that 7 has sufficient lifetime for being an intermediate and not merely a transition state. An alternative intermediate would be the enol 8. Although 8 cannot be excluded

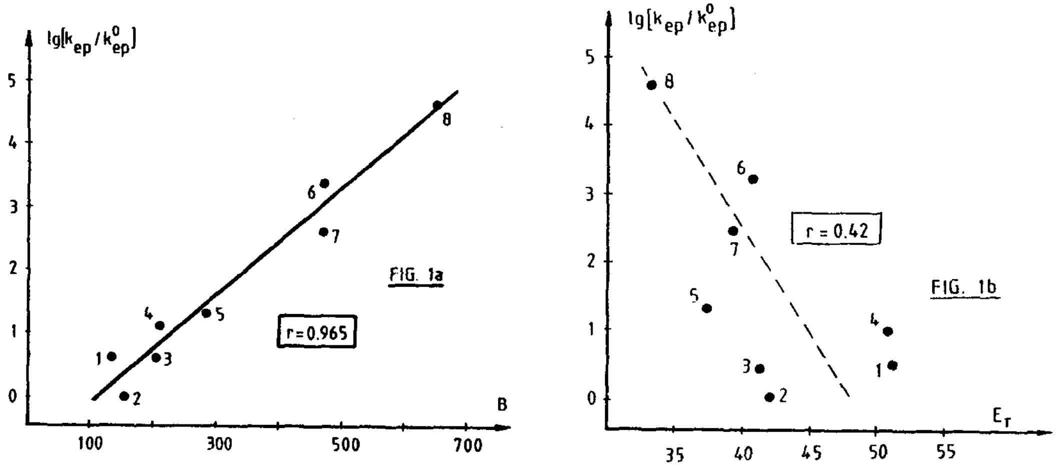
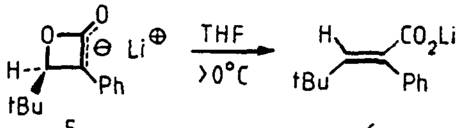


Fig.1 Correlations of k_{ep} vs. (a) B b) E_T. Reference value: k^{o}_{ep} = k_{ep} in Benzonitrile. Solvent numbers see Table I.



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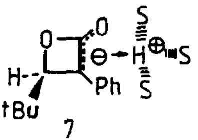

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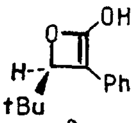

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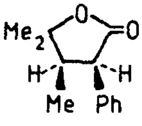

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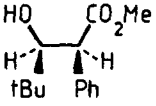

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rigorously, it appears unlikely, because the epimerization of 1 does not underly acid catalysis. So, for example, acetic acid has no extra effect on k_{ep} beyond its donicity (Fig.1). Similarly, trifluoroacetic acid in 1,2-dichlorobenzene (v/v 1:9) fails to epimerize 1 even at 140°C. This behavior of 1 differs from that of normal carbonyl compounds which are enolized by bases and acids with comparable rates[10]. A reasonable explanation could be seen in the considerable increase in ring strain which would occur during the conversion of 1 → 8 (ca. 4 kcal mole^{-1}, cyclobutane → cyclobutene[11]). In accordance with this argumentation the γ-lactone 9[12], which apart from the ring size has the same structural features as 1, rapidly epimerizes in trifluoroacetic acid-1,2-dichlorobenzene (1:9) at 140°C.

Kinetic Acidity. From the data of Table I it clearly emerges that k_{ep} and hence the kinetic acidity of 1 is unusually high for an ester derivative[13]: even the low donicity of solvents like acetic acid, tetrahydrofurane and acetophenone suffices to abstract the 3-H with measurable rates[14]. Apart from the activating influence of the 3-phenyl group this phenomenon is due to a steric reason, namely the loss of the unfavorable cis-eclipsed interactions on the way from 1 to 7. This effect can clearly be seen by comparing the k_{ep} of 1 to the 3-H/D-exchange rate of 2 (k_{H-D})under identical conditions (pyridine/D_2O, 140°C). The rate determining step of both reactions generates the same reactive intermediate 7. Therefore the ratio of $k_{ep}:k_{H-D}$ = 102 reflects the higher amount of strain release in 1. Similarly, 1 epimerizes 2960 times faster ($[D_5]$ pyridine, 140°C) than its open chain analogue 10, because the strain relief is far higher for the rigid lactone 1 than for the conformationally mobile ester 10.

References and Notes

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14. To exclude basic impurities as far as possible the kinetic experiments were performed in quartz tubes with carefully purified solvents and recrystallized 1.

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