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Highly Stereoselective Protonation of the Enolate of a Bicyclic Cycloheptatrienyl Lactone Occurs on the Hindered Face

Takashi Sugimura,* Wan Hyeok Kim,[†] Masami Kagawa, and Tadashi Okuyama*

Graduate School of Science, Himeji Institute of Technology,
Kohto, Kamigori, Ako-gun, Hyogo 678-1297, Japan

sugimura@sci.himeji-tech.ac.jp

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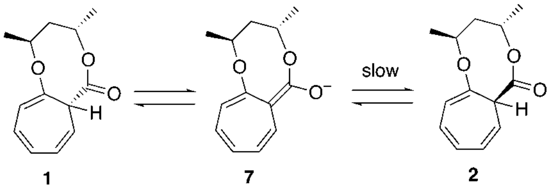
ABSTRACT



The H/D exchange of the lactone-fused cycloheptatriene 1 is over 1000 times faster than that of the epimer 2. Interconversion of 1 and 2 provides an equilibrium mixture of 1:0.7, showing a similar stability of the isomers. Protonation of the common enolate 7 occurs far more readily on the more hindered face. Cycloheptatrienide anion is bent and as stable as a divinylcarbanion.

There are usually correlations between kinetic and thermodynamic acidities of carbon acids, as represented by the Brϕnsted relationship.[1] Enolate formation from the carbonyl compound is a typical example.[2] Rates of enolization are evaluated from those of the H/D isotope exchange of the carbonyl compounds. We have found that the rate of enolization of the bicyclic cycloheptatrienyl lactones containing a 2,4-pentanediol (PD) tether (**1**−**3**) strongly depends on the stereochemistry of the ring junction as well as that of the tether.[3] The extreme case of the epimeric difference (**1** vs **2**) leads to a more than 1000-fold increase in kinetic acidity while maintaining a constant thermodynamic acidity. The protonation of a chiral enolate to create a new chiral center is also one of the important methods for organic synthesis, but simple protonation cannot usually be achieved with high stereoselectivity.[4]

Lactones **1** and **3** were prepared by the reported method.[5] Relative rates of the H/D exchange of **1**−**3** as well as the related esters **4**−**6** were measured in 5:1 (v/v) CD_3OD-D_2O containing the borate or carbonate buffer by means of ^1H NMR spectroscopy at 22.3 °C in the presence of a reference carbonyl compound.[6] Using the reported value of the rate constant (k_{OH} at 25 °C) for enolization of the reference compound,[2] kinetic acidity was evaluated as k_{OH} as summarized in Table 1.

Lactone **1** undergoes fast H/D exchange, but no detectable amount of the epimer **2** was formed during the exchange.

[†] A 2001 HUMAP exchange student from Dong-A University, Pusan, Korea. Encouragement by Professor Jong Pal Lee in this program is acknowledged.

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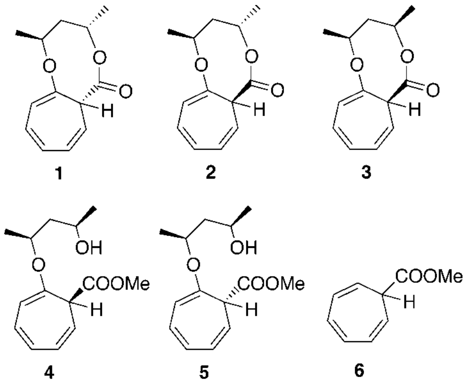


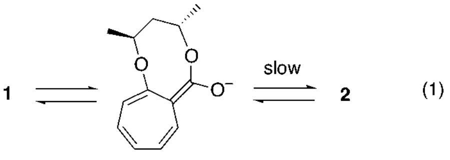
Figure 1. Cycloheptatrienyl lactones and esters.

Table 1. Kinetic Acidities of Cycloheptatrienes[a]

substrate	buffer/ref[b]	relative rate	k_{OH} (mol^{-1} dm^3 s^{-1})
1	B/A	0.94 ± 0.02[c]	22.1
2	B/A		<0.01[d]
3	B/A	0.295 ± 0.03[c]	6.9
4 (**5**)	C/B	13.4 ± 1.0	0.032
6	B/C	2.10 ± 0.02	0.52

[a] Measured in 5:1 (v/v) methanol-d_4−D_2O at 22.3 °C. [b] Buffer: borate (B) or carbonate (C). Reference: diphenylacetaldehyde (A), isobutyrophenone (B), or acetophenone (C). [c] Apparent relartive rate due to equilibrium formation of the hemiacetal (plus hydrate) of aldehyde A. A correction for this equilibrium is made in calculating k_{OH}. [d] Much smaller than the value evaluated for the solvolysis (0.024).

Since protonation of enolate **7** can lead to either of the epimers (eq 1), the protonation should be stereoselective by



7 (1)

at least 100 times (detection limit < 1%). The H/D exchange of **2** was actually very slow, and the solvolysis to give a methyl ester, an analogue of **4**, was much faster than the exchange. That is, kinetic acidity k_{OH} should be much smaller than the solvolysis rate, 0.024 mol^{-1} dm^3 s^{-1}. The rate of enolization of **1** is over 1000-fold greater than that of the epimer **2**. The thermodynamic stability can be evaluated from mutual isomerization. The isomerization between **1** and **2** was observed in the presence of alumina in an aprotic solvent like hexane giving a mixture of 1:0.7 from either side of the isomer.[7] The stabilities of **1** and **2** are essentially the same, the difference being less than 1 kJ mol^{-1}.

Lactone **3**, having a stereochemically different PD tether, had an exchange rate slightly smaller than that of **1**. The H/D exchanges of the ester analogues **4**−**6** are still slower: **4** undergoes epimerization to **5** at the same time to give an equimolar mixture. The rate of epimerization is one-half that of the H/D exchange as NMR kinetics showed. The protonation of the enolate of **4** (or **5**) is not stereoselective.

To summarize the results, energetics of the enolization of the epimeric pairs of lactone (**1** and **2**) and ester (**4** and **5**) are illustrated in Figure 2. Epimerization should occur through a common enolate ion under basic conditions. The epimers have a similar energy in both cases. The barriers for enolization are quite different between the epimers of the lactone, **1**/**2**, although such difference is not seen with the ester, **4**/**5**. In other words, the protonation of the enolate of the lactone is highly stereoselective, while that of the ester is nonstereoselective.

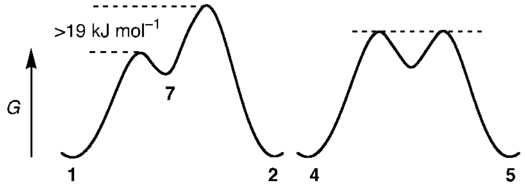


Figure 2. Energy diagrams of the two systems.

The contrasting observations must be due to the conformational restrictions within the bicyclic lactone. The enolate ion **7** derived from **1** or **2** has only a single stable conformation located by ab initio MO calculations at the HF/6-31G level. This common enolate has a bent seven-membered ring and can be protonated from the less hindered side to give the epimer **2**. This protonation was found experimentally to be a high energy process. A remarkable difference in conformation is found between the lactone forms **1** and **2**: the dihedral angles of the carbonyl and the α C−H bonds are 115° and 4.4° for **1** and **2**, respectively.[8] In the conformation of **2**, the enolate conjugation should be negligible on deprotonation, and this conformational strain may be reflected in the transition state for the enolization of **2** or the protonation of **7** leading to **2**. Such a conformational restriction is smaller for the enolization of **1**.

It may be worth noting here the acidity of cycloheptatriene. The cycloheptatrienide anion with 8 π electrons is often

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(6) (a) The substrate (0.05−0.1 mol dm^{-3}) and a reference compound (0.05−0.11 mol dm^{-3}) were dissolved in a basic buffer solution (0.6 mL) prepared from Borax or K_2CO_3/$KHCO_3$ in 5:1 (v/v) methanol-d_4−D_2O at the buffer ratio of unity and the total buffer concentration of 0.1 mol dm^{-3}. The solution was transferred to an NMR sample tube, and ^{1}H spectra were recorded at 22.3 ± 0.5 °C and an appropriate time interval. For the reference compounds, diphenylacetaldehyde, isobutyrophenone, and acetophenone were used. The k_{OH} values for enolization listed in ref 2 were used for evaluation of the k_{OH} from the relative rates obtained by the pseudo-first-order kinetic analysis. Equilibrium formation of the hemiacetal of diphenylacetaldehyde was observed, $K_{add} = 9.8$, and the.apparent relative rate is corrected by a factor of 1/10.8 ($= 1/(K_{add} + 1)$).[6b] (b) Chiang, Y.; Kresge, A. J.; Krogh, E. T. *J. Am. Chem. Soc.* **1988**, *110*, 2600−2607.

(7) The epimerization was completed within 10 min at room temperature. The ab initio MO calculations (HF/6-31G) show similar energies of **1** and **2**; **2** is more stable than **1** by 5.3 k*J* mol^{-1}.

(8) The same dihedral angle in the most stable conformation of **3** was calculated to be 130° (HF/6-31G) in conformity to the k_{OH} value.

assumed as an anti-aromatic species, and thus the pK_a of cycloheptatriene is high. However, the cycloheptatrienide ring is bent, and the middle double bond is isolated from conjugation. The carbanion should have a conjugative stability due to the other two double bonds, which makes the stability similar to that of a divinyl carbanion. In fact, the pK_a value evaluated for cycloheptatriene (36) is comparable to that for diphenylmethane (34).[9] The reliable pK_a value and enolization rate constant for ethyl acetate was recently determined: p$K_a = 25.6$ and $k_{OH} = 1.2 \times 10^{-3}$ mol^{-1} dm^3 s^{-1}.[10] From these values, the pK_a of **6** can reasonably be estimated to be 19 using the Brϕnsted β value of 0.4 for the correlation.[2]

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