Rapid [1,5] Hydrogen Migration on 7-Alkoxycarbonyltropilidenes under Conformational Regulation

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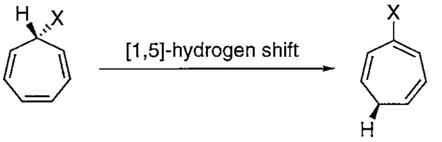
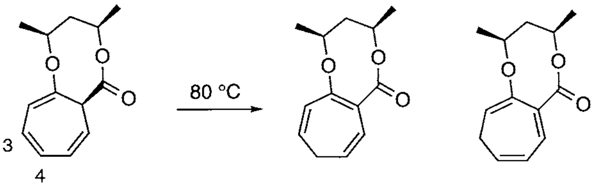
The thermal [1,5] hydrogen migration of 7-alkoxycarbonyl tropilidene was found to be accelerated by conformational regulation at the carbonyl group, which was mainly affected to the activation energy. Methyl substitutions on the 3- and 5-positions further increased the migration rate.

Hydrogen migrating reactions in conjugated polyene systems have been extensively studied based on molecular orbital analysis.[1] The thermal isomerization of tropilidene (1,3,5-cycloheptatriene) proceeding at 100 ± 20 °C is a typical example of [1,5] hydrogen migration. The migration rates mainly depend on the nature of the substituent (X) at the 7-position.[2] Kinetic experiments (X = Me, Ph, OMe, D, etc.) showed varied activation energies (E_a) of 108–134 kJ mol^{-1}, whereas the frequency factors (log A) remained in the range of 10–13, the latter of which indicate a highly ordered transition state for the reactions. The migration in a substrate having an ethoxycarbonyl group at the 7-position (X = COOEt, **1**) was reported to proceed at the higher temperatures of 140–160 °C.[3,4] The slower rate can be explained by the increment in E_a with the ester substitution.[5]



1. X = COOEt
1'. X = COOMe

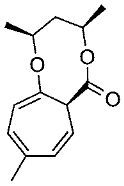
Recently, we have found that the thermal isomerization of **2** was unexpectedly fast and provided regioselective [1,5] hydrogen migration to the 4-position (Scheme 1).[6] In this communication, we would like to report the detailed study of the isomerization of **2** and its analogs to clarify the factors controlling the rate of the [1,5] hydrogen migration of 7-alkoxycarbonyltropilidene.



2 **3** quantitative **4** not found

Scheme 1.

The structural difference between 7-methoxycarbonyl-1,3,5-cycloheptatriene (**1'**) and **2** was estimated by calculation using the MOPAC93-PM3 method. In both compounds, the most stable conformers have the ester group at the equatorial positions.[7] The major difference is the dihedral angle of H7–C7–C=O; H7 and O are almost anti-periplanar in **1'**, whereas the angle is ca. 120° in **2**. Thus, the carbonyl group in **2** is possible to conjugate to and weaken the H7–C7 bond, which will be a factor that reduces the E_a in the reaction of **2**. The distance between H7 and C4 is shorter in **2** (2.847 Å) than in **1'** (2.884 Å), which will be a factor to accelerate the migration in **2**. By the same calculation, methyl substitution on the tropilidene ring of **2** only slightly affects the orientation of the carbonyl moiety, but the distance of H7–C4 can be changed; the 4-methyl analogue **5** has a similar distance of 2.848 Å, but the 3,5-dimethyl analogue **6** has a shorter distance of 2.820 Å.



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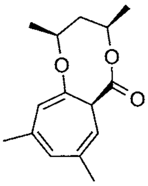

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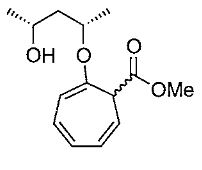

7

To investigate the effect of the fused lactone ring on the hydrogen migration rate in **2**, the monocyclic but electronically equivalent substrate **7** was prepared as a control compound.[8] When a solution of **7** in benzene-d_6 was heated, no isomerization nor decomposition was observed at 130 °C after two days. When the temperature was elevated to 150 °C, **7** was decomposed in part, but the produced regioisomers of **7** were still less than 5% after 2 days. Thus, the rate of the [1,5] hydrogen migration of **7** is much slower than **2** and even slower than **1**. This experiment clearly indicated that the rapid migration of **2** is not attributable to the extra substituent of the alkoxy group at the 1-position, but to the fixation of the conformation of **2** with the lactone ring.

The [1,5] hydrogen migration rates of **2** and its analogues, **5** and **6**[9], were compared at 80 °C in benzene-d_6 monitored by ^{1}H NMR. The hydrogen migration was highly regioselective to the 4-position in the cases of **2** and **6**, and then **3** and its dimethyl analogue were quantitatively obtained without any further reactions. In the case of **5**, some [1,3] hydrogen migration to the 2-position was observed in addition to the [1,5] migration to the 4-position.[10] The determined rates for the [1,5] migration at 80 °C were 7.1 x $10^{-7}/s^{-1}$ for **2**, 3.0 x $10^{-7}/s^{-1}$ for **5**, and 1.3 x $10^{-5}/s^{-1}$ for **6**. Thus, the methyl substitution at the 4-position reduces the migration rate 2.4 times, and those at the 3- and 5-positions accelerate the rate 18 times. The migration in **6** was so fast as it proceeded even at 60 °C (80% conversion after 1 week). The details of the hydrogen migration were clarified by kinetic study in a temperature range of 80–120 °C (except for **6**, 60–100 °C), the results of which are

Table 1. [1.5] Hydrogen migration rates of **2**, **5**, and **6** in benzene-d_6

Substrate	60 °C	80 °C	100 °C	120 °C
2		7.05 x 10^{-7}	4.32 x 10^{-6}	1.97 x 10^{-5}
5		2.99 x 10^{-7}	1.51 x 10^{-6}	6.06 x 10^{-6}
		(1.12 x 10^{-7})[a]	(5.46 x 10^{-7})[a]	(1.58 x 10^{-6})[a]
6	1.80 x 10^{-6}	1.25 x 10^{-5}	7.31 x 10^{-5}	

[a][1,3] Hydrogen migration to the 2-position.

Table 2. Activation energy and frequency factor for the [1,5] hydrogen migration in benzene-d_6

Substrate	E_a (kJmol^{-1})	log *A*
2	96.2 ± 2.5	8.1 ± 0.4
5	86.6 ± 3.3	6.3 ± 0.5
	(74.1 ± 4.3)[a]	(4.1 ± 0.7)[a]
6	95.4 ± 2.0	9.3 ± 0.4

[a][1,3] Hydrogen migration to the 2-position.

shown in Table 1.[11] The calculated E_a and log *A* are summarized in Table 2.

In all the three substrates, the activation energies are lower than those of the regular tropilidenes and much lower than the expected values for the 7-alkoxycarbonyl tropilidene. Considering the poor reactivity of **7** for the thermal isomerization, it was concluded that the conformational regulation by the lactone ring drastically decreased the activation energy resulting in the rapid migration. The regulation also resulted in smaller frequency factors partially compensating the low activation energies.[12]

In this communication, we found that the orientation of the C=O group at the 7-position is an important factor controlling the activation energy for the [1,5] hydrogen migration and it is the reason for the rapid migration in **2**. The results are consisted with the expectation from the analysis of the substrate conformation by the MO calculations.

References and Notes

1 R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, Weinheim (1970).

2 C. W. Spangler, *Chem. Rev.*, **76**, 187 (1976), and references therein.

3 A. P. ter Borg, H. Kloosterziel, and N. van Meurs, *Recl. Trav. Chim. Pays-Bas*, **82**, 717 (1963).

4 By our experiment, the [1,5] hydrogen migration of **1** proceeded at 130 °C and the rate constant was 3.0 x 10^{-5}/s^{-1}. In this case, the [1,7] hydrogen migration was also observed (2.0 x 10^{-6}/s^{-1}). Activation parameters could not obtained by our experimental method because of the high temperature reaction.

5 N. D. Epiotis, "Theory of Organic Reactions," Springer, Berlin (1978), pp. 192–214.

6 T. Sugimura, S. Nagano, and A. Tai, *Chem. Lett.*, **1998**, 45.

7 In the case of **2**, two conformations having the ester at the equatorial and axial positions are candidates for the most stable conformer. Calculated heat of formation for the equatorial conformation of **2**: –319.02 kJ mol^{-1}. For the axial one: –316.08 kJ mol^{-1}.

8 Transesterification of **2** with methanol was achieved in the presence of K_2CO_3 at room temperature to give **7** in a quantitative yield. The stereochemical purity at the 7-position was lost during the reaction.

9 Stereochemically pure **6** was prepared using the same procedure for **2** except 3,5-dimethylphenol was used instead of phenol. These details will be published elsewhere.

10 In the present study, the regioisomer produced through the [1,5] hydrogen migration to the 3-position was not detected at any temperatures. The production of the regioisomer in the reaction of **5** in the last report (Reference 6) might due to an impurity.

11 All reactions were monitored by ^{1}H NMR. A solution of the carefully purified tropilidene (32–35 mg) in benzene-d_6 (0.5 ml) was sealed in an NMR tube under vacuum and heated in a temperature controlled-oil bath. During the reactions in Table 1, no other product was detected at all. The observed reaction rates calculated from the ratio of the peak integration are well matched to a unimolecular reaction ($r > 0.996$).

12 J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Dover, New York (1963).