Tetrahedron Letters,Vol.25,No.38,pp 4183-4186 ,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

KINETIC CONTROL IN THE ACID-CATALYZED ISOMERIZATION OF TRANS-2-VINYL-1,6-DIMETHYLBICYCLO[4.3.0]NON-2-EN-7-ONE

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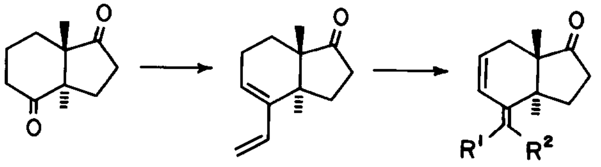
Abstract - The acid-catalyzed isomerization of the title compound (2) to the thermodynamically-favored Z isomer 4 proceeds first to the E-isomer 3.

During the past five years, we have used diene 2 as a key reactant in a variety of Diels-Alder reactions designed to construct tetracyclic intermediates for the synthesis of triterpenes. Preparation of 2 from trans-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (1)[1] was accomplished in two steps (>75% overall yield) by addition of vinylmagnesium chloride followed by dehydration (copper sulfate in refluxing benzene solution). Strong Bronsted acids must be avoided in the latter reaction because they induce isomerization of 2 to a mixture of stereoisomeric dienes 3 and 4.

(1)

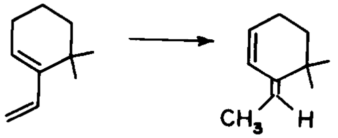


1 2 3 R'=H, R²=CH$_3$

4 R'=CH$_3$,R²=H

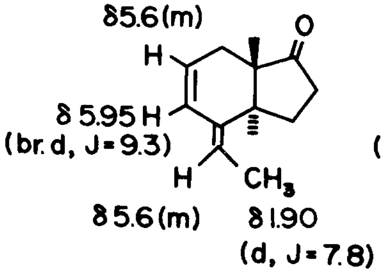
In the course of this work, we observed an interesting kinetic selectivity in the acid-catalyzed isomerization of 2. Since the corresponding isomerization of 6,6-dimethyl-1-vinylcyclohexene (5)[2] to 6 did not exhibit this phenomenon, the possibility that it reflected unexpected differences in conformer equilibria was considered. Our evidence and arguments are presented here.

(2)

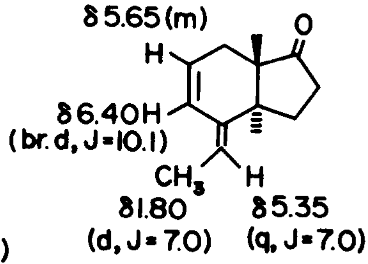


5 6

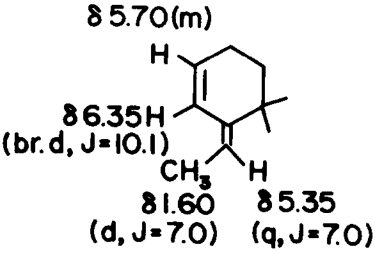
Treatment of **2** with 0.1 equivalent of p-toluenesulfonic acid in refluxing benzene for 1 hour gave the Z-isomer **4** in 85% yield (after purification). The isomerization of **5** to **6** also proceeded smoothly under similar conditions. When the acid-catalyzed isomerization of **2** was monitored by ^{1}Hnmr, a new set of signals appeared, reached a maximum after 20 minutes at 75°C and then faded as the spectrum of **4** grew stronger. Finally, careful treatment of **2** with p-toluenesulfonic acid in chloroform enabled us to isolate the intermediate in this isomerization as a crystalline product to which the E configuration **3** has been assigned.[3] Some of the important ^{1}Hnmr assignments for these compounds are shown in the accompanying formulas. A nuclear Overhauser effect for the δ1.8 methyl doublet and the δ6.4 multiplet was observed in the spectrum of **4**, but no equivalent effect was found for these signals in **3**. All efforts to observe and/or isolate an equivalent intermediate in the isomerization of **5** to **6** failed.



3



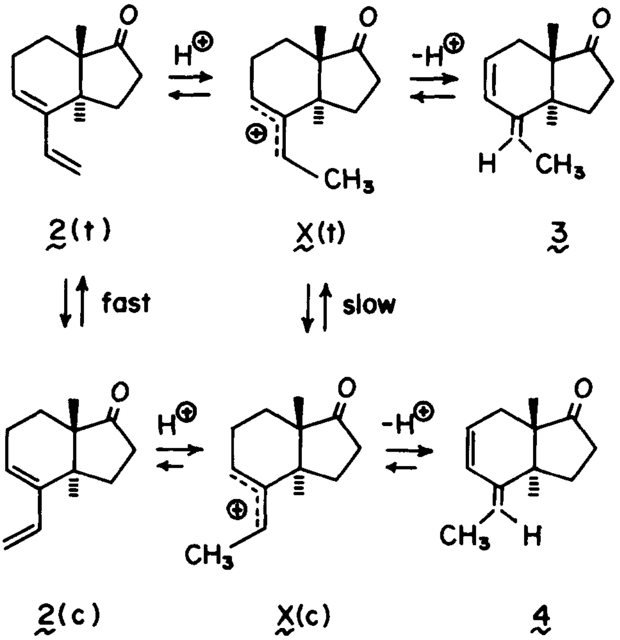
4



6

Scheme I illustrates our explanation for the rapid formation of the thermodynamically less-stable diene **3** from **2**. The barrier for conformational interconversion in simple dienes is low (<6 kcal/mole), and in the absence of steric hindrance effects, the s-trans conformer is more stable than the s-cis or s-skew conformers by ca. 2.1 kcal/mole.[4] Allylic carbocations, on the other hand, have conformational barriers in the 38 to 43 kcal/mole range[5] and such intermediates exhibit strong structural integrity. Indeed, the kinetic selectivity reported here requires that the deprotonation of cation **X(t)** be faster than its isomerization to **X(c)**. Furthermore, the low energy barrier for conformational isomerization of the diene demands that the activation energy **2(t)** ⟶ **3** be lower than for **2c** ⟶ **4**.[6] Since this does not appear to be true for the corresponding isomerization of **5**, we have looked for a unique conformational factor in **2** (or **X**) that might contribute to this difference. Evidence for such a factor has been found in the UV absorption spectra of **2**, **5** and related dienes.

Scheme I



The s-trans conformer of acyclic dienes generally has a larger molar absorptivity (ε) than the corresponding s-cis conformer.[4b,7] From the examples cited in Table I, we see that the UV absorption of **2** is similar to that of 1-vinylcyclohexene, indicating a similar s-trans : s-cis equilibrium for these compounds (presumably s-trans predominates). Diene **5**, on the other hand, appears to assume chiefly the s-cis (or s-skew) conformation.

Table I

Absorption Maxima and Molar Absorptivities of Some Conjugated Dienes

Compound	λ_{max}^{EtOH} (nm)	ε	Ref.
3-methylenecyclohexene	231 (hexane)	21,000	8
1-vinylcyclohexene	231	10,600	9
1,2-bismethylenecyclohexane	220	6,400	10
1,3-cycloheptadiene	246	7,500	11
2	235	11,900	This Work
5	237	6,600	This Work

The unexpected similarity of the molar absorptivity of **2** to that of 1-vinylcyclohexene rather than **5** may be attributed to structural distortion in **2**, introduced by the trans-fused five-membered ring. Molecular models indicate that the six-membered ring in **2** is forced into a boat (or twisted boat) conformation. This permits the s-trans diene conformation to experience less steric crowding than it does in **5**. We suggest that this factor helps to lower the activation energy of the **2(t)** $\longrightarrow$ **3** reaction relative to that for compound **5**.

Acknowledgements: We thank Mr. Yousef Abdallah for a generous sample of diene **5** and Professors Harold Hart and G. J. Karabatsos for their interest and advice.

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3. All new compounds have been characterized by elemental analysis, ^{1}Hnmr (250 MHz in $CDCl_3$ solution), UV-visible and mass spectrometry. ^{13}Cnmr spectra of **3** and **4** (69.8 MHz in $CDCl_3$ solution) displayed the following signals (TMS reference). **3**: δ 13.86, 19.19, 22.66, 29.66, 30.91, 33.54, 45.53, 51.91, 121.32, 125.32, 131.49, 141.05, 219.93 ppm. **4**: δ 12.00, 18.28, 23.36, 28.28, 30.20, 33.28, 45.00, 51.80, 118.92, 123.28, 124.88, 140.50, 219.00 ppm.
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(Received in USA 22 May 1984)