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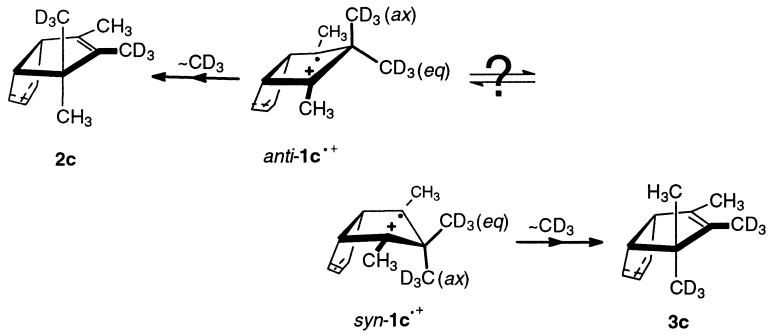


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# Stereochemical Memory versus Curtin−Hammett Behavior in the Rearrangement of 1,3-Cyclopentanediyl Radical Cations Derived from Housanes through Structural Effects on Conformational Control

Waldemar Adam,[†] Christian P. Librera,*[,†] and Alexei V. Trofimov[†,‡]

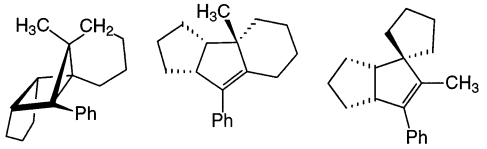
*Contribution from the Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Institute of Biochemical Physics, Russian Academy of Sciences, 117977 Moscow, Russia*

Received October 16, 2002; E-mail: librera@chemie.uni-wuerzburg.de

***Abstract:*** The electron-transfer-catalyzed rearrangement of the housanes **1** affords regioselectively the two cyclopentenes **2** and **3** by 1,2-migration of a group at the methano bridge. Appropriate ring annelation in the intermediary cyclopentane-1,3-diyl radical cation **1**$^{\bullet+}$ changes the stereochemical course of the rearrangement from complete stereoselectivity (*stereochemical memory*) for the structurally simple housane **1b** to partial loss of stereoselectivity through competing conformational interconversion for the tricyclic housane **1c**. Additional cyclohexane annelation, as in the tetracyclic housane **1a**, results in complete loss of stereocontrol through Curtin−Hammett behavior, as substantiated by the viscosity dependence on the product ratio of the rearrangement. Whereas in the radical cations **1b**$^{\bullet+}$ and **1c**$^{\bullet+}$ the 1,2-shifts ($k_2$ and $k_3$) are faster than the conformational *anti* ⇌ *syn* change ($k_1$, $k_{-1}$), the reverse applies for the radical cation **1a**$^{\bullet+}$. Such structural manipulation of conformational effects in radical cation rearrangements has hitherto not been documented.

## Introduction

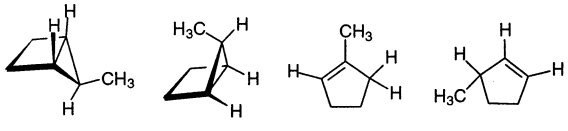
Organic radical cations command considerable attention in view of their unusual reactivity.[1,2] In this context, during the past few years we have extensively investigated the remarkably regioselective and diastereoselective rearrangement of the 1,3-radical cations, derived from housanes by electron-transfer oxidation, to their cyclopentene derivatives.[3−6] We have shown that the selectivity of these short-lived intermediates is controlled by internal factors such as electronic, steric, stereoelectronic, and conformational effects.[2−6] External influence of the medium (viscosity, polarity) has received to date much less attention. In this regard, we have reported most recently on the solvent effects in the rearrangement of the cyclopentane-1,3-diyl radical cation derived from the cyclohexane-annelated tetracyclic housane *anti*-**1a** to the cyclopentenes **2a** and **3a**, and examined the mechanism of this complex transformation by means of the viscosity dependence on the product selectivity.[7] From the observed viscosity dependence it was concluded that conformational interconversion of the intermediary radical cations is




*anti*-**1a** **2a** **3a**

faster than the 1,2-shift of the methyl group, which manifests Curtin−Hammett behavior.

These results are in contrast with those reported for the structurally simpler housane diastereomers *exo*-**1b** and *endo*-**1b**, which rearrange to the respective cyclopentenes **2b** (1,2-H shift) and **3b** (1,2-$CH_3$ shift).[5,8] The rearrangement is much faster than the *exo*-to-*endo* conformational change; that is, perfect *stereochemical memory* is observed.[5]




*exo*-**1b** *endo*-**1b** **2b** **3b**

EPR-spectral data indicate a puckered conformation for the simple *exo*- and *endo*-stereolabeled 2-methylcyclopentane-1,3-diyl radical cations. Furthermore, high-level computations[9] have

[†] Universität Würzburg.
[‡] Russian Academy of Sciences.

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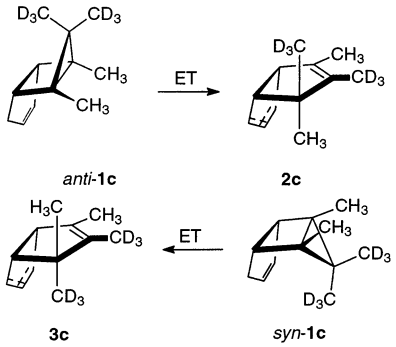
***Scheme 1***




disclosed that breakage of the one-electron bond in the puckered radical cation conformers generates the ring-opened radical cation conformers, for which a higher energy barrier was calculated for the *exo*-to-*endo* conformational change than for their rearrangement to the cyclopentenes **2b** and **3b**. This is consistent with the observed stereochemical memory effect.

The observed Curtin−Hammett behavior of the radical cations derived from the housanes *anti*-**1a** and *syn*-**1a** was attributed to cyclohexane annelation.[7] If this is the case, removal of the annelated cyclohexane ring should restore stereochemical memory in the electron-transfer reaction of the tricyclic housanes *anti*-**1c** and *syn*-**1c** (Scheme 1). The latter constitute hybrids of the tetracyclic (**1a)** and bicyclic (**1b**) housanes, and thus, the pertinent mechanistic question arises as to what extent the resulting radical cations *anti*-**1c**$^{\bullet+}$ and *syn*-**1c**$^{\bullet+}$ display stereochemical memory.

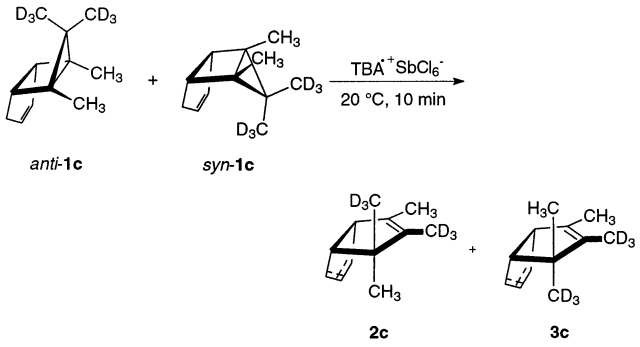
The $CD_3$ labels in the housanes *anti*-**1c** and *syn*-**1c** are essential to enable diastereochemical differentiation in the rearrangement products and thereby allow assessment of the product selectivity of the rearrangement by means of NMR spectroscopy. The present study provides a detailed mechanistic assessment of how structural features allow manipulation of conformational effects in the rearrangement of cyclopentane-1,3-diyl radical cations such that either stereochemical memory or Curtin−Hammett behavior is observed.

## Results and Discussion

The required diastereomeric triyclo[3.3.0.0$^{2,4}$]octanes (housanes) *anti*-**1c** and *syn*-**1c** were prepared as reported.[10] The *anti*:*syn*-housane ratio is controlled by the photolysis conditions of the azoalkane: At high temperature (>40 °C), the formation of the *anti* diastereomer is favored, whereas at low temperature (−75 °C), the photolysis leads to nearly equal amounts of the *anti*-**1c** and *syn*-**1c** housanes.

The desired 1,3 radical cations were generated by chemical electron transfer with tris(4-bromophenyl)aminium hexachloroantimonate (TBA$^{\bullet+}$SbCl$_6^-$) as one-electron oxidant in $CDCl_3$ at room temperature (ca. 20 °C). To suppress possible acid-catalyzed rearrangement,[4,6] the electron-transfer reactions were carried out in the presence of a slight excess (1.25 equiv) of the sterically hindered 2,6-di-*tert*-butylpyridine base as buffer. Control experiments had previously established that this hindered pyridine does not affect the product composition.[4] The product data of the electron-transfer reactions are summarized in Table 1.

***Table 1.*** Product Distribution (**2c**:**3c** Cyclopentene Ratios) for the Electron-Transfer-Induced Rearrangement of *anti*/*syn* Mixtures of the Housanes **1c** in Solvents of Various Viscosities




| entry | housane *anti*:*syn* | solvent ($\eta$, cP) | product distribution[a] (%) 2c | 3c | 2c:3c |
|---|---|---|---|---|---|
| 1 | >97: 3 | $CDCl_3$ | 90 | 10 | 9.00 |
| 2 | 93: 7 | $CDCl_3$ | 83 | 17 | 4.88 |
| 3 | 90:10 | $CDCl_3$ (0.58) | 81 | 19 | 4.26 |
| 4 | 90:10 | $CH_3CH(OH)CH_2OH$ (56.0) | 78 | 22 | 3.55 |
| 5 | 90:10 | $HO(CH_2)_4OH$ (89.2) | 80 | 20 | 4.00 |
| 6 | 84:16 | $CDCl_3$ | 76 | 24 | 3.17 |
| 7 | 73:27 | $CDCl_3$ | 69 | 31 | 2.23 |
| 8 | 69:31 | $CDCl_3$ | 67 | 33 | 2.03 |
| 9 | 51:49 | $CDCl_3$ | 57 | 43 | 1.33 |
| 10 | 49:51 | $CDCl_3$ | 56 | 44 | 1.27 |
| 11[b] | < 3:97 | $CDCl_3$ | 23 | 77 | 0.30 |

[a] Determined directly on the crude product mixture by $^1$H NMR spectroscopy (400 MHz, $CDCl_3$). The error was ca. 3% of the stated value. Conversions and material balances were >90% in all cases. TBA$^{\bullet+}$SbCl$_6^-$ is tris(4-bromophenyl)aminium hexachloroantimonate. [b] The product ratio **2c**:**3c** was extrapolated from Figure S-1 (Supporting Information).

Complete conversion of the housanes **1c** occurred within 10 min (Table 1). Although for all *anti*:*syn*-housane mixtures the **2c** diasteromer is formed preferentially, the cyclopentene ratio **2c**(*exo*):**3c**(*endo*) depends on the starting *anti*:*syn*-housane ratio (Table 1). For example, the pure *anti*-**1c** housane gave the two **2c** and **3c** diastereomers in a 90:10 ratio (entry 1), whereas an almost equal (49:51) mixture of the *anti*-**1c** and *syn*-**1c** housanes yielded the two diastereomeric cyclopentenes **2c** and **3c** in a 56:44 ratio (entry 10), that is, a decrease in the **2c**:**3c** ratio by ca. 8-fold. Since the pure *syn*-**1c** housane was not accessible [the highest proportion of *syn* isomer that may be obtained was the 49:51 *anti*:*syn*-housane ratio (entry 10)], its **2c**:**3c** cyclopentene ratio was extrapolated from a plot of the mole fraction $X_{\mathbf{2c}}$ of the cyclopentene product **2c** versus the mole fraction $X_{anti\text{-}\mathbf{1c}}$ of the housane *anti*-**1c** (see Figure S-1, Supporting Information). The extrapolated **2c**:**3c** ratio for the *syn*-**1c** housane alone was found to be 23:77 (Table 1, entry 11). Clearly, both housane diastereomers rearrange stereoselectively;[11] that is, the *anti*-**1c** housane affords mainly the **2c** cyclopentene (*exo* diastereomer) and the *syn*-**1c** housane mainly the **3c** product (*endo* isomer). However, the extent of stereoselection is higher for the *anti*-**1c** than for the *syn*-**1c** housane (entries 1 and 11). Therewith, a stereochemical memory effect is demonstrated also for the structurally more complex tricylic housane **1c**, but unlike the simpler housane **1b**, some *stereochemical leakage* is displayed by the **1c** substrate, since the *anti* diastereomer affords mainly **2c**, but also some **3c**, and vice versa (Scheme 1).

To examine the viscosity dependence of the rearrangement process, the electron-transfer reaction was carried out for a

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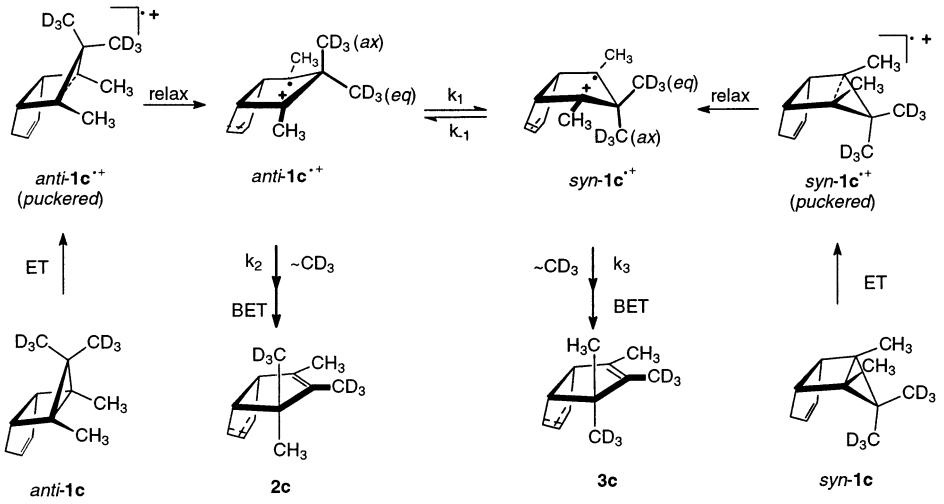
(11) Paquette, L. A.; Leichter, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 3653−3655.

**Scheme 2**



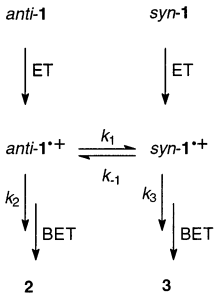

90:10 mixture of the *anti*-**1c** and *syn*-**1c** housanes at 20 °C in the low-viscosity $CDCl_3$ (entry 3) and in the much more viscous solvents 1,2-propanediol (entry 4) and 1,4-butanediol (entry 5), according to the previously described procedure.[7] Although the viscosity was varied by almost 200-fold, the **2c**:**3c** cyclopentene ratios were nearly the same within the experimental error (ca. 3%); thus, the electron-transfer-induced rearrangement of the isomeric housanes **1c** does not depend on the solvent viscosity. This behavior is in marked contrast with that reported previously for the structurally more complex tetracyclic housane *anti*-**1a**, for which a substantial viscosity effect was disclosed.[7]

To account for the partial stereochemical memory displayed by the product data in Table 1 for the housanes **1c**, the mechanism in Scheme 2 is proposed. Thus, on electron transfer, the *anti*-**1c** and *syn*-**1c** housanes afford the *puckered* radical cations *anti*-**1c**$^{\bullet+}$ and *syn*-**1c**$^{\bullet+}$ with the original housane geometry.[5,8,9] These puckered conformers subsequently relax to the ring-opened *twisted* structures *anti*-**1c**$^{\bullet+}$ and *syn*-**1a**$^{\bullet+}$ by breakage of the one-electron bond.[8] Some interconversion between the ring-opened radical cation conformers *anti*-**1c**$^{\bullet+}$ and *syn*-**1c**$^{\bullet+}$ takes place; however, the 1,2-shifts to the diastereomeric cyclopentenes **2c** ($k_2$) and **3c** ($k_3$) proceed faster than the *anti*-to-*syn* ($k_1$) and *syn*-to-*anti* ($k_{-1}$) conformational changes.

Analogous to carbocations, the rearrangement of the 1,3 radical cations is of the Wagner−Meerwein type,[2] and therefore, for migration to occur, the stereoelectronic requirements of a coplanar alignment of the migrating group relative to the migration terminus has to be fulfilled.[2,3,7,11] This requisite is best met for the *pseudoaxial* substituents, and hence, the $CD_3$ group that occupies the pseudoaxial position migrates in preference.[7,11] For that reason, the *anti*-**1c** diastereomer leads mainly to the *exo* product **2c**, while the *syn*-**1c** diastereomer affords mainly the *endo* product **3c**. Therefore, on removal of the cyclohexane annelation, the radical cation rearrangement switches from Curtin−Hammett behavior for the tetracyclic housane **1a** to partial stereochemical memory for the tricyclic housane **1c** (Scheme 2). These findings corroborate our recent conclusion that cyclohexane annelation is decisive for the unprecedented Curtin−Hammett behavior in the rearrangement of the radical cation derived from housane **1a**.[7]

For the evaluation of the quantitative extent of stereochemical loss through the conformational interconversion

**Scheme 3**




*anti*-**1c**$^{\bullet+}$(twisted) ⇌ *syn*-**1c**$^{\bullet+}$(twisted), we consider the general case in Scheme 3. It should be evident that, for the tricyclic housanes *anti*-**1c** and *syn*-**1c**, the ratios $k_2/k_1$ and $k_3/k_{-1}$ serve as a quantitative measure of stereoselectivity; that is, for the case $k_2 \gg k_1$ and $k_3 \gg k_{-1}$ perfect stereochemical memory applies, whereas for the case $k_2 \ll k_1$ and $k_3 \ll k_{-1}$ complete Curtin−Hammett behavior operates.[12]

The kinetics for the general mechanism in Scheme 3 has been analyzed by Seeman[12a] and applies to the rearrangement of the radical cations **1c**$^{\bullet+}$ presented herein.

From the product data in Table 1 we have calculated the selectivity ratios $k_2/k_1 = 6.7 \pm 0.5$ (from *anti*-**1c**) and $k_3/k_{-1} = 2.8 \pm 0.3$ (from *syn*-**1c**) in Scheme 3 for the rearrangement of the isomeric housanes (this kinetic analysis is given in the Supporting Information). Thus, the $CD_3$ migration in the *anti*-**1c**$^{\bullet+}$ conformer ($k_2$) proceeds ca. 7 times faster than the conformational *anti*-to-*syn* change ($k_1$), whereas the $CD_3$ transfer in the *syn*-**1c**$^{\bullet+}$ conformer ($k_3$) is only ca. 3 times faster than the *syn*-to-*anti* conformational change ($k_{-1}$). The preference for the *exo*-cyclopentene **2c** product ($k_2 > k_3$) is presumably due to the larger steric interaction with the annelated cyclopentene ring during the transposition of the pseudoaxial $CD_3^{ax}$ group in the radical cation conformer *syn*-**1c**$^{\bullet+}$. Consequently, such annelation in the radical cation causes some loss of diastereoselectivity in the direction **3c**(*endo*) to **2c**(*exo*) compared to the simple housanes **1b** (complete stereochemical memory). When, however, additionally cyclohexane annelation is introduced at the bridgehead position, as in the structurally

(12) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134. (b) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42−48. (c) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351−354.

more complex tetracyclic housane *anti*-**1a**, all stereochemical memory is erased because presumably the conformational changes $k_1$ and $k_{-1}$ are now faster compared to the rearrangement steps $k_2$ and $k_3$; consequently, Curtin−Hammett behavior is observed. Thus, appropriate ring annelation in the cyclopentane-1,3-diyl radical cation **1c**$^{\bullet+}$ changes the stereochemical outcome of the rearrangement from complete stereochemical memory (bicyclic housane **1b**) to partial stereoselectivity (tricyclic housane **1c**), and even to complete loss of stereocontrol (tetracyclic housane **1a**) through competing conformational equilibration (Curtin−Hammett conditions). Such structure−reactivity interplay is so far unprecedented.

Mechanistically relevant in this context are the viscosity effects: Whereas the **2**:**3** product ratio for the tetracyclic housane **1a** depends on the viscosity of the medium,[7] such influence was not observed for the tricyclic housane **1c**, examined in the present study (Table 1, entries 3−5). To rationalize this dichotomy mechanistically, it should be noted (Scheme 2) that, in the rearrangement of the housane **1c**, the opened radical cations *anti*-**1c**$^{\bullet+}$ and *syn*-**1c**$^{\bullet+}$ afford the two diastereomeric cyclopentenes **2c** and **3c** through the same structural changes. Consequently, viscosity cannot differentiate between these two radical cation conformers during the transposition because the same frictional interactions operate. In contrast, for the rearrangement of the two radical cation conformers *anti*-**1a**$^{\bullet+}$ and *syn*-**1a**$^{\bullet+}$ derived from the housane *anti*-**1a**, two structurally distinct products, **2a** ($\sim CH_3$) and **3a** ($\sim CH_2$), are generated. The viscosity effect on the rearrangement process resides in the difference of the frictional impositions by the solvent on the ring contraction, i.e., methylene group migration (major structural change) versus methyl migration (minor structural change).[7] In both cases, the initially generated puckered radical cations *anti*-**1**$^{\bullet+}$ and *syn*-**1**$^{\bullet+}$ with original housane geometry relax to the corresponding ring-opened conformers *anti*-**1**$^{\bullet+}$ and *syn*-**1**$^{\bullet+}$, which are in conformational equilibrium (Curtin−Hammett conditions). Clearly, the cyclohexane annelation in the radical cation *anti*-**1a**$^{\bullet+}$ promotes conformational reorganization to the *syn*-**1a**$^{\bullet+}$ confomer to compete more effectively with the 1,2-shift of the $CH_3$ group, such that $k_1$ and $k_{-1}$ are faster than $CH_3$ migration ($k_2$) and ring contraction ($k_3$). The stereoelectronic requisite for the 1,2-shift, namely, essential coplanar alignment of the migrating group with the migration terminus, is a less accessible conformation for the cyclohexane-annelated radical cation **1a**$^{\bullet+}$ than for the simpler derivative **1c**$^{\bullet+}$; thus, the partial stereochemical memory effect observed for the tricyclic **1c**$^{\bullet+}$ is erased by the facile conformational equilibration of the tetracyclic **1a**$^{\bullet+}$.

## Conclusion

The present study provides valuable mechanistic insight into the intricacies and complexities of the rearrangement of housane-derived radical cations. It has been demonstrated that structural changes allow manipulation of the conformational effects in the rearrangement of cyclopentane-1,3-diyl radical cations such that either stereochemical memory or Curtin−Hammett behavior is observed.

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**Supporting Information Available:** Kinetic analysis and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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