The Use of Stochastic Search in Looking for Homeomorphic Isomerism: Synthesis and Properties of Bicyclo[6.5.1]tetradecane

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Abstract: The stochastic search method of molecular mechanics was used to examine a series of bicyclic hydrocarbons leading to the prediction that bicyclo[6.5.1]tetradecane (**6**) was most likely to exhibit the homeomorphic isomerization process. Therefore, out,out-, in,out- and in,in-isomers of bicyclo[6.5.1]tetradecane were prepared by catalytic hydrogenation of the in- and out-isomers of bicyclo[6.5.1]tetradec-1(2)-ene (**5**), which were, in turn, made by the intramolecular McMurry olefination of keto aldehyde 3-(6-oxohexyl)cyclooctanone. The kinetics and thermodynamics of interconversion of the in- and out-isomers of the olefin and of the out,out- and in,in-isomers of the hydrocarbon via the homeomorphic isomerization process were measured.

Molecules containing bicyclic ring systems possess a unique kind of isomerism: the hydrogen atoms (or other functional groups) attached to the bridgeheads can point to the outside or the inside of the molecule. Thus, these molecules can exist as in,in-, in,out-, or out,out-isomers.[1] Special attention has been directed to the study of bicyclic ring systems with nitrogen atoms as bridgeheads;[1] however, several bicyclic hydrocarbons have been synthesized and examined for phenomena connected with their in/out-isomerism.[2] Recently, the stochastic search method[3] has been applied to 32 bicyclic hydrocarbons[4] to locate the lowest energy conformations of the out,out-, in,out-, and in,in-isomers. In the cases of the smaller bicyclics, the out,out-isomers are found to be more stable, but as the bridge lengths increase, the in,out-isomers become lower in energy, and eventually they are replaced by in,in-isomers as the predicted best. This is in agreement with experimental observations: whereas small bicyclic hydrocarbons have only been synthesized as out,out-isomers,[2b,c] larger ones have been obtained as in,out-isomers.[2d,f,h,i] Of course, it may depend on the synthetic route which isomer is synthesized.[2a,d,f,h,j] Gassman et al. have specifically prepared in, out-isomers.[2d,f,h] Even in cases where the route is not stereospecific, the most stable isomer may not always be obtained. The stochastic search study located the ring sizes where the changes in order of stability between the different isomers occur.

For sufficiently large bicyclic ring systems, it should be possible to invert both bridgeheads at once by pulling one of the bridging chains between the other two and turning the molecule inside out. This transformation has been called "homeomorphic isomerism" by Parks and Simmons,[2e,5] and if it occurs, it should interconvert the in,in- and out,out-isomers. In,out-isomers should not be converted to anything else, but their bridgeheads should interchange functionality. Changes in the low-temperature NMR spectra of large several bicyclic polyethers[2g] have been ascribed to this process.

In order to have an opportunity to observe such a process in a bicyclic hydrocarbon, we looked for one with almost the same energy for all three isomers. If the synthesis produced the in,in- or out,out-isomer, the formation of the other isomer and/or the observation of line broadening in the NMR spectrum would demonstrate homeomorphic isomerism. If the in,out-isomer were produced, line broadening in the NMR spectrum might be observable if the two bridgeheads are interchanged at a sufficient rate. Bicyclo[6.5.1]tetradecane was selected, since the stochastic search study predicted that the out,out-, in,out-, and in,in-isomers should have almost the same MM2 strain energy (42.15, 40.18, and 42.44 kcal/mol, respectively). In addition to our desire to observe homeomorphic isomerism in a hydrocarbon, we also hoped to measure the equilibrium constant between the in,in- and out,out-isomers in order to compare the results with the predictions of MM2.

Synthesis of Bicyclo[6.5.1]tetradec-1(2)-ene (5). For the synthesis of bicyclo[6.5.1]tetradecane, a route involving successive 1,4- and 1,2-additions to a monocyclic enone was employed (see Scheme I). Thus, Michael addition of the mixed cuprate **2**, readily available from 6-lithio-1-tetrahydropyranyloxyhexane and 1-hexynylcopper, to 2-cyclooctenone (**1**) furnished 3-(6-(tetrahydropyranyl)oxy)hexyl)cyclooctanone (**3**) in 81% yield. Removal of the THF group and Swern oxidation led to the keto aldehyde **4** (57%). The key step in this route, the intramolecular McMurry olefination[6] of **4** was carried out according to a procedure of Nickon[6b] and provided the bridgehead olefin **5** in 38% yield. This olefin possesses several intriguing properties, which are discussed in the following section.

Thermodynamics and Kinetics of the Homeomorphic Isomerism of Bicyclo[6.5.1]tetradec-1(2)-ene (5). The NMR spectra of **5** showed the presence of *two* olefins: in the ^1H NMR spectrum, two signals for olefinic protons are found at δ = 5.41 and 5.02 (ratio 1.4:1), and the ^{13}C NMR spectrum consisted of 28 signals, four of them in the olefinic region (see Experimental Section). One possible explanation for this finding is that both the in- and out-isomers of **5** were formed in the McMurry reaction (see Figure 3). The application of the stochastic search method shows that this assumption is reasonable. The MM2 strain energies for the best conformers of **5** are virtually identical (34.64 kcal/mol for *out*-**5**, 34.65 kcal/mol for *in*-**5**). Both of these structures had cis double bonds in the nine-membered ring. The possibility that

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(1) Alder, R. W. *Acc. Chem. Res.* **1983**, *16*, 321-327.

(2) (a) *out,out*-Bicyclo[5.3.1]undecan-11-one: Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Org. Chem.* **1967**, *32*, 2664-2669. (b) *out,out*-Bicyclo[3.3.3]undecane: Doyle, M.; Parker, W.; Gunn, P. A.; Martin, J.; MacNicol, D. D. *Tetrahedron Lett.* **1970**, 3619-3622. (c) *out,out*-Bicyclo[3.3.3]undecane: Leonard, N. J.; Coll, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 6685-6686. (d) *in,out*-Bicyclo[8.2.2]tetradecane system: Gassman, P. G.; Thummel, R. P. *J. Am. Chem. Soc.* **1972**, *94*, 7183-7184. (e) *in,out*- and *in,in*-Bicyclo[8.8.8]hexacosane: Parks, C. E.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 7184-7186. (f) *in,out*-Bicyclo[7.2.2]tridecane system: Gassman, P. G.; Korn, S. R.; Bailey, T. F.; Johnson, T. H. *Tetrahedron Lett.* **1979**, 3401-3404. (g) *in,out*-Bicyclic polyethers: Hains, A. H.; Karntiang, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2577-2587. (h) *in,out*-Bicyclo[6.2.2]dodecane system: Gassman, P. G.; Hoye, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 2496-2498 and 2498-2500. (i) *in,out*-Bicyclo[4.4.4]tetradecane: McMurry, J. E.; Hodge, C. N. *J. Am. Chem. Soc.* **1984**, *106*, 6450-6451. (j) *in,out*-Bicyclo[5.3.1]undecan-11-one: Winkler, J. D.; Hey, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6425-6427. (k) *in,out*- and *out,out*-Bicyclo[5.3.1]undecane: Winkler, J. D.; Sridar, V.; Rubo, L.; Hey, J. P.; Haddad, N. *J. Org. Chem.* **1989**, *54*, 3004.

(3) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150-3152.

(4) Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203.

(5) Parks, C. H.; Simmons, H. E.; *J. Am. Chem. Soc.* **1968**, *90*, 2431-2432.

(6) (a) McMurry, J. E.; *Acc. Chem. Res.* **1983**, *16*, 405-411. (b) Nickon, A.; Hrnjez, B. *Tetrahedron* **1988**, *44*, 1905-1944.

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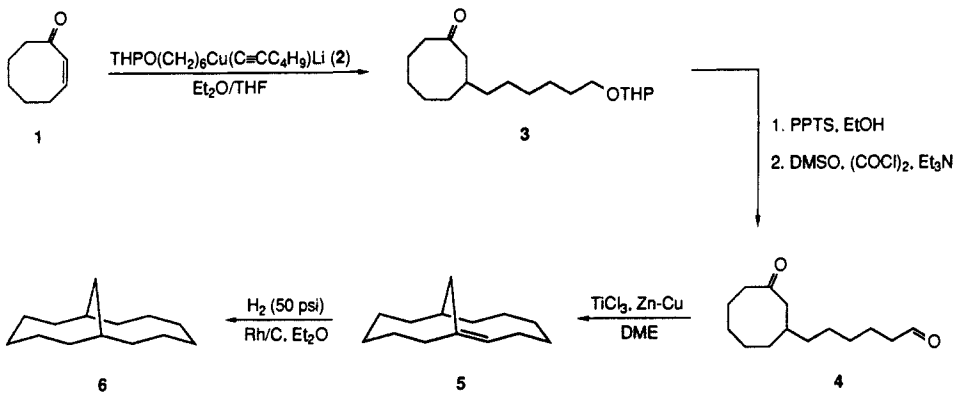
Scheme I



trans-cyclononene isomers were formed was considered unlikely since the stochastic search found that the best trans structure had 43.07 kcal/mol MM2 strain energy, 8.4 higher than the in- and out-cis-isomers. Since the strain energies for the olefin **5** are smaller than those of the corresponding hydrocarbon **6**, the bridgehead olefin **5** presents yet another example of a hyperstable olefin.[7,8]

Attempts to separate the two isomers of **5** by gas chromatography or thin-layer chromatography failed. However, on silica gel coated TLC plates that had been impregnated with silver nitrate[9] before use, two spots were detected. Accordingly, column chromatography with $AgNO_3$-treated silica gel served to separate *in*- and *out*-**5**. The ^1H NMR spectra of the two isomers allowed a preliminary assignment of their structures. The faster moving, major component of the mixture shows seven signals for protons in the region δ = 2.61–1.96; six protons are allylic, whereas the seventh is probably the bridgehead proton. In contrast to this, in the ^1H NMR spectrum of the minor, slower moving component, one very high-field shifted signal is found at δ = 1.22. If one assumes that the bridgehead hydrogen of the in-isomer is shielded by the anisotropic effect of adjacent carbon–carbon bonds, one would assign the in-structure to the minor component. For the bridgehead hydrogen of *out*-**5**, no such shielding and therefore a "normal" chemical shift of $\delta \sim 2$ is expected; therefore, the major component is assigned the out-structure. A similar argument was used by McMurry for assigning the signals of the bridgehead hydrogens of in,out-bicyclo[4.4.4]tetradecane.[21] The remaining spectral data for the isomers of **5** are not so useful for structural assignment. The chemical shifts of the bridgehead carbon atoms are very similar (*out*-**5**: δ = 37.8, *in*-**5**: δ = 35.8), and the shifts of the olefinic protons (*out*-**5**: δ = 5.41, and *in*-**5**: δ = 5.02) and carbon atoms (*out*-**5**: δ = 138.7 (s), 127.4 (d); *in*-**5**: δ = 145.6 (s), 120.5 (d)) show no clear correlation to an in- or out-structure. Additional evidence for the structural assignment of the isomers of **5** is given by the stereochemical course of their hydrogenation (see below).

As in the case of bicyclic hydrocarbons, the two isomers of **5** might be interconverted via the homeomorphic isomerization process (Figure 3). The separated isomers of **5** are stable at room temperature and remain unchanged for weeks; therefore, the activation barrier for this isomerization is substantial. However, when the samples were heated, the ratio of isomers changed. In order to study the thermodynamics of this process, samples of **5** were heated in NMR tubes to certain temperatures and allowed to equilibrate. The reaction was stopped by rapidly cooling the tubes back to room temperature, and the out:in ratios were determined from the integrals of the olefinic resonances in the ^1H NMR spectrum. Up to 80 °C, the initial ratio of out:in = 1.4 remains unchanged; at 90 °C, it is shifted to 1.70. The results at higher temperatures are as follows: 100 °C, out:in = 1.74; 110 °C, 1.79; 120 °C, 1.84; 130 °C, 1.96. From a Van't Hoff plot of these data the following parameters are obtained: ΔH = 0.7 kcal mol^{-1} and ΔS = 3.1 cal mol^{-1} deg^{-1}. Remarkably, the equilibrium constant increases with rising temperature instead of becoming closer to 1, the value one might expect.

One might discuss such an effect as being due to the predominant isomer being favored by entropy and disfavored by enthalpy with respect to the minor isomer. However, there is no obvious reason to expect substantial entropy differences between these different structures. There is another possible way of accounting for this phenomenon without assuming such entropy differences. If one assumed, for example, that a single conformer of the minor isomer (*in*-**5**) is lowest in energy but that there are a number of conformers of the major (out-) isomer which are slightly higher in energy and are increasingly populated at higher temperature, this would shift the equilibrium in the observed direction. Calculation of the Boltzmann populations with one in-conformer lowest in energy shows that at least four out-conformers would be needed to reproduce the equilibrium constants determined experimentally. The actual situation is probably more complicated. We note that the first 20 conformers found by the stochastic search span only 2.5 kcal/mol and of them six are in and 14 out. Although the stochastic search using the MM2 force field does very well in predicting the experimental result that the best conformers of the isomers are similar in energy, one cannot expect the energies to be more accurate than one or two kcal/mol. If one or two in-conformers were lowest in energy followed by a number of out-conformers, the temperature dependence would be as described.

We also studied the kinetics of the homeomorphic isomerism of **5**. Samples of **5** (mostly the out-isomer) were heated at a constant temperature for periods of time and cooled rapidly to room temperature, and the out:in ratio was determined by ^1H NMR spectroscopy. The following rate constants were measured for the reaction *out*-**5** to *in*-**5**: 90 °C, 8 × 10^{-4} s^{-1}; 100 °C, 2.3 × 10^{-3} s^{-1}; 110 °C, 6.3 × 10^{-3} s^{-1}. From these data, the following parameters were obtained: E_A = 28 kcal/mol and log A = 14.0. As expected for a unimolecular reaction, the preexponential factor corresponds to an activation entropy close to zero. To the best of our knowledge, this case represents the first observation of homeomorphic isomerism for a bicyclic bridgehead olefin. Cis–trans isomerization, if it could occur, would be expected to have a much higher barrier.

Synthesis of Bicyclo[6.5.1]tetradecane (6). The hydrogenation of a hyperstable olefin is usually difficult, since the saturated hydrocarbon formed is more strained than the starting olefin.[7,8] This proved to be the case for **5**. Attempts to produce hydrocarbon **6** by treatment of a solution of **5** in diethyl ether with 50 psi hydrogen and palladium on charcoal or platinum dioxide failed.

(7) Definition of and calculations on hyperstable olefins: (a) Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891–1900. (b) McEwen, A. B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1986**, *108*, 3951–3960.

(8) Syntheses of hyperstable olefins: (a) Murad, A. Ph.D. Thesis, Würzburg, 1979. Murad, A.; Hopf, H. *Chem. Ber.* **1980**, *113*, 2358–2371. (b) Aalbersberg, W. G. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1979**, 1939–1942. (c) Noble, K.-L. Ph.D. Thesis, Würzburg, 1980. Noble, K.-L.; Hopf, H.; Ernst, L. *Chem. Ber.* **1984**, *117*, 455–473. (d) Kukuk, H.; Proksch, E.; De Meijere, A. *Angew. Chem.* **1982**, *94*, 304; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 306. (e) Tobe, Y.; Kishimura, T.; Kakiuchi, K.; Odaira, Y. *J. Org. Chem.* **1983**, *48*, 551–555. (f) Lit. 2i. (g) Li, Z.; Jones, M., Jr. *Tetrahedron Lett.* **1987**, *28*, 753–754.

However, rhodium on charcoal turned out to be an effective catalyst for this transformation. Starting with the isomeric mixture of **5**, it takes 6 days with 50 psi H_2 to achieve complete consumption of the olefin. The target molecule, bicyclo[6.5.1]tetradecane (**6**), is isolated in ca. 90% yield. The identification of the isomers of **6** is simplified by the fact that the in,in- and out,out-isomers possess planes of symmetry, whereas the in,out-isomer is asymmetric. Therefore, the ^{13}C NMR spectra of *in,in-* and *out,out-***6** should each consist of eight signals, whereas the spectrum of *in,out-***6** should show 14 signals. This scheme has already been used for the structural assignment of several bicyclic molecules.[2a,c,j] The carbon spectrum of **6**, produced by hydrogenation of a mixture of *in-* and *out-***5**, consists of 28 signals. Obviously, all three isomers of **6** were formed, but some of their resonances are not resolved.

The two isomers of **5** show very different reactivities toward catalytic hydrogenation. If one starts with *in-***5**, the reaction is complete after 1 day, and the product is exclusively *in,out-***6** (92% yield; see Experimental Section). As expected, the ^{13}C NMR spectrum consists of 14 signals; the bridgehead carbon atoms are found at δ = 37.3 and 27.5. In the ^1H NMR spectrum, a broad multiplet at δ = 1.80–1.16 and two high field signals are found at δ = 1.06 and 0.90; the latter can be attributed to the in-bridgehead hydrogen (in the case of in,out-bicyclo[4.4.4]tetradecane, the resonances for the in- and out-bridgehead protons are found at δ = 0.81 and 2.50, respectively[2i]). As expected on steric grounds and observed in other cases,[2i,8] the hydrogenation of the bridgehead double bond of *in-***5** occurs exclusively from the outside of the molecule.

The catalytic hydrogenation of *out-***5**, however, takes 6 days for completion. The product, isolated in 91% yield, is a mixture of ca. 50% *in,out-***6**, ca. 40% *out,out-***6**, and ca. 10% *in,in-***6** (see Experimental Section). Incidentally, this is the first case in which the out,out-, in,out-, and in,in-isomers for a single bicyclic hydrocarbon are all reported. At first glance, it seems as if the hydrogenation of *out-***5** is not stereoselective and occurs from the outside (→ *out,out-***6** ⇄ *i,in-***6**) as well as from the inside (→ *in,out-***6**) of the starting olefin. However, we believe that the activated rhodium catalyst is able to promote the isomerization of the olefin *out-***5** to *in-***5**, which is then reduced (relatively) rapidly to *in,out-***6**. In the hydrogenation of *in-***5**, this isomerization cannot compete with the much faster reduction. The ^1H NMR spectrum of the isomeric mixture of **6** contains one low-field shifted resonance at δ = 1.92, which can be attributed to the bridgehead hydrogen of *out,out-***6**; the signal of the bridgehead proton of *in,in-***6** is too small to be detected directly. Thus, the major symmetrical hydrogenation product is *out,out-***6**, an assignment that is confirmed by a magnetization transfer experiment (see below). In the ^{13}C NMR spectrum of the mixture, aside from the peaks for *in,out-***6**, there are eight strong signals for *out,out-***6** and six weak signals for *in,in-***6**. The remaining two peaks are probably hidden under the stronger signals. The bridgehead carbon atoms are found at δ = 41.9 (*out,out-***6**) and δ = 43.1 (*in,in-***6**).

If one stops the reduction of *out-***5** before completion, one finds a triplet at δ = 5.50, in the ^1H NMR spectrum in addition to signals for **6** and *out-***5**. This is probably due to the formation of bicyclo[6.5.1]tetradec-1(13)-ene (**7**). A stochastic search study predicts that the MM2 strain energies of the best conformers of this olefin (*out-***7** 34.92 and *in-***7** 35.95 kcal/mol) are very close to those of **5**, so that the formation of this olefin, probably by addition of hydrogen to form the bridgehead radical as an intermediate, seems reasonable. The third possible bridgehead olefin, bicyclo[6.5.1]tetradec-1(14)-ene, has much higher predicted strain energies (out, 38.43; in, 39.91 kcal/mol) and is not detected during the catalytic hydrogenation of **5**. As already mentioned, isomers with the double bonds trans in the nine- or eight-membered rings are higher still in energy and can be excluded.

If one treats a solution of **5** in chloroform with an excess of DCl and analyzes the product with mass spectrometry, one finds that up to five deuterium atoms are incorporated into the olefin due to the increase in strain, no addition product is formed). Thus,

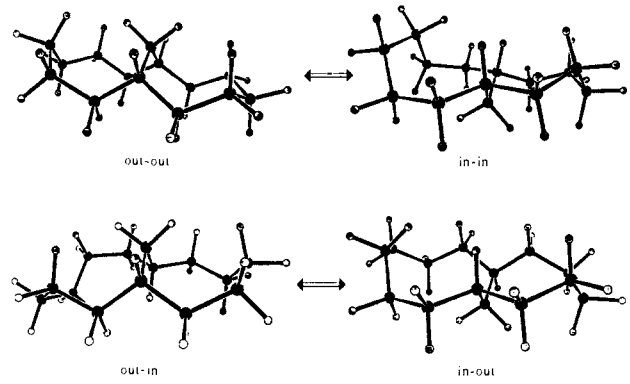


Figure 1. Homeomorphic isomerism in bicyclo[6.5.1]tetradecane (**6**).

under these conditions, all three possible regioisomeric bridgehead olefins must be formed by addition–elimination steps. Another interesting result is provided by the catalytic deuteration of *out-***5**. In the ^1H NMR spectrum after 5 days reaction time all signals but two (δ = 1.27, 0.90) have disappeared; i.e., deuterium has exchanged into *all but two positions* of **6**, obviously via consecutive dehydrogenation–hydrogenation steps. The peak at δ = 0.90 probably belongs to the in-bridgehead proton of *in,out-***6**; a dehydrogenation at this position from the outside would only be possible after inversion by homeomorphic isomerism, but this process does not occur for *in,out-***6** at room temperature (see below). The peak at δ = 1.27 might be attributed to the protons of the 1-carbon bridge; these could only be exchanged if the energetically unfavorable bicyclo[6.5.1]tetradec-1(14)-ene were formed.

Thermodynamics and Kinetics of the Homeomorphic Isomerism of Bicyclo[6.5.1]tetradecane (6). As pointed out in the introduction, homeomorphic isomerism should interchange the in,in- and out,out-isomers but only interchange the bridgeheads of the in,out-isomer. This could lead to line broadening in its NMR spectra, provided that this process was sufficiently fast. Figure 1 illustrates these isomerization processes. The conformers shown are those predicted to be the best of each type by the stochastic search. Notice that the in,out-isomer is chiral. The homeomorphic isomerism process, while it interconverts the in- and out-bridgeheads, should not lead to racemization. Rotating the product 180° brings the structure back to superimposability.

In order to observe this interchange, we heated a sample of *in,out-***6** in toluene-d_8 in an NMR spectrometer up to 110 °C. However, the ^{13}C NMR spectrum remained unchanged, and no line broadening was observed up to this temperature. Thus, the activation barrier for homeomorphic isomerism in *in,out-***6** is higher than ca. 30 kcal/mol. In contrast to this, line broadening could be detected in the ^{13}C NMR spectra of the mixture of *in,in-* and *out,out-***6** (see Figure 2). At 50 °C, the signals for the in,in-isomer start to broaden, and at 70 °C this occurs for the resonances of the out,out-isomer. At 90 °C, the signals for the *in,in-***6** disappear under the background noise. From the line widths, the following rate constants for the reaction of *out,out-***6** to form *in,in-***6** were obtained:[10] 60 °C, 0.6 s^{-1}; 70 °C, 1.7 s^{-1}; 80 °C, 5.2 s^{-1}; 90 °C, 11.5 s^{-1}. From these data, the following parameters were obtained: E_A = 24 kcal/mol and log A = 15.5. As in the case of the homeomorphic isomerism of olefin **5**, the preexponential factor corresponds to a small value for the activation entropy. From the intensities of the signals in the ^{13}C NMR spectrum at 50 °C, a ratio of *out,out-* to *in,in-***6** of 4 was estimated; this value is equivalent to a free-energy difference of ΔG = 0.9 kcal/mol. Although it was not possible to determine ΔH and ΔS by measuring the temperature dependence of the equilibrium constant, the prediction of MM2 that *in,in-* and *out,out-***6** are almost equal in energy is in good agreement with the experiment. Un-

(9) Cf.: Ajmal, M.; Mohammad, A.; Fatima, N. *J. Liq. Chromatogr.* **1986**, *9*, 1877–1902.

(10) *Dynamic NMR Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975.

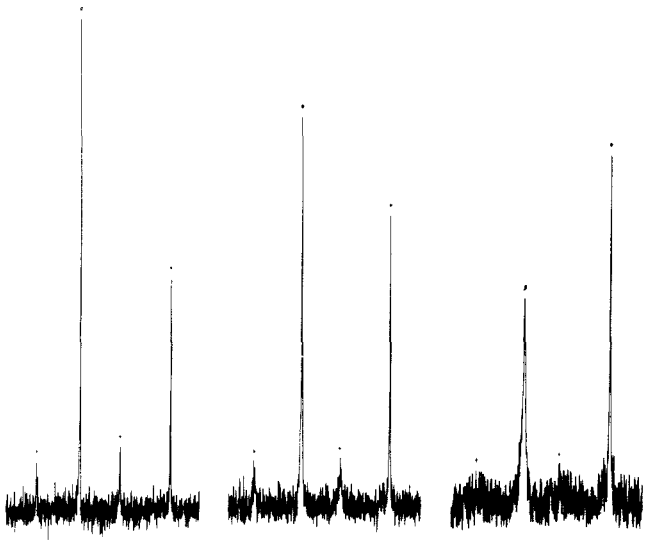


Figure 2. ^{13}C NMR spectra of a mixture of *in,out*-6(*), *in,in*-6(+), and *out,out*-6( ); region, δ = 45–38; solvent, toluene-d_8; temperature, 50 °C (left), 70 °C (middle), 90 °C (right).

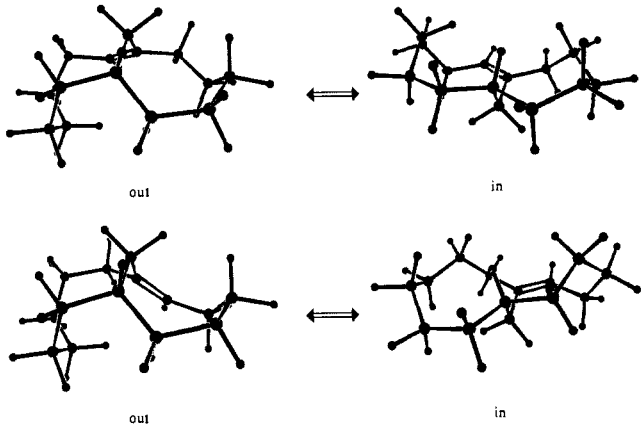


Figure 3. Homeomorphic isomerism in bicyclo[6.5.1]tetradec-1(2)-ene (5) and bicyclo[6.5.1]tetradec-1(13)-ene (7).

fortunately, we were not able to determine the energy difference between *in,out*-6 and the two symmetrical isomers, since no conditions for equilibrating them could be found.

Line broadening was also observed in the ^1H NMR spectrum for the signal of the bridgehead protons of *out,out*-6 at δ = 1.92. However, due to the large natural line width of this multiplet, no rate constants could be determined. In order to confirm that we are indeed observing the equilibrium *out,out*-6 $\rightleftharpoons$ *in,in*-6, we conducted a magnetization transfer experiment.[11] The sample of *in,in*- and *out-out*-6 in toluene-d_8 was heated in the NMR spectrometer to 100 °C, and the ^1H NMR spectrum was observed with decoupling in different parts of the proton spectrum. It was found that the signal at δ = 1.92 disappears if the decoupler frequency is set at δ = 1.21; thus, this is the chemical shift for the bridgehead protons of *in,in*-6. Cooling of the sample, with decoupling still on, caused the signal at δ = 1.92 to reappear, and at 70 °C it had the original intensity. This experiment confirms the structural assignment of *in,in*- and *out,out*-6 as well as the occurrence of homeomorphic isomerism in this system.

Conclusions

In this paper, it was shown that the predictions of MM2 in connection with the stochastic search method can be a very great help in searching for target molecules with certain properties. It allowed us to choose the hydrocarbon bicyclo[6.5.1]tetradecane (6), which was predicted to be suitable for the observation of homeomorphic isomerism. The experiments confirmed this expectation, and the thermodynamics and kinetics of this process could be studied not only for 6 but also for its precursor, bicyclo[6.5.1]tetradec-1(2)-ene (5). To our best knowledge, these cases represent the first direct observations of homeomorphic isomerism for any bridgehead olefin and for any bicyclic hydrocarbon. This work illustrates the value of applying theoretical and experimental methods together to attack problems related to stereochemistry.

Experimental Section

Reagents and Procedures. All reactions were carried out in thoroughly dried glassware under nitrogen. Diethyl ether, THE and DME were distilled from lithium aluminum hydride, and dichloromethane was distilled from P_4O_{10} prior to use. All other reagents were used without further purification. ^1H NMR spectra were recorded at 250 MHz or 500 MHz with a Bruker WM-250 or WM-500 spectrometer, respectively, in $CDCl_3$ as solvent and internal standard (δ = 7.27). ^{13}C NMR spectra were recorded at 62.9 MHz with a Bruker WM-250 spectrometer in $CDCl_3$ as solvent and internal standard (δ = 77.05); the multiplicities of the resonances were detected with the DEPT method.[12] IR spectra were recorded with a Nicolet 5-SX FT-IR spectrometer, and mass spectra were recorded with a HP 5985 GC-MS system (EI, 70 eV). High-resolution masses were obtained with a Kratos MS-80RFA instrument. Thin-layer chromatography was performed with precoated TLC plates silica gel 60-F254 (Merck, development with anisaldehyde), and column chromatography was performed with silica gel 230–400 mesh (Merck). For the separation of *in*- and *out*-5, 20 g of silica gel were mixed with 50 mL of a 0.2 M $AgNO_3$ solution, filtered, and dried at 110 °C for 6 h; the TLC plates were impregnated by dipping into 0.2 M $AgNO_3$ solution and drying at 110 °C for 15 min.[9]

6-Lithio-1-(tetrahydropyranyloxy)hexane:[13] 0.87 g (0.125 mol) of lithium wire (1% Na) is hammered flat and cut into pieces (ca. 10 × 3 × 1 mm). THF (40 mL) is added, and the mixture is cooled to between −10 and −20 °C. With vigorous stirring 11.0 g (0.05 mol) of 6-chloro-1-(tetrahydropyranyloxy)hexane[14] is added dropwise in 30 min. Stirring is continued for 3 h between −10 and −20 °C. The concentration of 6-lithio-1-(tetrahydropyranyloxy)hexane is determined to be 0.65 M by titration with diphenylacetic acid.[15]

3-(6-(Tetrahydropyranyloxy)hexyl)cyclooctanone (3). To a solution of 2.05 g (25 mmol) of 1-hexyne in 20 mL of diethyl ether is added with stirring at 0 °C 19.7 mL (25 mmol) of methyllithium (1.27 M solution in diethyl ether). After stirring for 15 min at 0 °C, 4.76 g (25 mmol) of copper(I) iodide is added in one portion. The suspension is stirred for another 30 min at 0 °C and then cooled to −20 °C, and 38.5 mL (25 mmol) of 6-lithio-1-(tetrahydropyranyloxy)hexane (0.65 M solution in THF) is added dropwise. Stirring for 30 min at −20 °C is followed by addition of 3.10 g (25 mmol) of 2-cyclooctenone (1)[16] in 5 mL of diethyl ether. The mixture is warmed up to 0 °C and stirred for 1 h at this temperature. The reaction is quenched by pouring the mixture into saturated NH_4Cl/NH_3 solution (pH = 8); the organic layer is separated, and the aqueous layer is extracted with diethyl ether (4 × 50 mL). The combined organic layers are washed with brine and dried over $MgSO_4$. Removal of the solvent is followed by column chromatography (silica gel, ethyl acetate/pentane = 1:9), yielding 6.28 g (81%) of 3 as a colorless liquid: IR (neat) ν = 2930 (vs), 2854 (vs), 1701 (vs), 1466 (s), 1352 (s), 1200 (s), 1137 (vs), 1078 (vs), 1034 (vs), 988 (s) cm^{-1}; 250 MHz ^1H NMR δ = 4.58 (t, 1 H, J = 2 Hz), 4.0–3.3 (m, 4 H), 2.5–2.2 (m, 4 H), 2.0–1.2 (m, 25 H); ^{13}C NMR δ = 217.2 (s), 98.8 (d), 67.6 (t), 62.3 (t), 47.4 (t), 42.9 (t), 38.0 (d), 37.3 (t), 33.4 (t), 30.8 (t), 29.7 (t), 29.6 (t), 27.7 (t), 27.1 (t), 26.2 (t), 25.5 (t), 24.8 (t), 23.8 (t), 19.7 (t); MS, m/z (%) = 310 (3, M^+), 281 (3), 225 (16), 209 (10), 191 (5), 182 (9), 167 (3), 165 (4), 149 (6), 135 (11), 125 (34), 109 (15), 101 (38), 97 (15), 95 (14), 85 (100), 81 (19), 69 (20), 67 (29), 57 (11), 55 (31); high-resolution mass spectrum (CI, M + H^+) calc 311.2586, found 311.2560.

3-(6-Hydroxyhexyl)cyclooctanone.[17] A solution of 6.21 g (20 mmol) of 3 and 0.50 g (2 mmol) of PPTS in 200 mL of anhydrous ethanol is heated to 55 °C for 3 h. After cooling to room temperature and addition of 600 mL of water the aqueous layer is extracted with diethyl ether (4

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× 50 mL); the combined organic layers are washed with water (93 × 100 mL) and dried over $MgSO_4$. The crude 3-(6-hydroxyhexyl)cyclooctanone obtained after removal of the solvent is used without further purification in the following oxidation.

3-(6-Oxohexyl)cyclooctanone (4).[18] To a solution of 1.9 mL (22 mmol) of oxalyl chloride in 50 mL of dichloromethane is added at −60 °C a solution of 3.1 mL (44 mmol) of DMSO in 10 mL of dichloromethane. After stirring for 10 min at −60 °C, a solution of the crude 3-(6-hydroxyhexyl)cyclooctanone in 20 mL of dichloromethane is added dropwise. The mixture is stirred for another 15 min at −60 °C, followed by addition of 13.9 mL (0.1 mol) of triethylamine. The mixture is warmed up to room temperature, and 100 mL of water is added; the organic layer is separated, and the aqueous layer is extracted with 100 mL of dichloromethane. The combined organic layers are dried over $MgSO_4$, and the solvent is removed in vacuo. To the crude product is added 50 mL of diethyl ether, and the precipitate formed is filtered off; removal of the solvent from the filtrate is followed by Kugelrohr distillation (130–140 °C/0.1 Torr), yielding 2.55 g (57%) of **4** as a colorless liquid: IR (neat) ν = 2935 (vs), 2857 (vs), 2718 (m), 1724 (vs), 1700 (vs), 1466 (s), 1446 (s), 1103 (s) cm^{-1} 250 MHz ^1H NMR δ = 9.67 (t, 1 H, J = 1.8 Hz), 2.4–2.2 (m, 6 H), 2.0–1.2 (m, 17 H); ^{13}C NMR δ = 216.9 (s), 202.4 (d), 47.0 (t), 43.6 (t), 42.8 (t), 37.8 (d), 36.8 (t), 33.2 (t), 29.0 (t), 27.6 (t), 26.7 (t), 24.5 (t), 23.6 (t), 21.8 (t); MS, m/z (%) = 224 (5, M^+), 206 (10), 196 (10), 188 (10), 181 (15), 173 (7), 163 (15), 153 (14), 148 (100), 135 (15), 133 (15), 125 (84), 121 (14), 111 (25), 107 (30), 97 (59), 95 (26), 93 (29), 83 (43), 81 (49), 79 (43), 69 (29), 67 (40), 55 (78); high-resolution mass spectrum (CI, M + H^+) calc. 225.1855, found 225.1848.

Bicyclo[6.5.1]tetradec-1(2)-ene (5).[6] The McMurry reagent is prepared by heating a mixture of 4.62 g (30 mmol) of titanium trichloride and 5.88 g (90 mmol) of a 3% zinc–copper couple in 300 mL of DME to reflux for 4 h. To the refluxing mixture a solution of 750 mg (3.3 mmol) of **4** in 150 mL of DME is added over a period of 24 h; after the addition, reflux is continued for another 2 h. The mixture is cooled to room temperature and filtered through Celite; to the filtrate is added 1 L of water. The aqueous layer is extracted with pentane (4 × 100 mL), and the combined organic layers are dried over $MgSO_4$. Removal of the solvent is followed by Kugelrohr distillation (80–90 °C/0.1 Torr), furnishing 243 mg (38%) of **5** as a colorless liquid. The in- and out-isomers can be separated by column chromatography on $AgNO_3$-impregnated silica gel with ethyl acetate/pentane = 1:100 as eluent: IR (neat) ν = 3033 (w), 2921 (vs), 2857 (s), 1481 (m), 1456 (m) cm^{-1}; 500 MHz ^1H NMR out-**5**, δ = 5.41 (dt, 1 H, J = 0.8/8.1 Hz), 2.61 (dd, 1 H, J = 3.6/14.0 Hz), 2.26–2.14 (m, 5 H), 1.96 (m, 1 H), 1.75–1.23 (m, 16 H); in-**5**, δ = 5.02 (t, 1 H, J = 8.0 Hz), 2.54–2.48 (m, 2 H), 2.35 (dd, 1 H, J = 8.2/14.0 Hz), 2.17 (t, 1 H, J = 13.3 Hz), 2.02–1.30 (m, 18 H), 1.22 (m, 1 H); ^{13}C NMR out-**5**, δ = 138.7 (s), 127.4 (d), 39.5 (t), 37.8 (d), 31.2 (t), 31.0 (t), 30.6 (t), 29.7 (t), 26.8 (t), 26.0 (t), 25.4 (t), 25.1 (t), 24.5 (t), 23.6 (t); in-**5**: δ = 145.6 (s), 120.5 (d), 40.1 (t), 38.4 (t), 36.6 t), 35.8 (d), 30.0 (t), 29.8 (t), 28.1 (t), 27.7 (t), 26.2 (t), 23.5 (t), 20.3 (t), 19.0 (t); MS, m/z (%) = 192 (15, M^+), 149 (10), 135 (20), 121 (49), 110 (21), 107 (17), 95 (49), 93 (38), 81 (77), 79 (56), 67 (63), 65 (12), 55 (20), 53 (18), 43 (100), 41 (99); high-resolution mass spectrum calc 192.1878, found 192.1866.

***in,out*-Bicyclo[6.5.1]tetradecane (*in,out*-6).** A mixture of 43 mg (0.22 mmol) of in-**5** and 5 mg of 5% rhodium on charcoal in 10 mL of diethyl ether is hydrogenated at 50 psi for 1 day. The catalyst is filtered off, and the solvent is removed in vacuo; the crude product is purified by Kugelrohr distillation 80–90 °C/0.1 Torr), yielding 40 mg (92%) of *in,out*-**6** as a colorless liquid: IR (neat) λ = 2919 (vs), 2848 (s), 1477 (s), 1450 (m) cm^{-1}; 500 MHz ^1H NMR δ = 1.,80–1.16 (m, 24 H), 1.06 (m, 1 H), 0.90 (m, 1 H); ^{13}C NMR δ = 39.2 (t), 37.3 (t), 37.3 (d), 31.0 (t), 28.6 (t), 28.5 (t), 27.7 (t), 27.5 (d), 27.3 (t), 24.1 (t), 24.1 (t), 21.0 (t), 20.3 (t), 19.9 (t); MS, m/z (%) = 194 (10, M^+), 166 (35), 152 (8), 137 (8), 123 (28), 110 (60), 96 (100), 81 (83), 79 (16), 69 (24), 67 (51), 55 (36), 41 (27); high-resolution mass spectrum calc 194.2035, found 194.2032.

***out,out*- and *in,in*-Bicyclo[6.5.1]tetradecane (*out,out*- and *in,in*-6).** A mixture of 49 mg (0.25 mmol) of *out*-**5** and 5 mg of 5% rhodium on charcoal in 10 mL of diethyl ether is hydrogenated at 50 psi for 6 days. The catalyst is filtered off, the solvent is removed in vacuo, and the crude product is purified by Kugelrohr distillation (80–90 °C/0.1 Torr), furnishing 45 mg (91%) of a mixture of *in,out*-**6** (ca. 50%), *out,out*-**6** (ca. 40%), and *in,in*-**6** (ca. 10%) as a colorless liquid: IR and MS, see in,-out-**6**; 500 MHz ^1H NMR *out,out*-**6**, δ = 1.92 (m, 1 H), 1.80–1.20 (m, 25 H); ^{13}C NMR *out,out*-**6**, δ = 41.9 (d), 35.9 (t), 35.2 (t), 32.4 (t), 29.6 (t), 29.1 (t), 26.3 (t), 24.4 (t); *in,in*-**6** δ = 43.1 (d), 40.7 (t), 37.2 (t), 32.7 (t), 26.0 (t), 23.5 (t).

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Microporous Aluminum Oxide Films at Electrodes. 7. Mediation of the Catalytic Activity of Glucose Oxidase via Lateral Diffusion of a Ferrocene Amphiphile in a Bilayer Assembly

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Abstract: Glucose oxidase was immobilized in the head group region of an organized bilayer self-assembled in a porous template of aluminum oxide film at a gold electrode. Immobilization of the enzyme involved interactions with the (ferrocenylmethyl)dimethyloctadecylammonium amphiphile, which forms the outer monolayer of the bilayer assembly. The same amphiphile mediates electrooxidation of glucose oxidase via lateral diffusion along the bilayer between the enzyme and the electrode surface. The enzyme immobilization does not restrict electroactivity of the ferrocene surfactant but it appears to bind ca. 60% of its population and thus restricts its participation in the electron transport process. These data lead to a postulate that the enzyme–surfactant interactions involve a much larger number of the ferrocene surfactant molecules than expected from the consideration of just electrostatic interactions.

Formation of organized molecular assemblies designed to perform a specific function is one of the emerging major goals in electrochemical research and other areas of chemistry.[1] Electrocatalytic systems are just one class of such assemblies. Their chemical composition often requires several components: catalyst, electron transfer mediator, and the structural components of a supporting matrix.[2] The structural design of such systems

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