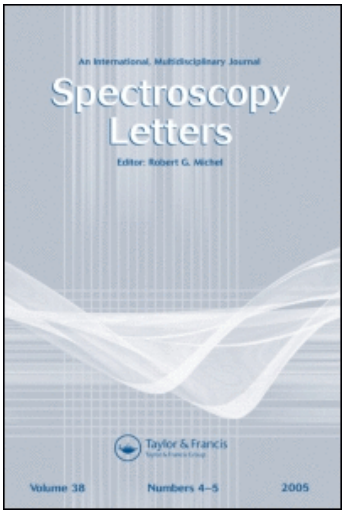

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Isotope Effects by Comparing ^{1}H- and ^{2}D-NMR Spectra of 9,9'-Bisbicyclo[4.3.0]-cyclonona-2,4,7-triene

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Abstract: Inverse secondary kinetic isotope effects are determined for the dimerization of all-*cis*-cyclononatetraenyl radical, **1**, to its corresponding dimer, all-*cis*-9,9′-bicyclonona-1,3,5,7-tetraene, **2**, (step 1, $k_H/k_D = 0.5$), and cyclization of the latter to 9,9′-bisbicyclo[4.3.0]cyclonona-2,4,7-triene, **3** (step 2, $k_H/k_D = 0.75$). These results are obtained by comparison of ^{1}H- and ^{2}D-NMR spectra of **3** and employment of a simple statistical method for acquiring kinetic data. This new strategy appears superior to conventional methods in being fast, simple, and less expensive.

Keywords: Cyclization, dimerization, ^{2}D-NMR, inverse secondary kinetic isotope effect, isotope effect

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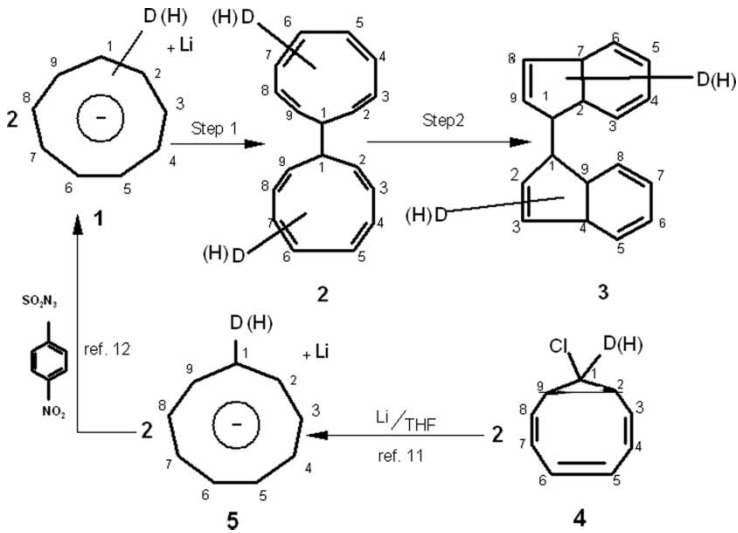
INTRODUCTION

^{2}D-NMR spectroscopy has been very often used to detect isotope effects.[1–3] For example, natural product analysis (wines, fruits, etc.) is based on this technique. ^{2}D-NMR is also applied for chemical reactions.[4–6] This work is based on a valuable NMR property, where the intensity of a given line is proportional to the number of nuclei contributing to that line, provided that certain instrumental precautions are taken.[7] We have already reported the dimerization of cyclononatetraenyl radical **1** to its corresponding dimer, all-*cis*-9,9'-bicyclonona-1,3,5,7-tetraene, **2**, and the cyclization of the latter to the cyclized dimer 9,9'-bisbicyclo[4.3.0]cyclonona-2,4,7-triene, **3** (Scheme 1, steps 1 and 2, respectively).[8–12] When mono-deuterated radical **1** is generated, deuterium scrambled **2** and then **3** are obtained. Precautions are necessary in order to ensure reliable intensity measurements for the ^{1}H- and ^{2}D-NMR of these products, including correct phasing of the spectra, slow recording, avoiding saturation, and accounting for nuclear Overhauser enhancements. Consequently, intensities of the ^{1}H-NMR peaks of the isolated **3** appear to be proportional to the number of corresponding nuclei [Eq. (1), Fig. 1a].

$$\frac{\text{Olefinic protons (5.6 ppm, 6H)}}{\text{Aliphatic proton (3.6 ppm, 1H) + Aliphatic proton (2.8 ppm, 2H)}} = 2.00 \quad (1)$$



Scheme 1. Reaction of **4** with lithium in THF yields **5**. Oxidation of **5** affords radical **1**, which dimerizes to **2**. Subsequent cyclization of **2** gives dimer **3** in 33% yield.

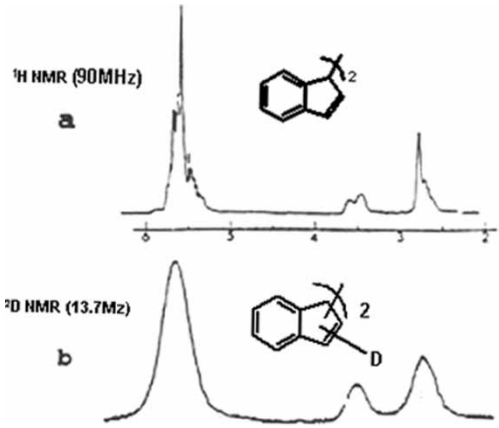


Figure 1. (a) ^{1}H-NMR (90 MHz) of 9,9'-bisbicyclo[4.3.0]cyclonona-2,4,7-triene, 3 in $CHCl_3$. (b) ^{2}D-NMR (13.7 MHz) of 9,9'-bisbicyclo[4.3.0]cyclonona-2,4,7-triene, 3 in $CHCl_3$.

Nevertheless, in the corresponding ^{2}D-NMR spectrum of **3**, this ratio becomes 1.79 [Eq. (2) Fig. 1b].

$$\frac{\text{Olefinic deuteriums (5.6 ppm, 6D)}}{\text{Aliphatic deuterium (3.6 ppm, 1D) + Aliphatic deuterium (2.8 ppm, 2D)}} = 1.79 \quad (2)$$

This means, in spite of all the above precautions (including adverse deuterium polarizability effects on integrations), the intensities of ^{2}D-NMR peaks do not correspond to the number of the contributing nuclei of deuterated **3**. In order to resolve this discrepancy, we explored the possibility of involvement of deuterium kinetic isotope effects in our synthesis of deuterated **2** and **3** (Scheme 1, steps 1 and 2, respectively).

EXPERIMENTAL

Proton and deuterium nuclear magnetic resonance (NMR) spectra are obtained using a JEOL JNM-EX90A spectrometer. Deuterochloroform ($CDCl_3$, purchased from Merck, Germany) is used as the solvent for proton NMR spectra. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS).

Deuterium NMR spectra are taken at 13.7 MHz in $CHCl_3$. A capillary tube, filled with aqueous lithium chloride, is inserted to serve as the lock. A small amount of $CDCl_3$ is used as an internal standard (7.26 ppm). The instrumental conditions are spectral width, 136 Hz; pulse width, 20 μs;

acquisition time, 30 s. Using the method of cut and weight for measuring the area under ^{2}D-NMR peaks, we encountered a better standard deviation than that of the electronic integrator. The former procedure has an error of about 1.74%.

Synthesis of Deuterated 4 (9-Deuterio-9-chlorobicyclo[6.1.0]nona-2,4,6-triene)

To a solution of cyclooctatetraene and dichloromethane-d_2 was added methyllithium, in ether, while cooling in an ice bath and under a nitrogen atmosphere. After completion of the addition, the mixture was stirred for a further 30 min at room temperature. Water was added to dissolve the precipitated lithium chloride. The aqueous layer was separated and washed with chloroform. The organic extracts were combined and dried over $MgSO_4$. The solvent and excess cyclooctatetraene were removed at reduced pressure. The residue was vacuum distilled. The proton NMR spectra of the residue shows a 3:1 mixture of syn- and anti-9-deuterio-9-chlorobicyclo [6.1.0]nona-2,4,6-triene. The proton NMR of *syn* shows a multiplet (6H) at 6.0 ppm and a singlet (2H) at 1.8 ppm. The proton NMR of *anti* shows a multiplet (6H) at 5.9 ppm and a singlet (2H) at 1.7 ppm.

Generation of Cyclononatetraenyl Radical, 2 and Its Dimerization to 1

9-Chlorobicyclo[6.1.0]nona-2,4,6-triene, **4**, is prepared using the method of LaLacetle and Benson.[13] Reaction of **4** with lithium in THF affords lithium cyclononatetraenide, **5**. Treatment of **5** with 4-nitrobenzenesulfonyl azide[14] results in generation of **1**. Radical **1** dimerizes to **2**.[10] Subsequent cyclization of **2** gives dimer **3** in 33% yield.[11] Deuterated **3** is obtained from deuterated **4** (9-deuterio-9-chlorobicyclo[6.1.0]nona-2,4,6-triene), following the above procedure.

The proton NMR of the unlabeled dimer **3** is obtained in $CDCl_3$: δ 5.4–5.9 (m, 12H, olefinic); 3.5–3.7 (broad d, $J = 12$ Hz, 1H, alkyl); 2.7–2.9 (m, 2H, alkyl) (Fig. 1a).

The deuterium NMR of deuterated dimer is shown in Fig. 1b. Proton and deuterium chemical shifts appear essentially the same when expressed in parts per million (ppm).[15]

RESULTS AND DISCUSSION

Inverse secondary kinetic isotope effects are determined for both the dimerization of all-*cis*-cyclononatetraenyl radical, **1**, to its corresponding dimer,

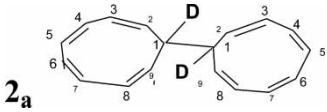
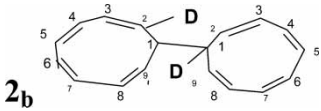
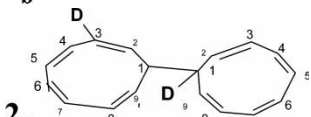
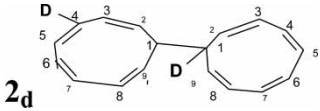
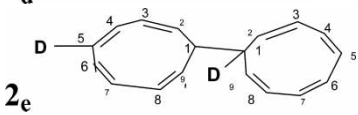
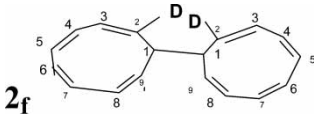
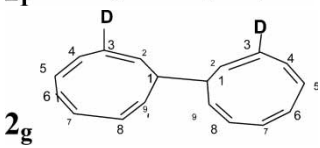
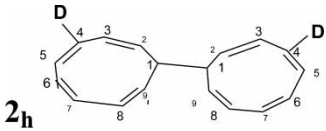
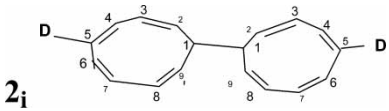
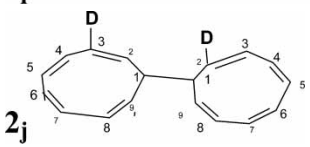
all-*cis*-9,9'-bicyclonona-1,3,5,7-tetraene, **2** (step 1, $k_H/k_D = 0.5$), and cyclization of the latter to 9,9′-bisbicyclo[4.3.0]cyclonona-2,4,7-triene, **3** (step 2, $k_H/k_D = 0.75$).

As one of sp^2-hybridized carbons in the ground state of radical **1** is converted to a sp^3-hybridized carbon in the transition state, lying between **1** and **2** (step 1), the hydrogen bonded to that carbon will experience an increased resistance to C–H bending. Due to the larger amplitude of vibration of C–H, the resistance to the bending mode will be greater for a C–H than a C–D bond, as a C–H bond is about 0.009 Å longer than a C–D bond.[16–18] Similarly, when sp^2-hybridized-carbons 2 and 7, as well as 4 and 9, in the ground state of **2**, were converted to sp^3-hybridized carbons in the transition state responsible for formation of **3** (step 2, Scheme 1), the hydrogens bonded to these carbons would experience an increased resistance to C–H bendings. This resistance will also be greater for a C–H bond than a C–D bond.

Here, we report prospects of involvement of kinetic isotope effects in steps 1 and 2, which explain the unexpected ratio of 1.79 for olefinic deuteriums/alkyl deuteriums, in ^{2}D-NMR spectrum of **3** (Fig. 1b). It is evident that finding a ratio of $k_H/k_D < 1$ is indicative of the involvement of an inverse secondary kinetic isotope effect, while a $k_H/k_D > 1$ corresponds to a normal secondary kinetic isotope effect.[16–18]

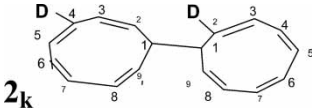
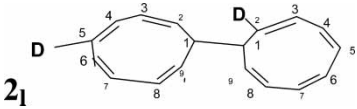
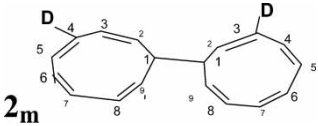
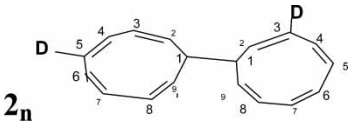
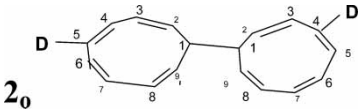
Statistical analysis of dimerizations (step 1) suggests that in the absence of any isotope effect, random dimerizations of **1** should yield equal populations of 81 forms of **2**. This point is illustrated by a square matrix with a 9×9 order. Each element in such a matrix represents a possible form of **2**. However, the presence of a C_s plane of symmetry in **1** reduces these 81 elements to 15 distinct isomers ($\mathbf{2_a}$–$\mathbf{2_o}$, Table 1). In the absence of any isotope effect, the statistical distribution of these isomers is directly proportional to total number of their corresponding element(s) in the square matrix of order 9×9. For example, 8 elements represent dimer $\mathbf{2_k}$. Hence, the ratio of its population is 8/81, while only one element corresponds to dimer $\mathbf{2_a}$ with a 1/81 ratio. For all practical purposes, kinetic isotope effects for dimerization, with an assumed factor of P will alter the statistical population of isomers $\mathbf{2_a}$ through $\mathbf{2_e}$, where at least one deuterium is attached to a sp^3 carbon. If P is found, the magnitude of k_H/k_D for dimerization (step 1) can be estimated. Hence, obtaining $P > 1$, $P < 1$, or $P = 1$ indicates normal, inverse, and no secondary kinetic isotope effect, respectively. In order to find P, one should simultaneously consider the secondary isotope effect for cyclization (step 2). Carbon numbers 1, 3, 5, 6, and 8 have the same hybridization in **2** and **3**, regardless of how ring closure occurs (bridging carbons 2 to 7 vs. 4 to 9), (Scheme 1, Table 2). Deuteriums attached to these carbons contribute very little to the magnitude of the secondary deuterium isotope effect for cyclization. On the other hand, carbons 2, 4, 7, and 9 have sp^2 hybridization in **2** and through cyclization in producing **3**, they become either sp^2 or sp^3 with probability factors of X or

Table 1. Random dimerizations of **1** yield populations of 81 forms of **2** confined to 15 isomers ($\mathbf{2_a}$–$\mathbf{2_o}$)

Isomers of **2**	Corresponding possible form(s) (Elements of the 9 × 9 matrix)	Ratio (With no isotope effect) × 81
 $\mathbf{2_a}$	(1,1)	1
 $\mathbf{2_b}$	(1,2),(1,9),(2,1),(9,1)	4
 $\mathbf{2_c}$	(1,3),(1,8),(3,1),(8,1)	4
 $\mathbf{2_d}$	(1,4),(1,7),(4,1),(7,1)	4
 $\mathbf{2_e}$	(1,5),(1,6),(5,1),(6,1)	4
 $\mathbf{2_f}$	(2,2),(2,9),(9,2),(9,9)	4
 $\mathbf{2_g}$	(3,3),(3,8),(8,3),(8,8)	4
 $\mathbf{2_h}$	(4,4),(4,7),(7,4),(7,7)	4
 $\mathbf{2_i}$	(5,5),(5,6),(6,5),(6,6)	4
 $\mathbf{2_j}$	(2,3),(2,8),(3,2),(3,9), (8,2),(8,9),(9,3),(9,8)	8

(*continued*)

Table 1. Continued

Isomers of **2**	Corresponding possible form(s) (Elements of the 9 × 9 matrix)	Ratio (With no isotope effect) × 81
 **2_k**	(2,4),(2,7),(4,2),(4,9), (7,2),(7,9),(9,4),(9,7)	8
 **2_l**	(2,5),(2,6),(5,2),(5,9), (6,2),(6,9),(9,5),(9,6)	8
 **2_m**	(3,4),(3,7),(4,3),(4,8), (7,3),(7,8),(8,4),(8,7)	8
 **2_n**	(3,5),(3,6),(5,3),(5,8), (6,3),(6,8),(8,5),(8,6)	8
 **2_o**	(4,5),(4,6),(5,4),(5,7), (6,4),(6,7),(7,5),(7,6)	8

Possible structural representation of dimer **2** are presented with their expected ratios, assuming no deuterium isotope effect. Numbers within parentheses indicate carbon to which deuteriums may be attached in each isomer, **2a–o**.

Y, respectively, depending on the mode of ring closure (bridging carbons 2–7 vs. 4–9).

In finding the ratio of X/Y, one may estimate the value of k_H/k_D for cyclization (step 2). Considering possible kinetic isotope effect parameter *X*, *Y*, and *P*, one may determine the extent of deuterium contribution of each of the 15 distinct isomers of **2** (**2_a**–**2_o**, Table 1, Fig. 1). When there is zero involvement of secondary kinetic isotope effect ($X = Y = P = 1$), then the two deuteriums of **3** should appear in ^{2}D-NMR spectrum at 5.6, 3.6, and 2.8 ppm with the intensity ratio of 6:1:2, respectively. However, the kinetic isotope effect will alter this ratio. Expected chemical shifts and intensities of all forms of **3_{a-o}** obtained through cyclization of isomers **2_a** through **2_o** are summarized in Table 2. Because no hybridization change occurs in going from **1** to **2** to **3**, structures **3_g**, **3_i**, and **3_n** contain 8, 8, and 16 deuteriums, respectively. Only five isomers of **2** (**2_{a-e}**) are subject to the kinetic isotope effects in step 1. Nine isomers of **3** (**3_b**, **3_d**, **3_f**, **3_h**, **3_j**, **3_k**, **3_l**, **3_m**, and **3_o**) are affected by kinetic isotope effects in step 2.

Table 2. Expected population ratio of deuteriums in ^{2}D-NMR spectrum of dimer **3** in terms of the probability factors X, Y, and P

Isomers of **3**	Expected deuterium intensities at 5.6 ppm (sp^2)	Expected deuterium intensities at 3.6 ppm (sp^3)	Expected deuterium intensities at 2.8 ppm (sp^3)
$\mathbf{3_a}$	—	—	$2P$
$\mathbf{3_b}$	$2PX$	—	$4P + 2PY$
$\mathbf{3_c}$	$4P$	—	$4P$
$\mathbf{3_d}$	$2PX$	$2PY$	$4P$
$\mathbf{3_e}$	$4P$	—	$4P$
$\mathbf{3_f}$	$4X$	—	$4Y$
$\mathbf{3_g}$	8	—	—
$\mathbf{3_h}$	$4X$	$4Y$	—
$\mathbf{3_i}$	8	—	—
$\mathbf{3_j}$	$8 + 4X$	—	$4Y$
$\mathbf{3_k}$	$8X$	$4Y$	$4Y$
$\mathbf{3_l}$	$8 + 4X$	—	$4Y$
$\mathbf{3_m}$	$8 + 4X$	$4Y$	—
$\mathbf{3_n}$	16	—	—
$\mathbf{3_o}$	$8 + 4X$	$4Y$	—
Total	$64 + 8P + 4PX + 32X$	$2PY$	$18P + 2PY + 16Y$

Therefore, the 15 distinct isomers can be divided into four groups.

(i) $\mathbf{3_g}$, $\mathbf{3_i}$, and $\mathbf{3_n}$ retain their hybridization through steps 1 and 2. They are not affected by kinetic isotope effects.
(ii) $\mathbf{3_{a-e}}$ change hybridization while going through step 1. Hence, they are only affected by kinetic isotope effect in step 1.
(iii) $\mathbf{3_b}$, $\mathbf{3_d}$, $\mathbf{3_f}$, $\mathbf{3_h}$, $\mathbf{3_j}$, $\mathbf{3_k}$, $\mathbf{3_l}$, $\mathbf{3_m}$, and $\mathbf{3_o}$ change hybridization while going through step 2. Hence, they are merely affected by kinetic isotope effect in step 2.
(iv) $\mathbf{3_b}$ and $\mathbf{3_d}$ change hybridization while going through both steps 1 and 2. Hence, they are affected by kinetic isotope effect in both steps 1 and 2.

Calculations

Dividing the total number of deuteriums expected to be attached at sp^2 carbons over those at sp^3 carbons (Table 2) and substituting $(2 - X)$ for (Y) and setting it equal to constant Q gives Eq. (3).

$$\frac{(64 + 8P + 4PX + 32X)}{[18 + 4P(2 - X) + 32(2 - X)]} = Q \tag{3}$$

Also, dividing the total number of deuteriums expected to be attached at sp^2 carbons over those expected to appear at 2.8 ppm in ^{2}D-NMR spectrum of **3** and substituting $(2 - X)$ for (Y) and setting the ratio equal to V gives Eq. (4).

$$\frac{(64 + 8P + 4PX + 32X)}{[18P + 2P(2 - X) + 16(2 - X)]} = V \tag{4}$$

In the absence of any isotope effect, values of P, X, and Y should be equal to one ($P = X = Y = 1$). Here, Eqs. (3) and (4) give the expected $Q = 2$ and $V = 3$, respectively. However, the integrated areas under ^{2}D-NMR peaks of **3** (Fig. 1b) give the experimental values of $Q = 1.79$ and $V = 2.72$. Considering $X + Y = 2$, while solving Eqs. (3) and (4), one finds the value of $X = 1.14$, $P = 1.96$, and $Y = 0.858$.

Therefore, for dimerization of all-*cis*-cyclononatetraenyl radical, **1**, to **2** (Scheme 1, step 1), the extent of isotope effect is proportional to $1/P = 0.51$. This means inverse secondary kinetic isotope effects is involved in dimerization of **1** with $k_H/k_D = 0.51$. On the other hand, for cyclization of all-*cis*-9,9′-bicyclonona-1,3,5,7-tetraene, **2** (Scheme 1, step 2), the extent of isotope effect is proportional to $Y/X = 0.75$. This indicates the involvement of secondary kinetic isotope effects in cyclization of **2** with $k_H/k_D = 0.75$.

This strategy for the determination of a secondary kinetic isotope effect appears superior to conventional methods for being fast, simple, and less expensive (where applicable).

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