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Conformational Dynamics of Tetraisopropylmethane and of Tetracyclopropylmethane[1]

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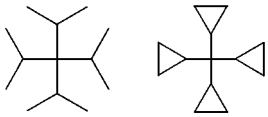
Abstract: Tetraisopropylmethane (**1**) exists in solution as a mixture of two types of conformers (D_{2d} and S_4 time-averaged symmetry) in the ratio 93:7 at −110 °C, interconverting with a barrier of 9.7 kcal mol^{-1}. Molecular mechanics calculations and the multiplicity of NMR signals at low temperature allow the assignment of these conformations. The only conformation populated in tetracyclopropylmethane (**2**) is the same type as the minor conformation (S_4 time-averaged symmetry) populated in **1**. ^{13}C NMR spectra at about −180 °C show that degenerate versions of this conformation interconvert with a barrier of 4.5 kcal mol^{-1}. Molecular mechanics calculations that characterize the six possible conformational types for these molecules, and the most important interconversion pathways, are reported. Calculated and experimental barriers match satisfactorily well.

Introduction

One of the more incomplete areas in the systematic study of conformations of small molecules involves the quaternary carbon center. Carbon with four primary alkyl chains,[2−4] epitomized by 3,3-diethylpentane[3] has been most thoroughly studied. In the present paper we discuss the case of carbon with four secondary alkyl substituents and report the two very different conformational stereodynamics of tetraisopropylmethane (**1**) and tetracyclopropylmethane (**2**).



1 **2**

The conformational properties of secondary alkyl groups are simplified if the group has some symmetry, as with isopropyl, cyclohexyl, or other cycloalkyl substituents.

Complexity increases progressively as two or more such groups are attached to a single central atom,[5,6] and there has been considerable interest recently[7−12] in molecules such as **1** and **2** with four identical secondary alkyl groups around a central atom.

While structures have been determined for an assortment of examples (see Table 1), there are no experimental observations of conformational dynamics. This is important, for a range of staggered conformation types can be adopted[10] and may coexist (see Chart 1), and each of these types has many degenerate and/or enantiomeric[13] forms.

We now report the coexistence and interconversion of different types of conformation in compound **1**, and the interconversion of degenerate versions (homomerisation) within

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(1) Conformational Studies by Dynamic NMR. 87. For part 86 see: Dell'Erba, C.; Gasparrini, F.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Novi, M.; Petrillo, G.; Pierini, M.; Villani, C. *J. Org. Chem.* **2002**, *67*, 1663.
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(5) Examples of conformational studies involving two geminal *sec*-alkyl groups can be accessed from a review: Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80−86, and subsequent citations thereof.
(6) Examples of conformational studies involving three geminal *sec*-alkyl groups can be accessed by reference to the citations of work on tris(isopropyl)methane in: Anderson, J. E.; Koon, K. H.; Parkin, J. E. *Tetrahedron* **1985**, *41*, 561−567.
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(12) Busch, B.; Dehnicke, K. *J. Organomet. Chem.* **1973**, *67*, 237−242.
(13) Conformations are enantiomeric in the same way as the two gauche conformations of butane, and they, and their degenerate versions, can interconvert by appropriate rotations of one or more secondary alkyl groups.

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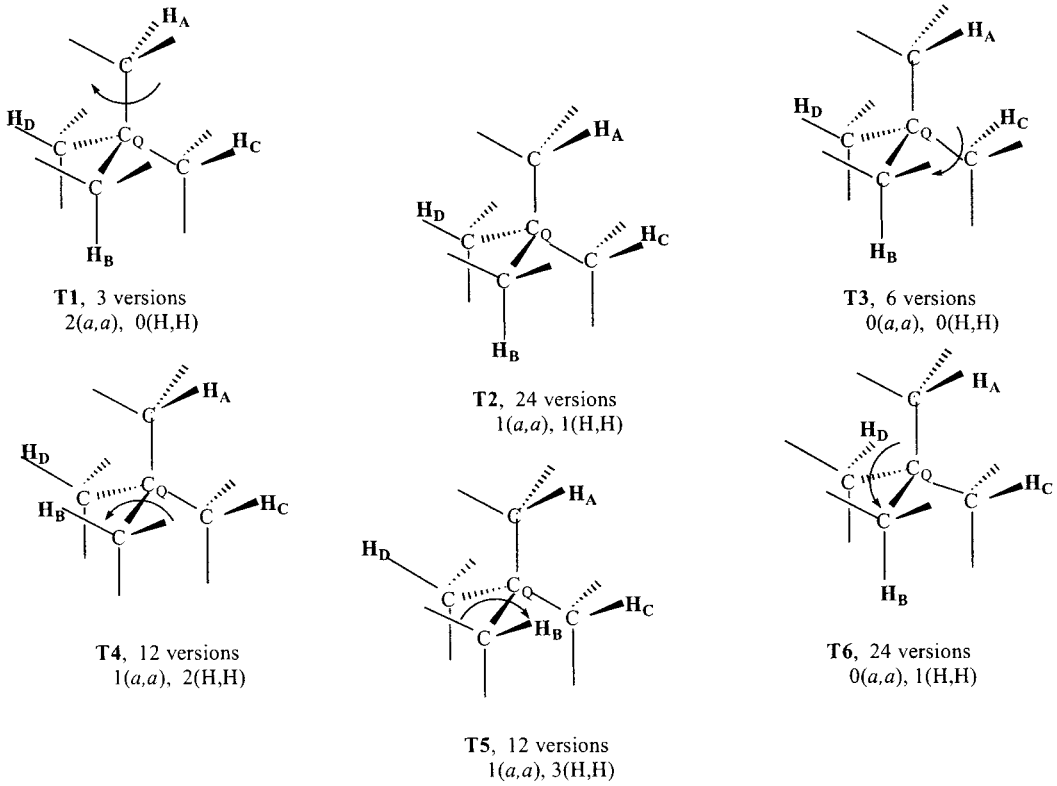
Chart 1 [a]



[a] One version each of the six conformational types **T1**−**T6** of compound **1** (and **2**). Types actually populated are **T1** and **T3** for compound **1** and **T3** alone for compound **2**. The versions shown for types **T1** and **T3**−**T6** can each be converted to **T2** by rotation of the one isopropyl group indicated. Structures are drawn with the labels for methyl groups omitted and with idealized staggered conformations. Minimum energy forms have torsion angles skewed as described in the text and in the Table 2. For compound **2**, methyl groups implicit in the diagram are replaced by CH_2 groups joined by a bond to form a cyclopropyl ring. Each type is uniquely defined by two criteria: (i) the number of anti, anti arrangements (a,a) of H−C−C−C−H chains that can be identified (thus, **T1** has two of these $\mathbf{H}_A$−C−C−C−$\mathbf{H}_B$ and $\mathbf{H}_C$−C−C−C−$\mathbf{H}_D$) and (ii) the number of 1,3-parallel arrangements of hydrogen atoms (H,H) (thus, **T6** has one of these, $\mathbf{H}_A$ with $\mathbf{H}_C$). For each type the number of degenerate/enantiomeric versions that exist are indicated.

Table 1. Structural Studies of Molecules of the Type R_4X[a]

	(isopropyl)$_4$X	(cyclohexyl)$_4$X	(cyclopropyl)$_4$X
cryst struct determination	**1**, X = C, **T1** X = $P^+[BPh_4]^-$, **T3**	X = C,**T1** X = Si, **T1**	**2**, X = C, **T3**
gas-phase electron diffraction	X = Si, **T1**		
vib spectroscopy			X = Si, **T1** X = Ge, **T1** X = Sn, **T1**

[a] **T1** or **T3** is the conformation determined experimentally.[7−12]

types, in both **1** and **2**. Experimental results from a dynamic NMR study are interpreted with the help of extensive molecular mechanics calculations.

Although various accounts[7−12] of the conformations of molecules such as tetraisopropylmethane (**1**) have been published, we propose a different, more simple version, tailored to a discussion of dynamic NMR results, but demonstrably in agreement[10] with the most rigorous previous discussion.[10,14]

There are three obvious staggered conformations for each bond joining an isopropyl group to the central carbon C_q, and four such bonds, so that there are $3^4 = 81$ conformations to consider. These fall into the six types **T1**−**T6**, one example of each of which is shown in Chart 1, whose rubric explains how these types differ and shows how any conformational minimum, viewed from any point, may be assigned readily to its type. The chart also indicates the number of degenerate and enantiomeric versions, which do indeed total 81. It is notable that as Chart 1 shows, a type **T2** conformation can be converted to any one of the five other types by rotation of about 120° of one appropriate isopropyl group.

Establishing these six conformational types says nothing about which are populated. Evidence on this depends on dynamic NMR observations supplemented by the structural evidence of Chart 1 and supported by molecular mechanics calculations of all of these types whether or not they are likely to be populated. Such calculations were carried out for compounds **1** and **2** by molecular mechanics **(**MM3 program[15]) and led to the minimum energy versions of **T1**−**T6**, which are described in Tables 2 and 3 and are best discussed before our experimental observations.

Perfect staggering of isopropyl-C_q bonds (as implied by the diagrams of Chart 1) is not expected, since this maximizes long-range methyl−methyl and other interactions, as is confirmed by X-ray and electron diffraction studies[7−11] and by our calculations. It is particularly notable that several of the

(14) Reference 10 discusses the possibilities for tetracyclohexylmethane in complex detail. The direct correlation of that work with the present discussion can be followed by recognizing that our **T1**−**T6** correspond to entries 1, 6, 2, 3, 5, and 8, respectively, in their Table 2, and to lines of drawings 1, 2, 4, 3, 6, and 5, respectively, in their Figure 2. The first three entries in their Table 3 correspond to the two different skewed versions of **T1**, and the perfectly staggered conformation intermediate between them. Structures **T1** and **T3** as drawn have D_{2d} and S_4 symmetry; structure **T1**, skewed (+ + − −) as described in the text, has S_4 symmetry.

(15) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8552−8566.

Table 2. MM3-Calculated[15] Torsion Angles (deg) and Relative Minimum Energy (kcal mol^{-1}) of Conformational Types **T1**−**T6** of Tetraisopropylmethane **1** (See Chart 1)[a]

conformation and degeneracy	$H_{A-}C-C_{q-}Pr^{i}_{B}$	$H_{B-}C-C_{q-}Pr^{i}_{A}$	$H_{C-}C-C_{q-}Pr^{i}_{D}$	$H_{D-}C-C_{q-}Pr^{i}_{C}$	rel energy
T1 (3-fold)	−169.5 (−179.6)	−169.5 (−181.0)	169.5 (179.8)	169.5 (178.5)	0.00
T2 (24-fold)	33	−175	177	162	2.10
T3 (6-fold)	58	−163	36	177	1.63
T4 (12-fold)	51	51	162	162	6.76
T5 (12-fold)	37	75	161	164	10.12
T6 (24-fold)	66	−165	150	48	3.30

[a] The angles found experimentally in the crystal for **T1**[11] are shown in parentheses.

Table 3. MM3-Calculated[15] Torsion Angles (deg) and Relative Minimum Energy (kcal mol^{-1}) of Conformational Types **T1**−**T6** of Tetracyclopropylmethane **2** (See Chart 1)[a]

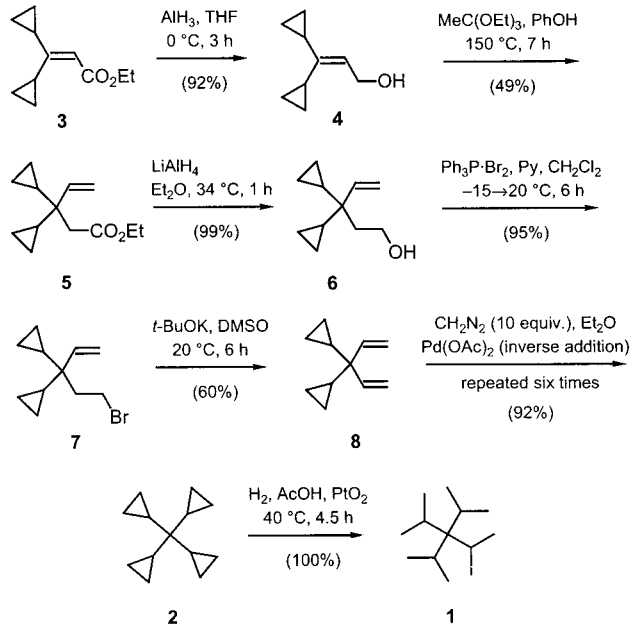
conformation and degeneracy	$H_{A-}C-C_{q-}C_yPr_B$	$H_{B-}C-C_{q-}C_yPr_A$	$H_{C-}C-C_{q-}C_yPr_D$	$H_{D-}C-C_{q-}C_yPr_C$	rel energy
T1 (3-fold)	166	166	165	165	11.84
T2 (24-fold)	66	−176	−153	−179	6.84
T3 (6-fold)	60 (54)	−178 (−176)	60 (57)	−178 (−179)	0.00
T4 (12-fold)	39	39	167	167	8.01
T5 (12-fold)	27	−76	180	149	6.82
T6 (24-fold)	54	180	−174	−62	0.43

[a] The angles found experimentally in the crystal for **T3**[11] are shown in parentheses.

conformational types **T1**−**T6** exist as a mixture of very similar conformations with torsion angles skewed on one side or the other of the perfect staggering implied by the diagrams.[16] Libration through the staggered conformation has a very low barrier, usually much less than 2 kcal mol^{-1}. This can be well-illustrated for conformation **T1**. In addition to the conformation described in Table 2, with torsion angles of −169.5, −169.5, +169.5, and +169.5°, (− − + +) for short, the conformation (+ + − −) can be reached by rotation of each isopropyl group by only 21° in the correct sense. There are two intermediate conformational minima of energy 0.8 kcal mol^{-1} higher, namely, (+175° +170° +175° +170°), so (+ + + +), and the corresponding (− − − −). The barrier to libration between (− − + +) and (+ + − −) is computed to be 1.2 kcal mol^{-1}. These four linked minima are local perturbations which are additional to the original 81 principal possibilities and correspond directly to conformations already discussed for tetracyclohexylmethane by Columbus and Biali.[10] Henceforth, when we discuss these types **T1**−**T6**, we mean the librating set skewed in one sense or the other in each case, and the time-averaged symmetry of these types refers to such NMR invisible dynamic equilibria. Experimental techniques with a shorter time scale[7−11] identify single skewed conformations.

Preparation of Materials. Tetracyclopropylmethane (**2**) was obtained by 2-fold cyclopropanation of dicyclopropyldiethenylmethane (**8**), which was prepared using ethyl 3,3-dicyclopropylacrylate (**3**) as the starting material.[11] The general synthetic strategy for the preparation of **8** was adopted from the recently reported preparation of 2,2-diethenyladamantane.[17] The allyl alcohol **4**, obtained by reduction of **3**, was transformed into **8** via an ortho ester Claisen rearrangement, subsequent reduction of the ester **5** with $LiAlH_4$ to the alcohol **6**, transformation to the bromide **7**, and its eventual dehydrobromination with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO, Scheme 1).[11] The cyclopropanation of **8** with diazomethane catalyzed by palladium(II) acetate gave good yields only when the catalyst was added in one portion to the solution of **8** and diazomethane.[18] Tetraisopropylmethane (**1**) was obtained by hydrogenolysis of hydrocarbon **2** over a platinum catalyst in acetic acid in quantitative yield.

Scheme 1 [a]



[a] Synthesis of tetracyclopropylmethane (**2**) and of tetraisopropylmethane (**1**).

Results

Tetraisopropylmethane (1). The proton NMR spectrum of compound **1** comprises a doublet and a septet of relative intensity 6:1. On lowering the temperature, both signals broaden at about −80 °C and then split and appear as two signals of relative intensity 93:7 at about −110 °C. These spectra are displayed in Figures 1 and 2, where the methine signal appears as two unequal septets, while the methyl signal is a major doublet and, significantly, a minor triplet due to overlap of two doublets. ^{13}C NMR signals of the methyl and methine carbons

(16) Skewing was described in detail by: Anderson, J. E. In *The Chemistry of Alkanes and Cycloalkanes*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1992; Chapter 3, p IIC.
(17) Giraud, L.; Huber, V.; Jenny, T. *Tetrahedron* **1998**, *54*, 11899−11906.
(18) Suda, M. *Synthesis* **1981**, 714.

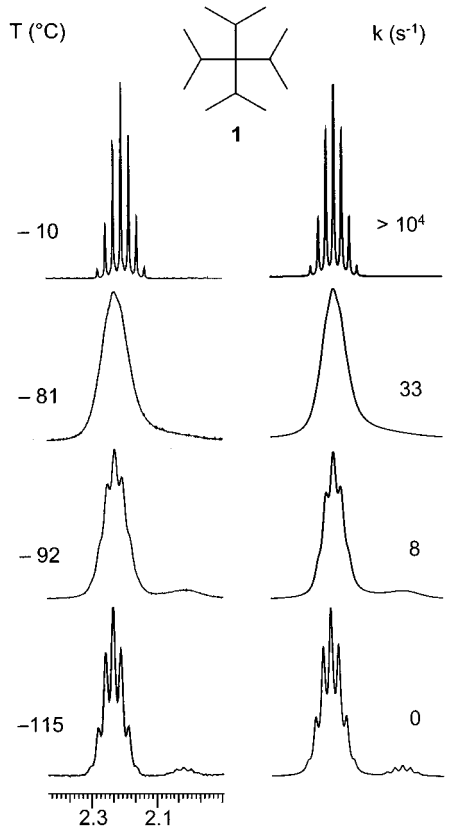


Figure 1. Experimental (left) ^{1}H NMR methine signal (400 MHz) of tetraisopropylmethane (**1**) in CD_2Cl_2 as a function of temperature. On the right is shown the computer simulation obtained with the rate constants reported and with proportions of the minor conformer equal to 6.5, 9, and 10% at −115, −92, and −81 °C, respectively.

show a maximum broadening at −72 and −75 °C, respectively, followed by resharpening on further cooling, However, poor signal intensity, due to decreasing solubility, prevented the observation of the expected minor set of signals.[19]

Complete line shape matching of the methine proton NMR spectra at various temperatures in the region of exchange broadening is shown in Figure 1 and gives a barrier ($\Delta G^{\ddagger}$) of 9.7 kcal mol^{-1}, for the interconversion for the more (**T1**) into the less stable (**T3**) conformer (the barrier for the reverse process is 8.9 kcal mol^{-1}).

Simulations at five different temperatures indicated a negligible $\Delta S^{\ddagger}$ value (1 ± 3 cal mol^{-1} T^{-1}); thus $\Delta H^{\ddagger}$ (9.9 ± 0.4 kcal mol^{-1}) is essentially equal to $\Delta G^{\ddagger}$ within the errors, as often observed in conformational processes. The fit of the major and minor signals of the methyl group was no better when the rate constant was the same as for the CH signal at all temperatures, or was twice that value, so associating two distinct conformational processes with the spectral changes is neither justified or excluded, as will be discussed later.

The calculations for the minimum energy forms of the six conformational types **T1**−**T6** given in Table 2 suggest that type **T1** (having the time-averaged D_{2d} symmetry, as displayed in Chart 1) is the most stable. In this conformation all methine

(19) At the temperature where the maximum line broadening is observed, the use of the appropriate formula (see: Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, New York, 1982; p 84) gives a barrier of 9.7 kcal mol^{-1} for the related interconversion process, which is equal to that obtained by the computer line shape simulation of the ^{1}H NMR spectra.

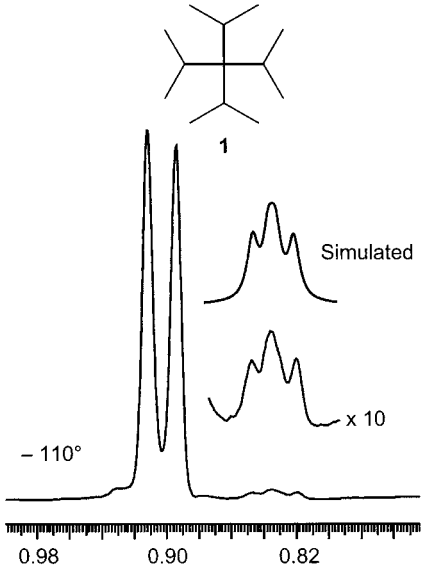


Figure 2. Methyl region of the ^{1}H NMR spectrum (400 MHz) of tetraisopropylmethane (**1**) in CD_2Cl_2 at −110 °C displaying two groups of signals due to a pair of conformers in a 93:7 proportion. Whereas the major signal is a doublet (J = 7.1 Hz), the minor one comprises two overlapping doublets, as demonstrated by the simulation reported in the inset (10-fold amplification). The simulation was obtained by using a shift difference of 4.6 Hz and J = 6.2 and 6.8 Hz.

groups are identical as are the methyl groups, particularly the two within any isopropyl group. Assignment of the major low-temperature signal to molecules adopting this **T1** conformation is thus plausible.

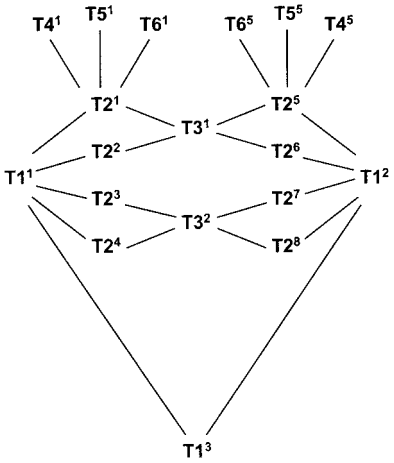
The second type of conformation interconverting with **T1**, appears at −110 °C as *one* septet for the methine protons (Figure 1), but as *two* doublets for the methyl groups (see Figure 2). This suggests that the conformation is type **T3** (which has the time-averaged S_4 symmetry displayed in Chart 1), calculated to be the second most stable. Thus, while the four methine protons are equivalent in **T3**, geminal methyl groups are distinct.[20] In **T2**, which is the other calculated low-energy conformation, all methyl groups and all methine groups are distinct from each other, and for **T4, T5**, and **T6** as well, more signals would be expected than are observed.

Therefore **T1** and **T3** are the two conformational types that are populated, but to understand the dynamic situation it should be recognized that there are three equivalent degenerate forms, **T1**^{1}, **T1**^{2}, and **T1**^{3}, with H_A anti to either C_B, C_C, or C_D, respectively. The relationship between them is that clockwise rotation of all isopropyl groups by about 120° takes **T1**^{1} to **T1**^{2}, whereas **T1**^{3} is reached by anticlockwise rotation from **T1**^{1}, or by further clockwise rotation from **T1**^{2}.

The easiest calculated stepwise interconversion of **T1**^{1} and **T1**^{2} is shown in Chart 2 and involves conformations of the two next most stable types. **T1**^{1} converts to **T3**^{1} via **T2**^{1} or **T2**^{2} by two clockwise isopropyl group rotations. Clockwise rotation of a third and fourth isopropyl group takes **T3**^{1} on to **T1**^{2} via a different type **T2** conformation. Other routes linking **T1**^{1} and **T1**^{2} or **T1**^{3} through the network, involve conformations **T4**−**T6** of higher energy and are not shown. An extensive calculation of the interconversion of **T1** with **T3**, which allowed the second isopropyl group to rotate somewhat to ease the rotation of the

(20) One methyl of a geminal pair in **T3** is for example *anti*, *anti* to a distant hydrogen, while the other is *anti*, *anti* to a distant methyl group.

Chart 2 [a]



[a] The populated part of the conformational diagram for tetraisopropylmethane **1** linking the six conformational types **T1**−**T6**. Each line in the top half of the diagram corresponds to rotation of an appropriate isopropyl group. Three degenerate versions of the major populated conformational type **T1** (i.e. **T1**[1], **T1**[2], **T1**[3]**)** are at the top left, the top right, and bottom of the triangle, respectively. These are linked by six different **T1**−**T2**−**T3**−**T2′**−**T1′** pathways. Two of the six versions of the minor populated type **T3** (i.e. **T3**[1], **T3**[2]**)** are also shown. Eight of the 24 forms of intermediate conformations type **T2** are shown in the central section of the triangle. Two views of the relationship of less stable conformational types **T4, T5**, and **T6** are shown at the top, but very many degenerate/enantiomeric forms of these and many less likely interconversions are omitted.

first, identifies a pathway with a barrier of 11.3 kcal mol^{-1}, which is fairly close to the experimentally measured barrier of 9.7 kcal mol^{-1}.

Tetracyclopropylmethane (2). The NMR spectrum of compound **2** comprises three signals coupled together, and while it shows a great deal of broadening at low temperatures, there are no changes that can be certainly associated with a conformational process becoming slow on the NMR time scale. The proton-decoupled ^{13}C NMR spectrum is more informative for while the three singlets seen at room-temperature persist with no unequal broadening even at −165 °C, below this temperature the methylene carbon signal broadens and eventually splits into two broad signals of equal intensity, separated by 3 ppm at about −180 °C (Figure 3). A fit of the line shape gives a barrier of about 4.5 kcal mol^{-1} for a conformational process.

Molecular mechanics calculations for the minimum energy forms of the six conformations **T1**−**T6** of compound **2** are shown in Table 3 along with critical torsion angles which define each of the cyclopropyl group conformations. The complete conformational diagram of **2** is the same as that for **1**, but Chart 2 used for compound **1** is not appropriate for compound **2**. The order of stability of conformations is quite different from that in compound **1**, and in particular conformations **T3** and **T6** are remarkably more stable than the others. The most stable by calculation is **T3** (time-averaged S_4 symmetry), which should show equivalent methine carbon atoms and two distinct signals for adjacent methylene groups. Since all methine carbons and all methylene carbons are different in structure **T6** (C_1 symmetry), the low-temperature NMR spectrum shows that the preferred conformation of compound **2** is type **T3**. The spectrum quality at −180 °C is such that a population of conformation **T6** lower than 10% might have escaped detection.

The pathway for interconverting different versions of conformation **T3**, which would make methylene groups equivalent

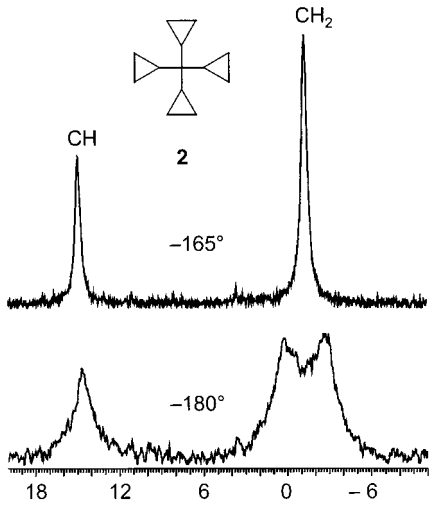
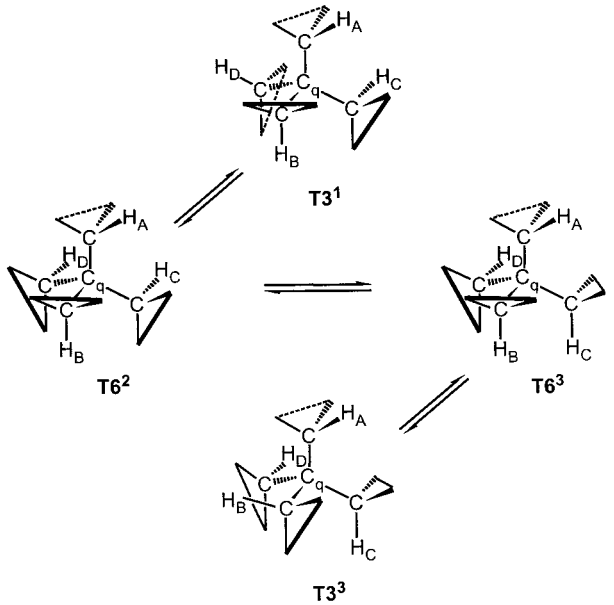


Figure 3. ^{13}C NMR signals (125.7 MHz) of the CH and CH_2 carbons of tetracycloproplymethane (**2**) in $CHF_2Cl/CHFCl_2$ at two different temperatures. At −165 °C (top) the methylene carbons still display a single line, which splits, however, into a pair of equally intense lines at −180 °C (bottom).

Scheme 2 [a]



[a] Interconversion of two versions of a type **T3** conformation of the cyclopropyl compound **2** by three successive cyclopropyl group rotations, visiting two versions of a type **T6** conformation. In this process, which leads overall to a homomerization of the **T3** conformational types, the two methylene groups on C_A, for example, change environments. In **T3**[1], one methylene group is anti, anti to a hydrogen, H_B, while in **T3**[3], the other methylene group has become anti, anti to H_C. The version **T3**[1] shown can convert to four different versions of **T6**, depending on which cyclopropyl group rotates first.

on the NMR time scale, was investigated by calculating the energy of the molecule as a function of the appropriate dihedral angles.[21] Scheme 2 shows that rotation of three cyclopropyl groups in turn takes conformation **T3**[1] to **T6**[2], then to **T6**[3], and then finally to **T3**[3]. If, in Chart 2, tetracyclopropylmethane structures are envisaged, this interconversion links the top side and the left-hand side of the triangle. The barrier to this process is calculated to be 3.6 kcal mol^{-1}, only slightly lower than the

(21) This was calculated by using the dihedral drive option in the MM3 molecular mechanics program.

4.5 kcal mol^{-1} measured experimentally, but in reasonable agreement for a complicated molecule like **2**, with four cyclopropyl groups. The barrier to interconversion of **T3^1** with **T3^2** by way of conformation **T2** (the stereomutation route for compound **1**) is calculated and, as expected, at 9.3 kcal mol^{-1} is very much higher than the experimental value of 4.5 kcal mol^{-1}.

Discussion

Now that the conformational types **T1**−**T6** have been introduced and used to interpret the spectra of compounds **1** and **2**, it is helpful to review the conformations found in earlier examples R_4X mentioned in the Introduction;[7−12] see Table 1. A **T1** type conformation has been found in the crystal for tetraisopropylmethane **1**,[11] for tetracyclohexylmethane,[10] and for tetracyclohexylsilane.[7] An electron diffraction study[9] has shown that the conformation adopted by tetraisopropylsilane in the gas phase is a type **T1**, with isopropyl groups skewed by 15°. The same conformation has been suggested for tetracyclopropyl derivatives of silicon, germanium, and tin in the gas phase on the basis of vibrational spectroscopy.[12]

The type **T3** conformation has been found in crystals of tetracyclopropylmethane (**2**)[11] and in tetraisopropylphosphonium tetraphenylborate (*i*-Pr)$_4$P$^+${B(Ph)$_4$}$^-$. [8] Since conformational types **T1** and **T3** are the only two known to be populated in such compounds, it is fitting that we are able to demonstrate that these types coexist in solutions of compound **1**.

In a molecule as crowded as **1**, the most serious intramolecular steric strain results from methyl−methyl parallel 1,3-interactions. Each of these is of a magnitude of about 5.7 kcal mol^{-1} if molecular mechanics calculations of the chair equilibrium in *cis*-1,3-dimethylcyclohexane are taken as a model, but are presumably somewhat less in more flexible acyclic systems. Columbus and Biali have pointed out,[10] and inspection of models readily confirms this, that for tetracyclohexylmethane the two most stable conformational types **T1** and **T3** have four parallel 1,3-interactions, while **T2, T6, T4,** and **T5**, progressively less stable than these, have five, five, six, and seven such interactions, respectively. The same is calculated for conformations **T1**−**T6** of compound **1**. Each (H,H) interaction listed in Chart 1 implies a methyl−methyl interaction elsewhere in the molecule which is additional to the basic number of four present in **T1** and **T3**. The complete preference for one or the other of these last two conformations is undoubtedly linked to these interactions.

It is an interesting question why the preferred conformations of **1** and **2** are so dramatically different, why in the two molecules the relative energy of **T1** and **T3** reverses by about 15 kcal mol^{-1}, according to our calculations. The bond lengths to the central carbon are dramatically shorter in the cyclopropyl compound **2** than in the isopropyl compound **1**, both in the crystal (1.527 Å vs 1.599 Å) and by calculation (1.544 Å vs 1.594 Å), so undoubtedly, interactions of cyclopropyl groups are greater than those of isopropyl groups. Calculations suggest, however, that these bond lengths are similar in both **T1** and **T3** type conformations, so it is to the details of these calculations that we must look for information on the high strain in the **T1** conformation of the tetracyclopropyl compound **2**. It turns out that the bond−angle distortion energy in this conformation is uncommonly high, being 9.7 kcal mol^{-1} higher than for the **T3** conformation. This can be related directly to the opening up of the central C−C$_q$–C bonds in both (a,a) chains to 124°, whereas this bond angle is only 114° in the **T1** conformation of compound **1**, the most stable conformation for that compound.

While we can thus explain the preference of compound **2** for conformation **T3**, this does not explain the other occurrence of **T3** conformations (Table 1). Tetraisopropylphosphonium tetrafluoroborate has much longer bonds from the central phosphorus atom to the isopropyl groups and as a result has reduced parallel 1,3-interactions in all conformations.

The other efficient way of relieving interactions after lengthening of bonds to the quaternary carbon, and opening up of C−C−C bond angles, is the cooperative skewing of torsion angles.[16] Experimental results and calculations both show that such skewing does take place, and since the barrier to the libration between the (+ + − −) and (− − + +) forms of **T1** for compound **1** is 1.2 kcal mol^{-1}, this is a measure of the stabilization skewing produces. The calculations on compounds **1** and tetracyclohexylmethane suggest that when there are four groups around a central atom, there are two complementary skewings in opposite senses, whereas in triisopropylmethane all three groups are skewed in the same sense.[6]

We conclude that parallel 1,3-interactions dominate the conformational analysis of the compounds we have been considering. The two conformational types with fewest such interactions (i.e. four) are the only ones for which there is evidence.

A percipient reviewer has pointed out that for compound **1**, the rate of **T3**−**T3′** interconversion should be half the rate of **T3**−**T1** interconversion if the only accessible pathway is **T3**−**T2**−**T1**−**T2′**−**T3′**. To this point, we add our own realization that, in compound **1**, **T3**−**T3′** interconversion might take place more easily by way of **T6** (as found for compound **2**), although **T3**−**T1**−**T3′** is clearly also taking place.

We simulated changes in the spectrum of compound **1** with temperature, using different relative rates for the two interconversions, but we could not see any improvement in matching experimental spectra, on those with the assumption that rates are the same. This negative result may be inconclusive since the **T3** signal appearance is undoubtedly dominated by exchange with the substantial excess population of **T1**. Molecular mechanics calculations are little help here, since the best calculated **T1**−**T3**, **T3**−**T6**, and **T6**−**T6′** transition states have very similar energies of 11.3, 10.9, and 11.2 kcal mol^{-1} above the global minimum.

The picture suggested therefore by NMR observations, calculations, and the example of compound **2**, is that when occasionally a molecule of compound **1** gets out of the major type **T1** conformation via **T2** into a minor, type **T3** conformation, it has a comparable likelihood of following one of four **T3**−**T6**−**T6′**−**T3′** circuits, or of converting back to the original, or on to a new, type **T1** conformation again via **T2** conformations.

Recently reported interconversion barriers[11] for **1** and **2** computed at the B3LYP/6-31+G** level do not agree with experiments we report here. On the other hand, our molecular mechanics calculations are decisive in interpreting the various NMR data, particularly for assigning the interconversion pathways. Although these pathways appear to be quite different in the two compounds investigated, the fair agreement of

experimental and calculated barriers (9.7 vs 11.3 kcal mol^{-1} for **1** and 4.5 vs 3.6 kcal mol^{-1} for **2**, respectively) gives confidence in the present interpretation. [22]

Experimental Section

Diethyl ether and tetrahydrofuran (THF) were dried by distillation from sodium benzophenone ketyl, pyridine and DMSO from calcium hydride, and CH_2Cl_2 from P_2O_5. All other chemicals were used as commercially available. Organic extracts were dried over $MgSO_4$. Routine NMR spectra were recorded on a Bruker AM 250 instrument (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR). Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements. Chemical shifts refer to $\delta_{TMS} = 0.00$ according to the chemical shifts of residual $CHCl_3$ signals. Mass spectra were measured with Finnigan MAT 95 (EI at 70 eV, CI with NH_3). GC analyses were performed on Siemens Sichromat 1−4. Preparative GC separations were performed on Intersmat 130 and Varian Aerograph 920 instruments (20% SE 30 on Chromosorb W-AW-DMCS, 1200 mm × 8.2 mm column). Melting points were determined on a Büchi 510 capillary melting point apparatus; values are uncorrected. Thin-layer chromatography (TLC) analyses were performed on precoated sheets, 0.25 mm Sil G/UV$_{254}$ (Macherey-Nagel). Silica gel grade 60 (230−400 mesh; Merck) was used for column chromatography.

3,3-Dicyclopropylprop-2-en-1-ol (4). To a stirred suspension of AlH_3, prepared in situ by the addition of $LiAlH_4$ (37.5 g, 988 mmol) to a solution of $AlCl_3$ (45.0 g, 337 mmol) in anhydrous THF (40 mL) under argon in an ice bath, was added a solution of ethyl 3,3-dicyclopropylacrylate, prepared according to a literature procedure,[23] (27.0 g, 149.8 mmol) in anhydrous THF (50 mL) within 30 min. Stirring was continued for 3 h at 0 °C before the reaction was quenched by *very slow and careful* addition of MeOH (18 mL), then water (75 mL), then 10% aqueous NaOH solution (80 mL), and H_2O again (150 mL). The mixture was diluted with diethyl ether (500 mL) and filtered. After drying the solution was concentrated under reduced pressure to give the desired product (19.12 g, 92%) as a colorless liquid: bp 85 °C (3 mbar); ^{1}H NMR ($CDCl_3$) δ 5.30 (t, J = 6.8 Hz, 1 H), 4.28 (d, J = 6.8 Hz, 2 H), 1.71−1.62 (m, 1 H), 1.53 (s, 1 H), 0.96−0.91 (m, 1 H), 0.78−0.57 (m, 4 H), 0.56−0.50 (m, 2 H), 0.39−0.32 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 144.0 (C), 121.6 (CH), 58.9 (CH_2), 12.51 (CH), 12.46 (CH), 5.2 (2 CH_2), 4.9 (2 CH_2). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.18.

Ethyl 3,3-Dicyclopropylpent-4-enoate (5). A mixture of 3,3-dicyclopropylprop-2-en-1-ol (19.0 g, 137.5 mmol), triethyl orthoacetate (43.878 g, 49.58 mL, 270.5 mmol), and phenol (1.511 g, 16.1 mmol) was heated with stirring under argon at 150 °C for 7 h in an apparatus equipped with a 10 cm Vigreux column and condenser to remove formed EtOH. After cooling, the reaction mixture was diluted with diethyl ether (200 mL); washed successively with 5% aqueous HCl solution (2 × 50 mL), water (50 mL), 5% aqueous $NaHCO_3$ solution (100 mL), and brine (50 mL); dried; and concentrated under reduced pressure. Chromatographic purification of the residue (300 g of silica gel, 35 × 5 cm column, 10:1 hexane/ether) afforded the desired product (14.14 g, 49%) as a colorless oil, R_f = 0.23. The product can also be isolated by distillation in essentially the same yield, but will be less pure; bp 55−58 °C (0.7 mbar); ^{1}H NMR ($CDCl_3$) δ 5.53 (dd, J = 10.8, 17.8 Hz, 1 H), 5.16 (dd, J = 1.8, 17.8 Hz, 1 H), 5.03 (dd, J = 1.8, 10.8 Hz, 1 H), 4.06 (q, J = 7.8 Hz, 2 H), 2.37 (s, 2 H), 1.18 (t, J = 7.8 Hz, 3 H), 0.78−0.70 (m, 2 H), 0.31−0.23 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 171.7 (C), 139.7 (CH), 115.2 (CH_2), 59.8 (CH_2), 44.9 (CH_2), 40.2 (C), 16.1 (2 CH), 15.1 (CH_3), 0.2 (2 CH_2), −0.5 (2 CH_2). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.13; H, 9.82.

3,3-Dicyclopropylpent-4-en-1-ol (6). A solution of ethyl 3,3-dicyclopropylpent-4-enoate (14.05 g, 67.45 mmol) in anhydrous diethyl ether (50 mL) was added dropwise to a suspension of $LiAlH_4$ (2.563 g, 67.5 mmol) in Et_2O (200 mL) at a rate maintaining a gentle reflux. After 1 h of heating under reflux, quenching the reaction with saturated solution of Na_2SO_4, and filtration, the precipitate was additionally extracted overnight with Et_2O in a Soxhlet apparatus. The combined ethereal solutions were dried and concentrated under reduced pressure to give **6** (11.21 g, 100%) as a colorless oil. The residue was pure enough to be used without further purification: ^{1}H NMR ($CDCl_3$) δ 5.43 (dd, J = 10.5, 17.5 Hz, 1 H), 5.15 (dd, J = 2.0, 17.5 Hz, 1 H), 5.03 (dd, J = 2.0, 10.5 Hz, 1 H), 3.77 (t, J = 7.6 Hz, 2 H), 2.15 (s, 1 H), 1.69 (t, J = 7.6 Hz, 2 H), 1.20−1.05 (m, 1 H), 0.61−0.35 (m, 3 H), 0.34−0.22 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.0 (CH), 114.9 (CH_2), 59.5 (CH_2), 42.4 (CH_2), 39.2 (C), 16.4 (2 CH), −0.1 (2 CH_2), −0.5 (2 CH_2). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.73; H, 10.86.

5-Bromo-3,3-dicyclopropylpentene (7). To a solution of triphenylphosphine (19.78 g, 75.40 mmol) in anhydrous dichloromethane (150 mL), was added bromine (12.051 g, 3.88 mL, 75.40 mmol) at −30 to −15 °C over a period of 10 min. After an additional 15 min of stirring, a solution of 3,3-dicyclopropylpent-4-en-1-ol (**6**) (11.94 g, 71.81 mmol) and anhydrous pyridine (5.68 g, 5.81 mL) in CH_2Cl_2 (15 mL) was added dropwise at −15 °C. The mixture was stirred at ambient temperature for an additional 6 h. After evaporation of the solvent, pentane (100 mL) was added, and the mixture was stirred for 3 h and then filtered. The precipitate was thoroughly washed with pentane (3 × 50 mL), and the combined pentane extracts were filtered through silica gel (0.5 cm layer). The solvent was evaporated under reduced pressure to give the desired product (15.64 g, 95%) as a slightly yellow oil which was pure enough to be used without further purification: ^{1}H NMR ($CDCl_3$) δ 5.39 (dd, J = 10.5, 17.5 Hz, 1 H), 5.16 (dd, J = 1.8, 17.5 Hz, 1 H), 5.10 (dd, J = 1.8, 10.5 Hz, 1 H), 3.52 (t, J = 8.8 Hz, 2 H), 2.06 (t, J = 8.8 Hz, 2 H) 1.20−1.05 (m, 1 H), 0.68−0.51 (m, 1 H), 0.32−0.25 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 139.4 (CH), 115.8 (CH_2), 44.0 (CH_2), 41.6 (C), 29.7 (CH_2), 16.1 (2 CH), 0.0 (2 CH_2), −0.5 (2 CH_2); MS (EI) m/z 230, 228 (M^+, 1%), 202, 200 ($M^+ - C_2H_4$, 22%), 121 (75%), 119 (58%), 93 (100%), 79 (95%). Anal. Calcd for $C_{11}H_{17}OBr$: C, 57.65; H, 7.48. Found: C, 57.24; H, 7.67.

3,3-Dicyclopropylpenta-1,4-diene (8). To a solution of potassium *tert*-butoxide (*t*-BuOH; 9.82 g, 87.52 mmol) in anhydrous DMSO (100 mL) was added a solution of 5-bromo-3,3-dicyclopropylpentene (13.37 g, 58.34 mmol) in anhydrous DMSO (25 mL) at 20 °C over a period of 0.5 h. The reaction mixture was stirred at 20 °C for 6 h and then poured into ice-cold water (300 mL) and extracted with pentane (3 × 50 mL). The combined pentane solutions were washed with water (3 × 100 mL), dried, and carefully concentrated at ambient pressure. The residue was distilled under reduced pressure to give the desired compound **8** (5.2 g, 60%) as a colorless liquid, bp 58−60 °C (12 mbar). An analytical sample was purified by preparative GC: MS (CI) m/z 149 ($M^+ + H$, 5%), 135 ($M^+ + H - CH_2$, 32%), 123 (44%), 121 ($M^+ + H - C_2H_4$, 100%). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.01; H, 10.91. The ^{1}H and ^{13}C NMR spectra have previously been published..[11]

Tetracyclopropylmethane (2) (Applying the Cyclopropanation Protocol of Suda[18]). To a precooled (−20 °C) solution of diazomethane [prepared from 9.07 g (87.7 mmol) of *N*-methyl-*N*-nitrosourea] and 3,3-dicyclopropylpenta-1,4-diene (1.30 g, 8.77 mmol) in diethyl ether (100 mL) in a 1 L Erlenmeyer flask was added a solution of $Pd(OAc)_2$ (100 mg, 0.445 mmol, 5.1 mol %) in CH_2Cl_2 (1 mL) in one portion.

(22) A recent more rigorous search of the potential energy surface of tetraisopropylmethane (**1**) at the B3LYP/6-31+G** level of theory disclosed that the internal rotations of isopropyl groups in **1** are very complex. A low-energy conformation with S_4 symmetry converts into a degenerate S_4 structure with a barrier of about 4 kcal mol^{-1}. The highest barrier for conversion of the S_4 to a C_1 structure (which is close in energy to a set of C_2, D_2, and D_{2d} structures) is computed to be 9.3 kcal mol^{-1}. This value actually is in very good agreement with the experimentally determined barrier for the isopropyl rotation in **1**. (Schreiner, P. R.; Rinderspacher, C. Personal communication to A.dM.)

(23) (a) Jorgenson, M. J. *J. Am. Chem. Soc*. **1969**, *91*, 6432−6443. (b) Portevin, B.; Benoist, A.; Rémond, G.; Hervé, Y.; Vincent, M.; Lepagnol, J.; De Nanteuil, G. *J. Med. Chem.* **1996**, *39*, 2379−2391.

(*Caution! This reaction proceeds very violently.*) The temperature immediately increased to 25 °C. The reaction mixture was stirred for an additional 10 min, filtered through a 3 cm pad of Celite, and carefully concentrated under reduced pressure. The residue was taken up with a new 100 mL portion of diazomethane solution, and the procedure was repeated again several times with GC monitoring after each cyclopropanation. After six repetitions, the product was purified by column chromatography (120 g of silica gel impregnated with 3% $AgNO_3$, 20 × 3 cm column, hexane) to give **2** (1.42 g, 92%) of 99% purity. An analytical sample was purified by preparative GC: MS (CI) *m*/*z* 177 ($M^+ + H$, 100%), 120 ($M^+ - 2\ C_2H_4$, 100%. The ^1H and ^{13}C NMR spectra of the compound, as well as the X-ray crystal structure analysis, have previously been published.[11]

Tetraisopropylmethane (1). The vigorously stirred suspension of PtO_2 (200 mg, 0.88 mmol, 55 mol %) in acetic acid (10 mL) was exposed to an atmosphere of hydrogen at a pressure of 1.2 bar for 30 min. After this, a solution of the hydrocarbon **2** (280 mg, 1.59 mmol) in pentane (2 mL) was added in one portion, and hydrogenation was continued for 4.5 h. The reaction mixture was taken up with pentane (50 mL); washed successively with water (2 × 50 mL), 5% aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (50 mL); dried and concentrated under reduced pressure to give pure **1** (293 mg, 100%) as a colorless solid; mp 74−76 °C. No molecular ion peak could be observed in the EI-mass spectrum of **1**. The ^1H and ^{13}C NMR spectra of **1** as well as the X-ray crystal structure analysis for **1** have previously been published.[11]

NMR Measurements. The ^1H and ^{13}C variable temperature spectra of **1** were obtained in CD_2Cl_2 at 400 and 100.6 MHz, respectively (Varian, Mercury). The samples for the very low temperature measurements of **2** were prepared by connecting to a vacuum line the NMR tubes containing the compound and some C_6D_6 for locking purpose and condensing therein the gaseous solvents (CHF_2Cl and $CHFCl_2$ in a 4:1 (v/v) ratio) under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the 500 MHz spectrometer (Varian, Inova) operating at 125.7 MHz for ^{13}C. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Line shape simulations for compounds **1** and **2** were achieved by using a PC version of the DNMR-6 program.[24] In the case of the proton CH signal of **1** the matrix needed to simulate the corresponding dynamic process should be that exchanging an AX6 with a BX6 spectrum. Since this situation is not allowed by the program, we substituted it with a matrix exchanging an AX4 with a BX4 spectrum. Each simulated dynamic spectrum of this type was subsequently added, point by point, to two equally simulated spectra shifted, respectively, by a *J* and by 2*J* values, taking care of adding the *J* shifted spectrum twice in order to obtain the 1:2:1 ratio needed to transfom the AX4 into the AX6 system (and likewise the BX4 into the BX6 system). These final spectra matched the experimental ones if the appropriate *k* values had been used. As mentioned, the barrier obtained in this way is equal to that derived from the corresponding ^{13}C spectra.[19]

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