

# Articles

## Conformational Study of *trans*-Cyclododecene by Dynamic NMR Spectroscopy and Computational Methods

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The  $^{13}\text{C}$  spectrum of *trans*-cyclododecene (**1**) dissolved in propane showed seven peaks for the olefinic carbons at  $-164.5\text{ }^\circ\text{C}$ , corresponding to three conformations of  $C_1$  symmetry and a fourth conformation, with a population of 20.1%, of  $C_2$  symmetry. The populations of the  $C_1$  conformations were 57.0, 18.6, and 4.3%. Conformational space was searched for **1** using MM2. Free energies and populations were calculated by MM3, and the results of the low-temperature NMR study are discussed in terms of these calculations and the  $^{13}\text{C}$  chemical shifts calculated for eight conformations by the GIAO method at the HF/6-311G\* level. The conformations of **1** and cyclododecane (**2**) are compared.

### Introduction

The conformations of cycloalkenes are of interest for comparison with the conformations of the corresponding cycloalkanes. The stable conformations of the larger cycloalkanes generally have one or more CCCC dihedral angles close to  $180^\circ$ , and these positions could accommodate a *trans* double bond without excessive strain from the requirement of near-planarity for the double bond. However, the lowest-energy conformation of *trans*-cyclododecene does not resemble the most stable conformation of cyclododecane at low temperatures. Cyclododecane at temperatures near  $-150\text{ }^\circ\text{C}$  prefers the boat–chair–boat (BCB) conformation, although this is not the only conformation populated,<sup>1</sup> but five conformations were found<sup>2</sup> for *trans*-cyclododecene at  $-155\text{ }^\circ\text{C}$ , and the conformation with the highest population was of  $C_1$  symmetry, which is not consistent with a structure based on BCB cyclododecane. The conformation of lowest enthalpy for cyclododecane has  $D_4$  symmetry,<sup>3</sup> while the structure for a silver nitrate complex of *trans*-cyclododecene was found by X-ray crystallography<sup>5</sup> to resemble another conformation of cyclododecane, with  $C_2$  symmetry. We have carried out a low-temperature  $^{13}\text{C}$  NMR study of *trans*-cyclododecene to obtain information about the conformations in solution. A search of conformational space using Allinger's MM2 program was also made, and the free energies of the conformations that were found were estimated by MM3.  $^{13}\text{C}$  chemical shifts calculated by the GIAO method are reported for eight of the conformations.

### Experimental Section

High-purity propane was purchased from MG Industries, and *trans*-cyclododecene (**1**), labeled as 99% pure, was obtained from Wiley Organics. The *trans*-cyclododecene actually contained about 9% of the *cis* isomer, as shown by the  $^{13}\text{C}$  NMR spectrum, and the pure *trans* isomer was obtained by preparative gas chromatography. A  $1/4\text{ in.} \times 8\text{ ft}$  custom-made column from Supelco containing 35% silver nitrate (39%) in tetraethylene glycol (61%) on 80/100 chromosorb PAW<sup>6</sup> was used. The temperatures of the injection port, column, and detector were 140, 100, and  $230\text{ }^\circ\text{C}$ , respectively.

A 15% solution of **1** in propane was prepared in a 5 mm thin-walled NMR tube, and a small amount of TMS was added for an internal reference. *Caution:* high pressure. The sample tube was stored and handled below  $0\text{ }^\circ\text{C}$  most of the time. Spectra were recorded on a General Electric model GN-300 wide-bore NMR spectrometer operating at 75.58 MHz for carbon. The  $^{13}\text{C}$  spectra for **1** were obtained from  $+17.8\text{ }^\circ\text{C}$  to  $-164.5\text{ }^\circ\text{C}$  with a 5 mm dual probe. A pulse width of 8.2  $\mu\text{s}$ , corresponding to a tip angle of  $83^\circ$ , was used. The pulse repetition period was 10 s at  $17.8\text{ }^\circ\text{C}$  and  $-164.5\text{ }^\circ\text{C}$  and 1 s at the intermediate temperatures. A sweep width of  $\pm 10\text{ }500\text{ Hz}$ , data size of 64 K, 2800–3600 pulses, and 3.0 Hz line broadening were used. Spinning was discontinued below about  $-120\text{ }^\circ\text{C}$ . Because ejecting the sample at lower temperatures was difficult, due to ice formation on the inner wall of the stack, the temperature calibrations were performed separately, using a copper–constantan thermocouple immersed in the same solvent contained in a nonspinning dummy sample tube and under conditions as nearly identical as possible. The emf's were measured with a Leeds and Northrup model 8690-2 millivolt potentiometer. The uncertainty in the temperatures was estimated to be  $\pm 2\text{ }^\circ\text{C}$ .

The conformational space of **2** was searched initially by the grid-search method of Osawa with Allinger's MM3 program included in Spartan 3.0.<sup>7</sup> The use of this search technique with grid steps of  $10^\circ$ ,  $30^\circ$ , or  $120^\circ$  did not generate the seventh

(1) Pawar, D. M.; Smith, S. V.; Mark, H. L.; Odom, R. M.; Noe, E. A. *J. Am. Chem. Soc.* **1998**, *120*, 10715.

(2) Pawar, D. M.; Noe, E. A. *J. Am. Chem. Soc.* **1996**, *118*, 12821.

(3) Allinger, N. L.; Chen, K.; Lii, J.-H. *J. Comput. Chem.* **1996**, *17*, 642. For a summary of earlier studies, see ref 4.

(4) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982; pp 107, 108.

(5) Ganis, P.; Giuliano, V.; Lepore, U. *Tetrahedron Lett.* **1971**, 765.

(6) Supelco, Inc., Supelco Park, Bellefonte, PA 16823-0048. The use of a similar column for separation of *cis* and *trans* isomers of cyclododecene was described by: Cope, A. C.; Moore, P. T.; Moore, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1744.

(7) Spartan version 3.0 from Wavefunction, Inc., Irvine, CA.

(8) Saunders, M. *J. Comput. Chem.* **1991**, *12*, 645.

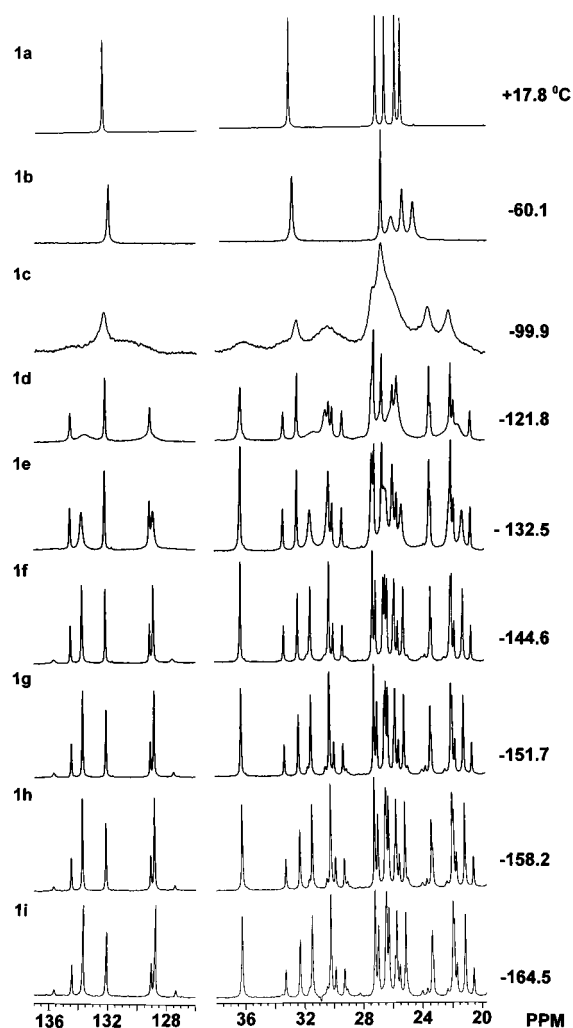
conformation found by Saunders<sup>8</sup> using a stochastic search method with MM3 (conformations numbered in order of increasing strain energy), so the search for **2** was repeated using MM2 and a grid step of 30°, and the missing conformation was found by this procedure. This MM2 structure and the first nine MM3 structures were used to prepare input for an external MM3 program<sup>9</sup> installed on a Silicon Graphics IRIS workstation. Geometry optimization was accomplished by the block diagonal procedure followed by full matrix minimization, and harmonic vibrational frequencies were calculated. Relative strain energies, relative free energies at two temperatures, and populations were obtained. The relative strain energies and the CCCC dihedral angles were in good agreement with the published results<sup>8</sup> for **2**.

Saunders<sup>8</sup> found with his stochastic search method the following numbers of conformations for the cycloalkanes of 9 to 12 carbons (MM2, MM3): cyclononane (8, 8); cyclodecane (18, 16); cycloundecane (40, 29); and cyclododecane (111, 90). These results indicate that the number of conformations found for the larger rings by MM2 may be larger than those obtained by MM3, and on the basis of this work and our results for **2** described above, the conformational space of **1** was searched using MM2 and a grid step of 30°. The first 25 of the structures obtained in this way were used as input for the external MM3 program. Geometries were optimized as described for **2**, and relative strain energies and relative free energies at two temperatures were obtained. One of two equivalent structures was deleted, and another conformation with a calculated imaginary frequency was also removed, resulting in 23 conformations.

The geometries determined by MM3 for the first eight conformations of **1** according to strain energy were used as starting points for the ab initio calculations. The Gaussian 94 series of programs<sup>11</sup> was used for full geometry optimization, first at the HF/3-21G\* level and then at the HF/6-311G\* level, but calculation of vibrational frequencies and free energies at this level was considered to be beyond the capacity of the CRAY supercomputer and was not done. The gauge-including atomic orbitals (GIAO) method<sup>12</sup> was used to calculate isotropic absolute shielding constants for the carbons of TMS and the eight conformations of **1** at the HF/6-311G\* level, and the chemical shifts of the cycloalkene, relative to TMS, were obtained by subtraction.

## Results and Discussion

The <sup>13</sup>C spectrum of **1** at +17.8 °C shows the expected six signals at  $\delta$  132.35 (C=C), 33.28, 27.39, 26.79, 26.09, and 25.73 (Figure 1). A small impurity peak at  $\delta$  25.11 from the compound or solvent did not interfere with the low-temperature study. The signals are broad by -99.9 °C, with an exchange-broadened olefinic carbon peak from a *C*<sub>2</sub> conformation appearing at  $\delta$  132.17 and superimposed on a broader absorption from rest of the conformations. At -121.8 °C, three fairly sharp peaks for the *C*<sub>2</sub> conformation and a *C*<sub>1</sub> conformation were observed in this region, along with two broad peaks, one



**Figure 1.** Low-temperature <sup>13</sup>C NMR spectra of *trans*-cyclododecene (**1**) in propane.

**Table 1.** Experimental <sup>13</sup>C Chemical Shifts, Populations, and Relative Free Energies for Conformations of *trans*-Cyclododecene at -164.5 °C

no.	symmetry/ <sup>13</sup> C chemical shifts (ppm, $\delta$ )	populations (%)	relative free energies (kcal/mol)
1	<i>C</i> <sub>1</sub> (133.67 and 128.78)	57.0	0.000
2	<i>C</i> <sub>2</sub> (132.07)	20.1	0.225
3	<i>C</i> <sub>1</sub> (134.42 and 129.03)	18.6	0.242
4	<i>C</i> <sub>1</sub> (135.64 and 127.38)	4.3	0.558

of which overlaps with the peak at lower frequency for the *C*<sub>1</sub> conformation. By -144.6 °C, two small, exchange-broadened signals for the doubly bonded carbons of the minor conformation have appeared, and these sharpen at lower temperatures.

Seven peaks are found for **1** in the olefinic carbon region at -164.5 °C, and these are assigned in Table 1 to three conformations of *C*<sub>1</sub> symmetry and one of *C*<sub>2</sub> symmetry. The finding of seven peaks in the olefinic region suggests that 35 peaks should be present in the CH<sub>2</sub> region of the spectrum. Not all of the expected peaks can be identified in this region of the spectrum, and this is assumed to be due to overlap of some of the peaks. However, on the basis of peak heights, there are peaks that appear to be associated with each of the four conformations identified in the olefinic region.

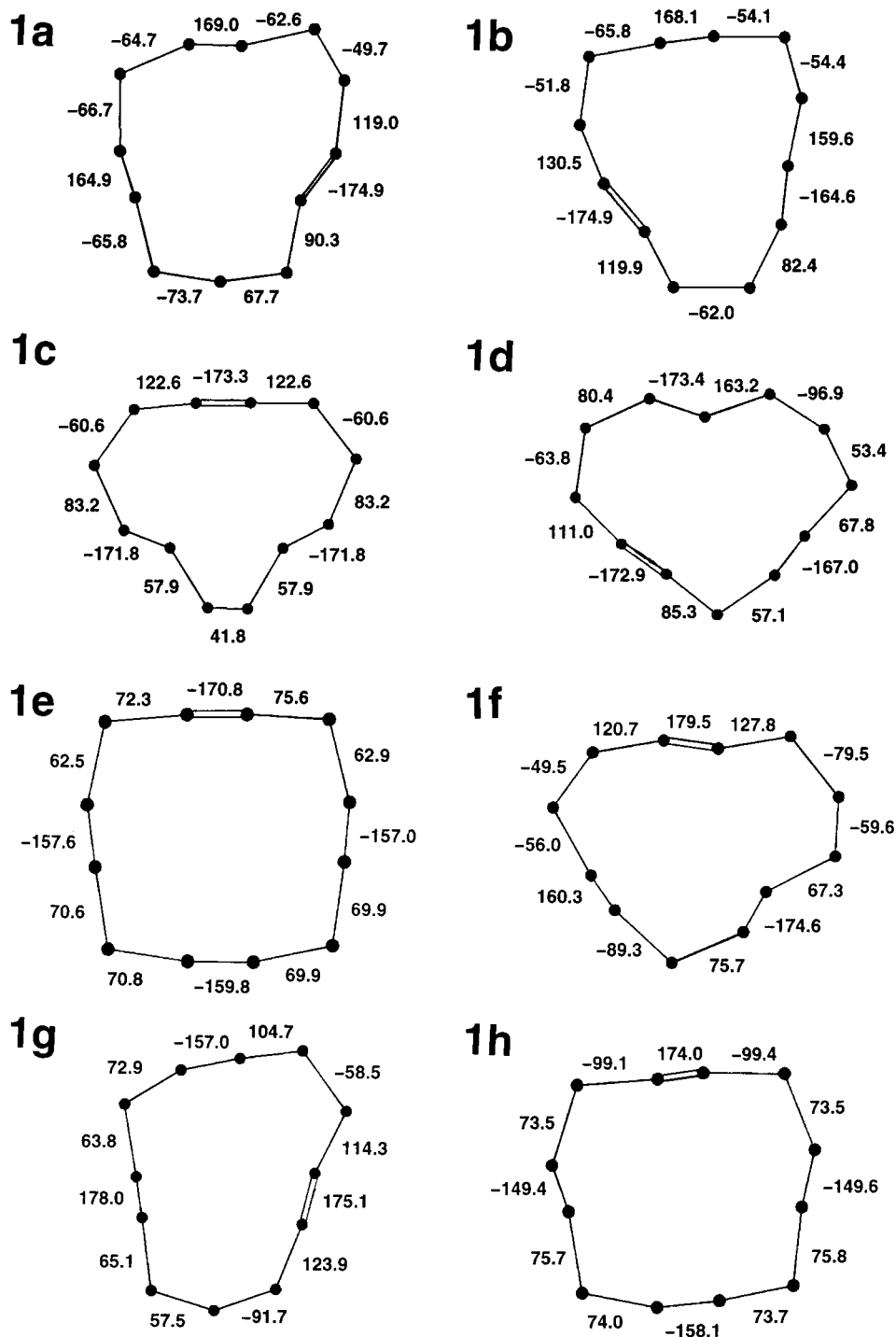
The first eight conformations for **1** predicted by Allinger's molecular mechanics force field (MM3) are shown

(9) Version MM3 (94) was used. The latest version of the MM3 program, which is referred to as MM3 (96), is available to academic users from the Quantum Chemistry Program Exchange and to commercial users from Tripos Associates, 1699 South Hanley St., St. Louis, MO 63144.

(10) Several search methods are compared in: Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

(11) Gaussian 94, Rev. E. 2: Frisch M. J.; Trucks, G. W.; Gill, P. M. W.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Cheeseman, J. R.; Gomperts, R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, J. V. O.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Fox, D. J.; Head-Gordon, M.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

(12) Forsyth, D. A.; Sebarg, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 9483.

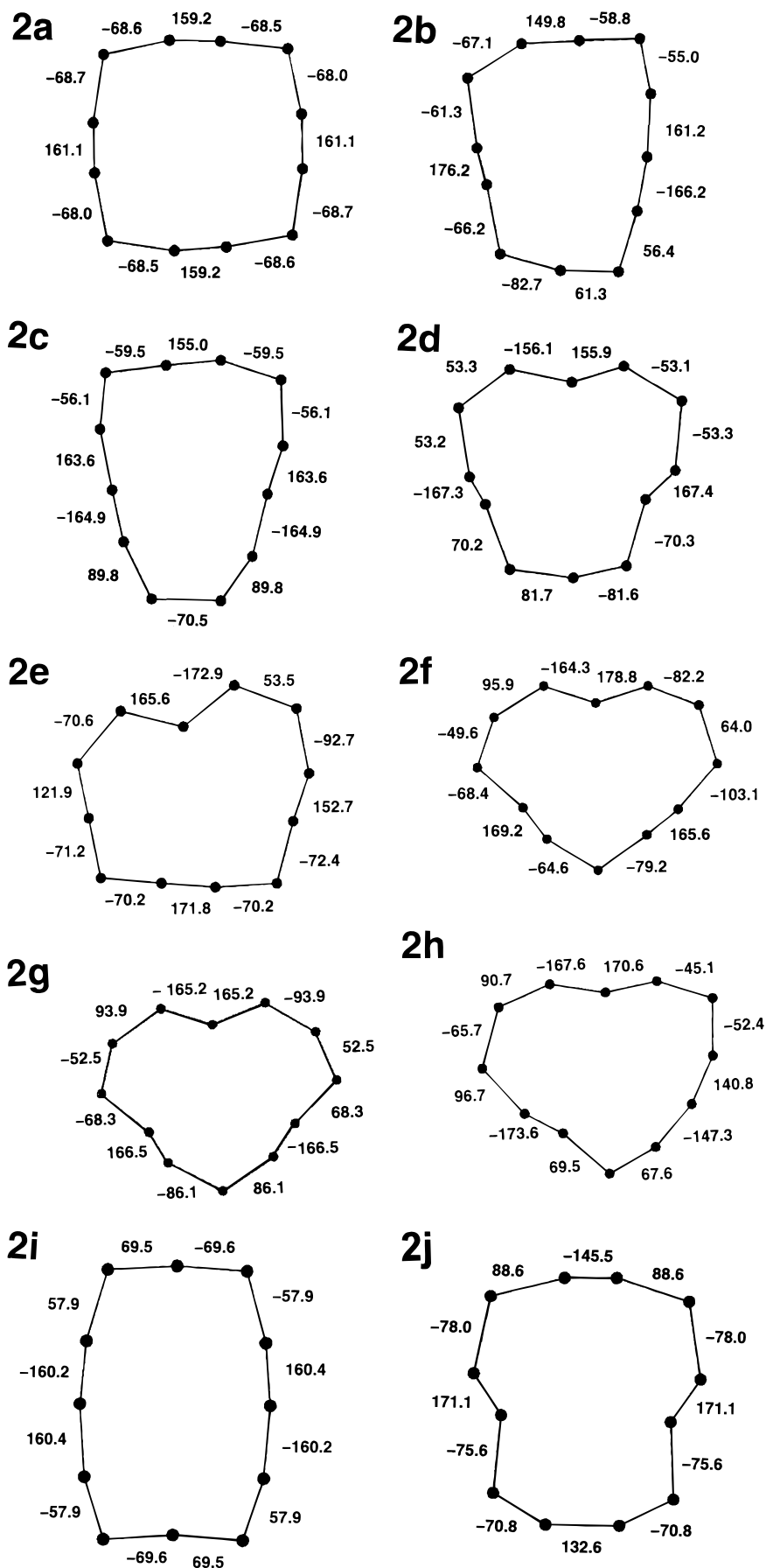


**Figure 2.** Conformations of *trans*-cyclododecene (**1**) in order of increasing MM3 strain energies. The numbers refer to the CCCC dihedral angles.

in order of increasing strain energy in Figure 2, and the symmetries, relative strain energies, relative free energies, and estimated populations for the first 23 conformations are listed in Table 2. Conformation **1b** is calculated to have the lowest free energy at  $-164.5$  °C, and conformation **1a** is only slightly higher. These conformations both have  $C_1$  symmetry and may correspond to the first and third conformations of Table 1, although the calculated difference in free energy is small, and it is not possible to know which of these conformations will actually have the lower free energy. Conformations **1d**, **1f**, and **1g** have  $C_1$  symmetry and are possible structures for the fourth conformation of Table 1; conformation **1d**

has the lowest calculated free energy of these conformations at  $-164.5$  °C, but the other two cannot be completely excluded on this basis. Of the four conformations in Table 2 with  $C_2$  symmetry (**1c**, **1e**, **1h**, and **1i**), **1e** has the lowest calculated free energy at  $-164.5$  °C, but **1h** is only 0.24 kcal/mol higher in energy, and the experimental structure found<sup>5</sup> for a silver nitrate complex of **1** corresponds to **1h**.

Chemical shifts were calculated to see if they could be useful in combination with the MM3 results for the assignment of conformations to the peaks in Figure 1. The results are shown in Table 4. The uncertainty in the calculated chemical shifts is high; for example, the



**Figure 3.** Conformations of cyclododecene (**2**) in order of increasing MM3 strain energies. The numbers refer to CCCC dihedral angles.

**Table 2. Symmetries, Relative Strain Energies, Relative Free Energies, and Populations of Different Conformations of *trans*-Cyclododecene, Calculated Using Allinger's MM3 Program**

conformer/ symmetry	rel strain energies (kcal/mol)	25.0 °C		-164.5 °C	
		rel free energies (kcal/mol)	popu- lations	rel free energies (kcal/mol)	popu- lations
<b>1a</b> ( $C_1$ )	0.000	0.184	0.241	0.162	0.309
<b>1b</b> ( $C_1$ )	0.052	0.000	0.329	0.000	0.655
<b>1c</b> ( $C_2$ )	1.010	1.955	0.012	1.453	0.001
<b>1d</b> ( $C_1$ )	1.311	0.884	0.074	0.936	0.009
<b>1e</b> ( $C_2$ )	1.593	0.705	0.100	0.776	0.018
<b>1f</b> ( $C_1$ )	1.596	1.737	0.018	1.700	0.000
<b>1g</b> ( $C_1$ )	1.706	0.902	0.072	1.216	0.002
<b>1h</b> ( $C_2$ )	1.723	1.044	0.056	1.020	0.006
<b>1i</b> ( $C_2$ )	1.932	3.054	0.002	2.464	0.000
<b>1j</b> ( $C_1$ )	1.957	2.093	0.009	1.964	0.000
<b>1k</b> ( $C_1$ )	2.151	1.656	0.020	1.771	0.000
<b>1l</b> ( $C_1$ )	2.362	1.933	0.013	1.928	0.000
<b>1m</b> ( $C_1$ )	2.441	3.094	0.002	2.957	0.000
<b>1n</b> ( $C_1$ )	2.651	1.785	0.016	2.061	0.000
<b>1o</b> ( $C_1$ )	2.801	2.263	0.007	2.417	0.000
<b>1p</b> ( $C_1$ )	2.906	1.737	0.018	2.194	0.000
<b>1q</b> ( $C_1$ )	2.990	3.186	0.002	2.617	0.000
<b>1r</b> ( $C_1$ )	3.096	1.945	0.012	2.262	0.000
<b>1s</b> ( $C_1$ )	3.193	2.936	0.002	2.941	0.000
<b>1t</b> ( $C_1$ )	3.306	2.658	0.004	2.833	0.000
<b>1u</b> ( $C_1$ )	3.740	3.538	0.000	3.637	0.000
<b>1v</b> ( $C_1$ )	4.010	3.491	0.000	3.476	0.000
<b>1w</b> ( $C_1$ )	4.014	4.015	0.000	4.013	0.000

**Table 3. Symmetries, Relative Strain Energies, Relative Free Energies, and Populations of Different Conformations of Cyclododecane, Calculated Using Allinger's MM3 Program**

conformer/ symmetry	rel strain energies <sup>a</sup> (kcal/mol)	25.0 °C		-164.5 °C	
		rel free energies (kcal/mol)	popu- lations	rel free energies (kcal/mol)	popu- lations
<b>2a</b> ( $D_4$ )	0.00	0.02	0.346	0.00	0.999
<b>2b</b> ( $C_1$ )	1.67	0.00	0.357	1.49	0.001
<b>2c</b> ( $C_2$ )	2.47	0.57	0.137	1.96	0.000
<b>2d</b> ( $C_3$ )	2.88	0.92	0.076	2.49	0.000
<b>2e</b> ( $C_1$ )	3.84	1.32	0.038	2.91	0.000
<b>2f</b> ( $C_1$ )	4.48	1.69	0.021	3.57	0.000
<b>2g</b> ( $C_3$ )	4.49	2.68	0.000	3.98	0.000
<b>2h</b> ( $C_1$ )	4.56	1.74	0.019	3.50	0.000
<b>2i</b> ( $C_{2v}$ )	4.92	5.41	0.000	5.57	0.000
<b>2j</b> ( $C_2$ )	4.93	2.37	0.006	3.90	0.000

<sup>a</sup> Previously reported in ref 8.

calculated shifts for the olefinic carbons of **1e** and **1h** ( $\delta$  139.2 and 136.7) are both substantially to higher frequency than the experimental value for the  $C_2$  conformation ( $\delta$  132.07). The somewhat closer agreement for **1h** may support the assignment of this conformation. The calculations may estimate relative trends in chemical shifts better than absolute values. As noted by a reviewer, the experimental chemical shift of the olefinic carbons of the  $C_2$  conformation is bracketed by the three  $C_1$  experimental pairs, and in Table 4 the olefinic carbon shift of **1h** is similarly bracketed by those of **1a**, **1b**, and **1d**, while the shift of **1e** is not. This provides additional support for the tentative assignment of **1h** to the  $C_2$  conformation of **1**. The major  $C_1$  conformation shows a  $\text{CH}_2$  peak at the highest frequency for this group of carbons ( $\delta$  36.25); the highest-frequency peaks calculated for the  $\text{CH}_2$  carbons of **1a** and **1b** are at  $\delta$  31.3 and 34.1, respectively, which may support the assignment of **1b** to this conformation.

**Table 4. GIAO Chemical Shifts (in ppm) of Different Conformations of *trans*-Cyclododecene, Calculated at the HF/6-311G\* Level Using the Gaussian 94 Program**

carbon <sup>a</sup>	conformer/symmetry							
	<b>1a</b> ( $C_1$ )	<b>1b</b> ( $C_1$ )	<b>1c</b> ( $C_2$ )	<b>1d</b> ( $C_1$ )	<b>1e</b> ( $C_2$ )	<b>1f</b> ( $C_1$ )	<b>1g</b> ( $C_1$ )	<b>1h</b> ( $C_2$ )
1	134.5	138.3	136.5	134.2	139.2	133.6	132.9	136.7
2	138.8	133.8	136.5	139.0	139.2	140.0	139.8	136.7
3	31.3	28.9	33.8	34.5	26.9	31.5	29.7	30.8
4	28.0	25.6	27.4	26.2	29.8	23.7	23.4	24.9
5	28.1	20.9	24.8	28.7	20.2	29.4	29.1	20.7
6	23.9	20.6	26.1	29.7	25.7	24.8	22.9	25.9
7	20.6	25.3	23.5	25.9	20.8	28.8	21.5	21.7
8	26.0	25.1	23.5	23.4	20.8	25.8	27.2	21.7
9	19.9	23.1	26.1	28.4	25.7	25.2	25.2	25.9
10	22.0	29.1	24.9	20.8	20.2	26.2	23.0	20.7
11	25.1	26.2	27.4	27.6	29.8	25.6	25.6	24.9
12	29.0	34.1	33.8	27.6	26.9	28.8	34.4	30.8

<sup>a</sup> The ring carbons of the conformations as drawn in Figure 2 are numbered clockwise, beginning with the first olefinic carbon.

The preferred [3333]<sup>13</sup> conformation (**2a**) of cyclododecane was recently calculated by MM4<sup>3</sup> to have an enthalpy 1.78 kcal/mol lower than the next most stable conformation, but the free-energy difference was smaller (0.32 kcal/mol at + 25 °C), as the high symmetry ( $D_4$ ) of **2a** leads to a low entropy for this conformation. At room temperature, the populations of four conformations were calculated<sup>3</sup> to be 55, 32, 9, and 5%. MM3 strain energies<sup>8</sup> and free energies for **2** are summarized in Table 3, and the latter predict that **2a** should predominate at -165 °C, while nearly equal populations of **2a** and **2b** are estimated for room temperature. Conformation **2a** has a low vibrational frequency (29  $\text{cm}^{-1}$  by MM4<sup>3</sup> and 26  $\text{cm}^{-1}$  by MM3<sup>8</sup>), which increases the uncertainty in the calculated free energy of this conformation.

Experimental studies of **2** confirm the presence of **2a** as the only conformation observed in solution at low temperatures<sup>14</sup> and in the solid state,<sup>15</sup> and a combination of electron diffraction and force field calculations was used to study the compound in the vapor phase.<sup>16</sup> This conformation has four dihedral angles near 160°, which would appear suitable for location of a trans double bond, but the resulting alkene (**1e**) has  $C_2$  symmetry, and the most populated conformation of **1** has  $C_1$  symmetry and cannot be based on **2a**. Conformation **1h** was calculated to have a free energy that is only a little above that of **1e** and was found for a silver nitrate complex by X-ray crystallography;<sup>5</sup> the dihedral angles of **1h** resemble those of **2j**. The  $C_1-C_2$  bond of **1h** is parallel to the  $C_7-C_8$  bond, and the  $C_4-C_5$  and  $C_{10}-C_{11}$  bonds are crossed. For **1e**, both corresponding pairs of bonds are crossed. Conformations **1a** and **1b** were calculated to have dihedral angles close to those of **2b** and **2c**, respectively, but do not match among the remaining conformations of **2** in Figure 3 has yet been found for **1d**. The results for **1** and **2** and for the 10-membered rings<sup>1,2</sup> demonstrate that the preferred conformation of a *trans*-cycloalkene cannot reliably be assumed to be derived from the preferred conformation of the corresponding cycloalkane and that

(13) For the nomenclature used here and the calculations of Dale for cyclododecane, see: (a) Dale, J. *Top. Stereochem.* **1976**, *9*, 199. (b) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115.(14) Anet, F. A. L.; Cheng, A. K.; Wagner, J. J. *J. Am. Chem. Soc.* **1972**, *94*, 9250.(15) Dunitz, J. D.; Shearer, H. M. M. *Helv. Chim. Acta* **1960**, *43*, 18.(16) Atavin, E. G.; Mastryukov, V. S.; Allinger, N. L.; Almenningen, A.; Seip, R. *J. Mol. Struct.* **1989**, *212*, 87.

the number of populated conformations can be considerably greater for the olefins than for the saturated hydrocarbons, at least at low temperatures.

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**Supporting Information Available:** Expanded  $^{13}\text{C}$  NMR spectrum of the  $\text{CH}_2$  carbons, comparison of the dihedral angles for four conformations of *trans*-cyclododecene and cyclododecane, and conformations **1i–w** of *trans*-cyclododecene. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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