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Conformational Analysis of (1*R**,4*S**,7*S**)-7-[(*R**)-1,2-Butadienyl]-1-methylbicyclo[2.2.1]hept-2-ene and (1*R**,4*S**,7*S**)-7-[(*S**)-1,2-Butadienyl]-1-methylbicyclo[2.2.1]hept-2-ene. Molecular Modeling as a Complement to NMR for Stereochemical Analysis

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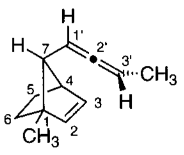
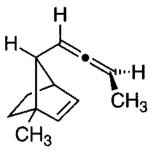
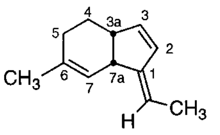
Earlier we reported[1] on the synthesis and thermal rearrangement of (±)-(1*R**,4*S**,7*S**)-7-[(*R**)-1,2-butadienyl]-1-methylbicyclo[2.2.1]hept-2-ene (**1a**) and (±)-(1*R**,4*S**,7*S**)-7-[(*S**)-1,2-butadienyl]-1-methylbicyclo-[2.2.1]hept-2-ene (**1b**). Both **1a** and **1b** were shown to undergo Cope rearrangements to (±)-*cis*-1-ethylidene-3a,4,5,7a-tetrahydro-6-methylindene (**2**) and (±)-*cis*-1-ethylidene-3a,4,5,7a-tetrahydro-3a-methylindene (**3**) with greater than 90% stereoselectivity. Assignment of absolute stereochemistry to these rearrangements relies upon proper assignment of stereochemistry to the diastereomeric allenylnorbornenes **1a** and **1b** as well as trienes **2** and **3**.



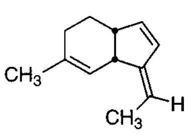
1a



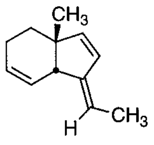
1b



(*E*)-**2**



(*Z*)-**2**



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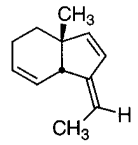
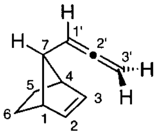


(*Z*)-**3**

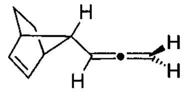
The stereochemistry of **2** and **3** was easily assigned using NOE difference spectroscopy alone; e.g., irradiation of the =CHC*H*$_3$ resonance led to NOE enhancements of about 3% for the H2 resonances of (*E*)-**2** and (*E*)-**3**, but no enhancements were detected for the H2 resonances of (*Z*)-**2** and (*Z*)-**3**.[1] However, due to the relative freedom of rotation about the C$_7$−C$_{1'}$ bond in **1**, NOE experiments were less conclusive in distinguishing between **1a** and **1b**. We now report on the results of a theoretical conformational analysis study of **1a** and **1b**, which nicely complements our earlier NOE results.

Results

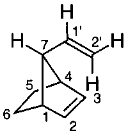
A theoretical conformational analysis study was first performed on the parent compound, *syn*-7-propadienylbicyclo[2.2.1]hept-2-ene (*syn*-7-allenylnorbornene) (**4**). It was optimized at the RHF/6-31G*//RHF/6-31G* level (total ab initio energy −385.567943 hartrees) and gave a HC$_7$−C$_{1'}$H dihedral angle (ω_1) of 180.0°. An AM1 conformer search, based on stepwise rotation of the C$_7$−C$_{1'}$ bond, yielded only a single minimum structure ($\omega_1 =$ 180°) with a heat of formation of 76.7 kcal/mol (cf. Figure 2c).



4$_c$



4$_e$



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The conformer search was then repeated at the RHF/STO-3G//RHF/STO-3G ab initio level, and this time, three conformers were located. The most abundant conformer, 74.2%, had $\omega_1 = 180.0°$, once again. The other two conformers, each with a population of 12.9%, had $\omega_1 = 56.5°$ and −56.5° and were each 1.0 kcal/mol higher in energy than the minimum energy conformer.

These results, which indicate that the lowest energy conformer is the one with the allenyl moiety fully extended away from the norbornene ring, **4**$_e$, are in contrast to the results of MM2 calculations (cf. Figure 1c). Such calculations give minima for $\omega_1 = 70°$ and −70° and local maxima at $\omega_1 = 143°$ and −143° corresponding to steric energies of −19.7 and −19.0 kcal/mol, respectively. The global maximum, with a steric energy of −18.1 kcal/mol, occurs at $\omega_1 = 0.0°$, corresponding to the fully collapsed conformation **4**$_c$. Thus the full range of steric energies is only 1.6 kcal/mol. The discrepancy between the MM2 and AM1 results is not surprising in view of the fact that MM2 calculations don't take electronic interactions into account, only steric ones; presumably, unfavorable π-interactions between the allenyl and alkene moieties contribute to an energy increase for all conformations with $|\omega_1| < 180°$.

Conformer searches were then performed on the dimethyl-substituted allenylnorbornenes **1a** and **1b**. At the AM1 level, only one conformer was located for **1a**. It had $\omega_1 = 174.0°$ in the direction that has the allenyl moiety rotated slightly in the direction away from the bridgehead methyl group. The same calculation on **1b** gave $\omega_1 =$ 175.0°, again with the allenyl moiety rotated away from the bridgehead methyl. Both structures had a heat of formation of approximately 63.3 kcal/mol.

When the above calculation was repeated at the RHF/STO-3G//RHF/STO-3G ab initio level, however, three conformers were located for each of the diasteriomers **1a** and **1b**. For **1a**, these conformers had ω_1 values of −179.2°, 52.3°, and −41.8°, where the minus signs correspond to rotation of the allene moiety in the direction toward the bridgehead methyl group. These angles correspond to populations of 84.8%, 11.4%, and 3.8%, respectively. In the case of **1b**, the corresponding ω_1 values and populations were found to be −179.1° (85.0%), 52.2° (11.7%), and −42.9° (3.3%).

Not surprisingly, these results are once again in contrast to those obtained from MM2 calculations. As shown in Figure 1a for structure **1a**, local minima were found at −149.0° and −50.3°, local maxima at −98.0° and 118.9°, and the global minima and maxima at 60.7° and 0.1°, respectively. Similarly (cf. Figure 1b) for structure **1b**, local minima were found at −154.4° and −49.3°, local maxima at −1.6° and 122.2°, and global minima and maxima at 58.8° and −95.7°, respectively. Figure 1c

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[1] Duncan, J. A.; Hendricks, R. T.; Kwong, Katy S. *J. Am. Chem. Soc.* **1990**, *112*, 8433−8442.

S0022-3263(95)01418-6 CCC: $12.00

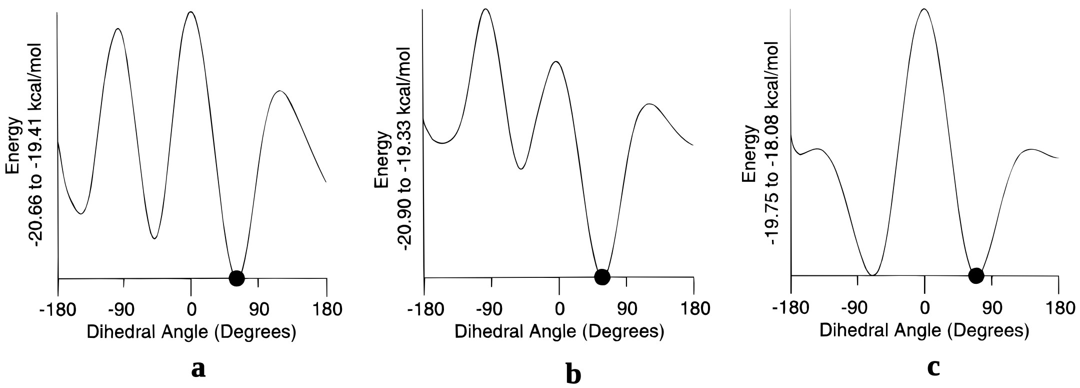


Figure 1. MM2 calculations with rotation about the $HC_7-C_{1'}H$ dihedral angle (ω_1) from −180° to 180° in 0.05° steps: (a) **1a**; (b) **1b**; (c) **4**.

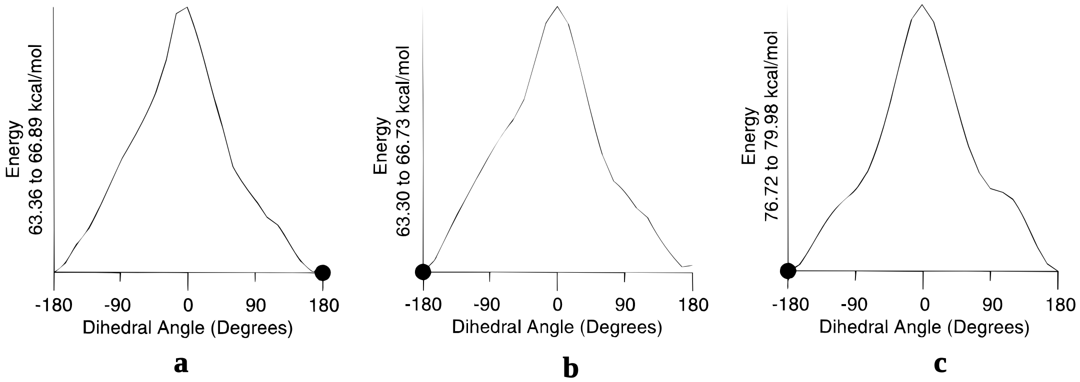


Figure 2. AM1 calculations with rotation about the $HC_7-C_{1'}H$ dihedral angle (ω_1) from −180° to 180° in 15° steps: (a) **1a**; (b) **1b**; (c) **4**.

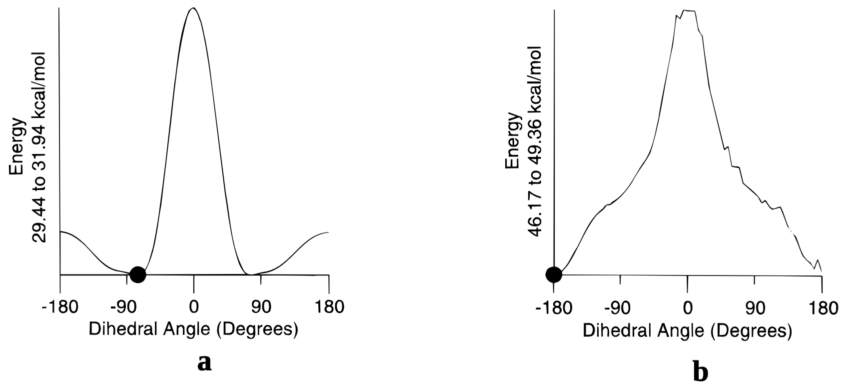


Figure 3. Calculations on **5** with rotation about the $HC_7-C_{1'}H$ dihedral angle (ω_1) from −180° to 180° in 5° steps: (a) MM2; (b) AM1.

depicts the comparable results of MM2 calculations on allenylnorbornene **4**, made reference to above. The higher minima at approximately −50°, relative to the minima at approximately 60°, in Figure 1, parts a and b, almost certainly result from steric crowding of the methyl groups, which would also be expected to be greater at −50° for compound **1b** than for **1a**.

The results of AM1 calculations, which show only one minimum and one maximum, are depicted in Figure 2. The bulges on the left sides of Figure 2, parts a and b, are no doubt also a consequence of crowding of the methyl groups which should be greater for structure **1b** than **1a**.

In addition, both the MM2 and AM1 results imply that the bridgehead and allenyl methyl groups remain largely staggered [i.e., one $C_7-C_1-C_{\text{bridgehead}}H$ (ω_2) and one $HC_{3'}-C_{\text{allenyl}}H$ (ω_3) dihedral angle about 180°] during 360° rotation about the $C_7-C_{1'}$ bond in **1a** and **1b**. The MM2 calculations indicate that the bridgehead methyl deviates from this norm by less than 3.9% and the allenyl methyl by less than 1.2%. Similarly, AM1 calculations suggest a deviation of less than 8.8% and 3.7% for the bridgehead and allenyl methyl groups, respectively.

For comparison, we also performed a similar conformational analysis on *syn*-7-ethenylbicyclo[2.2.1]hept-2-ene (*syn*-7-vinylnorbornene) (**5**), based on stepwise rotation of the corresponding $C_7-C_{1'}$ bond. The result of the MM2 calculation is shown in Figure 3a, which is very similar to the result obtained for allenylnorbornene **4** as depicted in Figure 1c. An AM1 conformer search yielded only a single minimum structure ($\omega_1 = 179°$) with a heat of formation of 46.2 kcal/mol (cf. Figure 3b), and the similarity of Figures 2c and 3b is clearly evident. When the conformer search on vinylnorbornene **5** was repeated at the RHF/STO-3G//RHF/STO-3G level, three conform-

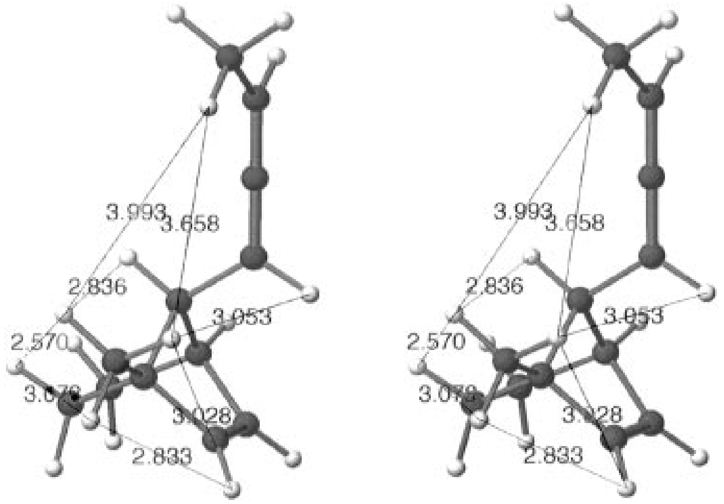


Figure 4. Stereoview of fully optimized RHF/6-31G*//RHF/6-31G* structure of **1a** (total ab initio energy −463.643434 hartrees), showing selected hydrogen atom distances. A frequency calculation confirmed the structure to be a minimum.

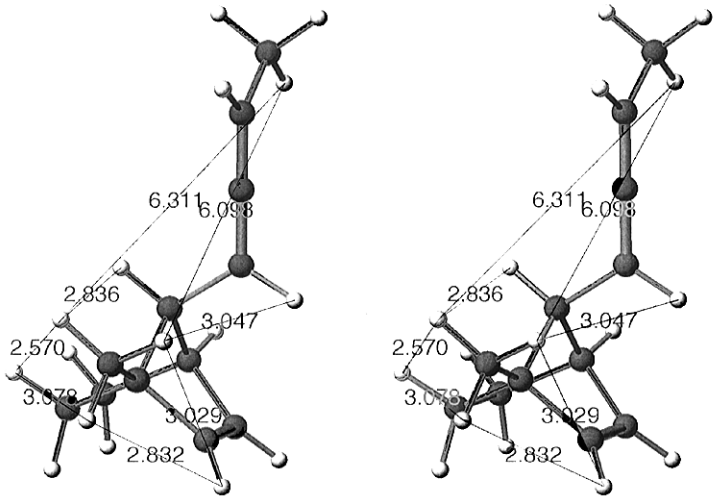


Figure 5. Stereoview of fully optimized RHF/6-31G*//RHF/6-31G* structure of **1b** (total ab initio energy −463.643410 hartrees), showing selected hydrogen atom distances. A frequency calculation confirmed the structure to be a minimum.

ers were located as was the case in the similar conformer search conducted for allenylnorbornene **4**. The most abundant conformer, 83.0%, had $\omega_1 = 180.0°$ The other two conformers, each with a population of 8.5%, had $\omega_1 = 60.0°$ and $-60.0°$ and were each 1.5 kcal/mol higher in energy than the minimum energy conformer. These results suggest that the presence of the $C_{2'}-C_{3'}$ π-bond in allenylnorbornenes **1a**, **1b**, and **4** has little influence on their conformational behavior.

Discussion

On the basis of theoretical results reported above, it is evident that the fully extended conformations of **1a** and **1b**, best represented by the fully optimized RHF/6-31G*//RHF/6-31G* structures shown in stereoscopic views in Figures 4 and 5, are highly preferred over any other conformation. Thus it appears tenable to interpret the NOE enhancements observed from saturation of the bridgehead methyl groups in diastereomers **1a** and **1b** in terms of these extended conformations alone.

Table 1. Atom Distances and NOE Enhancements for Optimized 1a

atom	atom distance (Å)	% NOE enhancement[a]
H_1-H_a	2.8	2.7 (3.0)
H_3-H_a	3.0	
H_1-H_b	3.1	0.9 (1.2)
H_2-H_b	2.6	
H_2-H_c	2.8	1.1 (1.1)
H_3-H_d	3.1	(~1.4)
H_2-H_e	4.0	0.4 (0.2)
H_3-H_e	3.7	

[a] Enhancements measured at 25 °C (no parentheses) and −50 °C (parentheses) in $CDCl_3$ with saturation of the bridgehead CH_3 resonance. Data taken from ref 1.

Tables 1 and 2 give the atom distances between hydrogen atom nuclei on the bridgehead methyl group (1−3) and various other hydrogen nuclei (a−e) in the fully optimized **1a** and **1b** structures, as shown on the annotated **1a** and **1b** structures below. Only hydrogen atom nuclei a−e which are closest to hydrogen nuclei 1−3 on the bridgehead methyl group are shown. The same distance values are also displayed on the structures depicting the optimized structures found in Figures 4 and 5. NOE enhancements[2] are only observable when at least one of the hydrogen atom nuclei on the bridgehead methyl group (1−3) is less than 3.7 Å away from the hydrogen nuclei (a−e) experiencing the enhancement in the fully optimized RHF/6-31G*//RHF/6-31G* structures

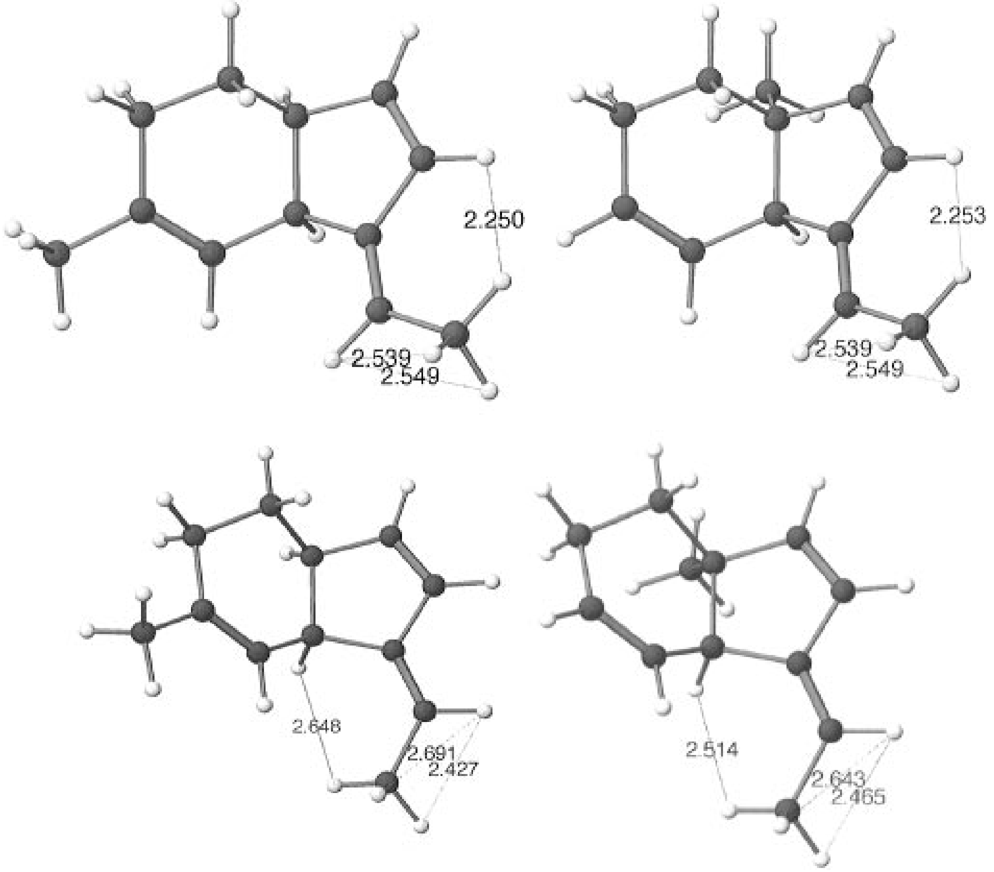


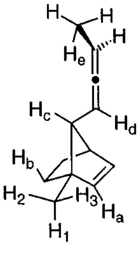
Figure 6. Fully optimized RHF/6-31G*//RHF/6-31G* structures: (top left) (*E*)-**2**; (top right) (*E*)-**3**; (bottom left) (*Z*)-**2**; (bottom right) (*Z*)-**3** (total ab initio energies −463.697151, −463.692099, −463.694207, and −463.689029 hartrees, respectively). Hydrogen atom distances for nuclei involved in measurable NOE enhancements are shown.

Table 2. Atom Distances and NOE Enhancements for Optimized 1b

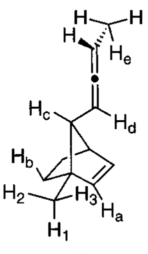
atom	atom distance (Å)	% NOE enhancement[a]
H_1-H_a	2.8	2.5 (2.6)
H_3-H_a	3.0	
H_1-H_b	3.1	0.9 (1.2)
H_2-H_b	2.6	
H_2-H_c	2.8	1.2 (1.0)
H_3-H_d	3.0	(~1.4)
H_2-H_e	6.3	0.0 (0.0)
H_3-H_e	6.1	

[a] Enhancements measured at 25 °C (no parentheses) and −50 °C (parentheses) in $CDCl_3$ with saturation of the bridgehead CH_3 resonance. Data taken from ref 1.

1a and **1b**. Furthermore, internuclear distances of less than 3.1 Å appear to be required to achieve an enhancement ≥1%. All internuclear distances associated with nuclei giving no observable NOE enhancement are greater than 4.4 Å. The only exception is for H_{endo}-6 where a probable NOE enhancement is obscured by off-resonance effects.[1]



1a



1b

The interpretation of the NOE enhancements observed for **1a** and **1b,** described above, is also supported by a similar comparison of observed NOE enhancements vis-a-vis certain internuclear distances for the thermal rearrangement products **2** and **3**, for which conformational effects are not as relevant as they are for **1a** and **1b**. Figure 6 depicts the fully optimized RHF/6-31G*//RHF/6-31G* structures for (*E*)-**2**, (*E*)-**3**, (*Z*)-**2**, and (*Z*)-**3**. For (*E*)-**2** and (*E*)-**3**, NOE enhancements were observed for H_2 and, of course, $=CHCH_3$; whereas enhancements were only observed for H_{7a} and $=CHCH_3$ in the case of (*Z*)-**2** and(*Z*)-**3**.[1] (Possible NOE enhancements for other resonances were either affected by or obscured by the nonselective nature of the saturation of the $=CHCH_3$ resonance or by being overlapped with other resonances.)

In conclusion, the results of the thorough conformational analysis study reported above strongly confirm the initial assignment—made in reference 1—of structure **1a** to the diastereomer of *syn*-(1,2-butadienyl)-1-methylbicyclo-[2.2.1]hept-2-ene that gives an observable (0.2−0.4%) NOE enhancement (cf. Tables 1 and 2) of the allenyl methyl hydrogen atom nuclei upon saturation of the bridgehead methyl resonance.[3]

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(2) NOE results, taken from ref 1, were obtained using NOE difference spectroscopy: Upon irradiation of the bridgehead methyl group, an NOE enhancement was clearly observed for one of the epimers of **1** but not observed over the noise level for the other epimer. Clearly, the fact that we had both epimers **1a** and **1b** available to us for direct comparison was critical in enabling us to make the necessary distinction between the two.

(3) These results also confirm the stereochemistry for the **1** → **2** + **3** rearrangement to be **1a** → 95% (*E*)-**2** + (*Z*)-**3** and **1b** → 96% (*Z*)-**2** + (*E*)- **3**, as was originally suggested in ref 1.

Computational Methods

All geometry optimizations and conformer searches were performed using either Gaussian 92[4] or Spartan[5] programs. The MM2 and AM1 calculations resulting in the plots in Figures 1−3 were performed using CAChe[6] software, running MOPAC. The structures appearing in Figures 4−6 were obtained by converting Spartan molecules to CAChe ones. (Gaussian 92 output was first used as input to generate Spartan molecules in certain cases.)

Acknowledgment. The author wishes to express his appreciation to Professor Alan Shusterman, of Reed College, for many helpful discussions during the course of this project.

Supporting Information Available: Coordinates and energies for structures **1a**, **1b**, (*E*)-**2**, (*Z*)-**2**, (*E*)-**3**, (*Z*)-**3**, and **4**, optimized at the RHF/6-31G*//RHF/6-31G* level (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[4] Gaussian 92, Revision G.3, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1992.

[5] Spartan, Version 3.1. Wavefunction, Inc. 18401 Von Karman, Suite 370, Irvine, CA 92715.

[6] CAChe, Release 3.5. CAChe Scientific Inc., Beaverton, OR.