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NMR and Molecular Mechanics Studies of the Conformational Dynamics of Tricyclo[3.3.3.0^{3,7}]undecane Derivatives

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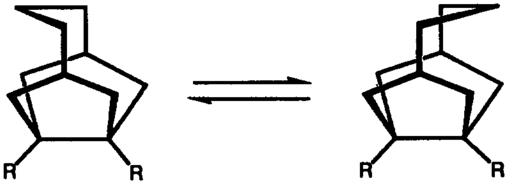
Abstract: Dynamic NMR studies and molecular mechanics calculations both indicate that twisting about the C_3-C_7 bond facilitates flipping of the trimethylene bridge in the tricyclo[3.3.3.0^{3,7}]undecane ring system.

In our recent report of the synthesis and study of tricyclo[3.3.3.0^{3,7}]undec-3(7)-ene (1)[1] we noted that both the ^{1}H and ^{13}C NMR spectra are temperature dependent. The observations that in the ^{1}H NMR spectra all the resonances but those for the bridgehead protons exhibit temperature-dependent broadening and coalescence; whereas, in the ^{13}C NMR spectra only the allylic and olefinic carbons do, allowed us to assign flipping of the trimethylene bridge, shown below, as the conformational process responsible for the temperature dependence of the NMR spectra. From the frequency differences ($\Delta\nu$) at low temperatures and the temperatures (T_c) at which coalescence was observed, free energies of activation were obtained from the equation,[2]

$$\Delta G^\ddagger = -RT_c \ln\{\pi\Delta\nu h\,(2)^{-1/2}/kT_c\}$$

The experimental data and values of $\Delta G^\ddagger$ obtained from them are given in Table 1. The apparent lack of temperature dependence in the values of $\Delta G^\ddagger$, measured at temperatures that span nearly 25°, suggests that $\Delta S^\ddagger$ is small. Since $\Delta G^\ddagger$ for bridge flipping in 1 is thus indicated to be close to $\Delta H^\ddagger$, MM3 molecular mechanics calculations[3] were performed in order to calculate the energy required for this process. As shown by the results in Table 2, the calculations provide a value of 14.94 kcal/mol, which is in excellent agreement with the average value of $\Delta G^\ddagger = 14.9 \pm 0.1$ kcal/mol for the free energies of activation measured by NMR. The computed value of the entropy of activation is $\Delta S^\ddagger = 0.4$ eu, supporting our inference from the NMR data that $\Delta S^\ddagger$ is small and justifying our averaging the values of $\Delta G^\ddagger$ obtained at different temperatures.



1, R-R = ——
2, R-R = $OC(CH_3)_2O$
3, R = OH
4, R = OMs
5, R-R = $(Ph_3P)_2Pt$
6, R-R = CH_2
7, R = H

Several of the intermediates in the synthesis of 1 were also found to have temperature dependent ^{1}H and ^{13}C NMR spectra. The measured values of $\Delta\nu$ and T_c and the values of $\Delta G^\ddagger$ obtained from them are also given in Table 1 for acetonide 2, diol 3, dimesylate 4, and the $(Ph_3P)_2Pt$ complex (5) of 1.[4] Although the values of $\Delta G^\ddagger$ for bridge flipping in 5 are similar to those in 1,

Table 1. Dynamic ^{1}H and ^{13}C NMR Data for Compounds **1** - **5**.

Compound	Sites Exchanged[a]	Δv (Hz)	Tc (K)	ΔG‡ (kcal/mol)[b]
1, R-R = ———	H_{2n} (H_{4n}), H_{8n} (H_{6n})	167.9	316	14.8
	H_{2x} (H_{4x}), H_{8x} (H_{6x})	112.0	308	14.6
	C_3, C_7	48.9	304	15.0
	C_2 (C_6), C_8 (C_4)	386.5	328	14.9
2, R-R = $OC(CH_3)_2O$	H_{2n} (H_{4n}), H_{8n} (H_{6n})	193.4	238	11.0
	H_{2x} (H_{4x}), H_{8x} (H_{6x})	158.1	236	11.0
	C_3, C_7	66.5	228	10.9
	C_2 (C_6), C_8 (C_4)	423.0	248	11.0
3, R = OH	C_2 (C_6), C_8 (C_4)	377.2	214	9.5
4, R = OMs	H_{9n} (H_{11n}), H_{9x} (H_{11x}),	265.5	198	8.9
	C_2 (C_6), C_8 (C_4)	872.8	210	9.0
5, R-R = $(Ph_3P)_2Pt$	H_{2n} (H_{4n}), H_{8n} (H_{6n})	126.6	305	14.4
	H_{2x} (H_{4x}), H_{8x} (H_{6x})	171.7	301	14.1
	C_2 (C_6), C_8 (C_4)	536.7	329	14.7

[a] n = endo, x = exo. [b] Estimated precision of individual values = ± 0.2 kcal/mol

the values for **2** are about 4 kcal/mol lower; and those for **3** and **4** are lower still.

We found this variation initially surprising, because, at first sight, it would appear unlikely that the substituents at C_3 and C_7 could have a significant effect on ΔG‡ for trimethylene bridge flipping. Therefore, we performed MM3 calculations on **2** and **3**. Calculations on **4** were simulated by calculations on **3** in which the O-H bonds were required to be oriented away from each other, the orientation of the O-S bonds in **4** that would place the mesyl groups in the sterically least encumbered environment. We modeled the metallocyclopropane ring in **5** with the cyclopropane ring in **6**, and we also performed calculations on the saturated hydrocarbon (**7**), a molecule which is, as yet, unknown.

With the exception of diol **3**, the equilibrium geometries were initially optimized in C_s symmetry, the same symmetry as the equilibrium geometry of **1**. A favorable, side-by-side orientation of the O-H dipoles in **3** requires that it have only C_1 symmetry, which is why the MM3 energy of **3** was calculated to be 5.33 kcal/mol below that of our model for **4**, in which the O-H dipoles were constrained to point in opposite directions. Vibrational analyses showed all of the C_s geometries, except for that of **6**, to have at least one negative force constant; so the geometries were reoptimized in C_1 symmetry, which allows the C-R bonds at C_3 and C_7 to deviate from an eclipsed geometry. However, as shown in Table 2, the dihedral angle between these bonds remains small; and the associated energy lowerings amount to only 0.09 kcal/mol for our model for **4** and 0.01 kcal/mol for **7**. The 1.28 kcal/mol energy lowering for acetonide **2** is a little larger, because, without the imposition of C_s symmetry, the 1,3-dioxolane ring in **2** can adopt a non-planar, puckered conformation.

Again with the exception of **3**, the transition states were all initially optimized in C_{2v} symmetry, the same symmetry as the transition state for trimethylene bridge flipping in **1**. As expected, bridge flipping in our models for **4** and **5** (i.e., **6**) and in **7** was calculated to have nearly the same energy barrier as in **1**. The barrier in **2** was also calculated to be almost the same as that in **1**, when the energy of the C_{2v} transition state for **2** was compared with the energy of the C_s ground state, in which the 1,3-dioxolane ring is also constrained to be planar. The results of these calculations support the reasonable supposition that substituents at C_3 and

Table 2. Results of MM3 Calculations on Ground and Transition State Energies (kcal/mol) for Trimethylene Bridge Flipping in 1 - 3, a Constrained Diol Model for 4, a Cyclopropane model (6) for 5, and the Saturated Hydrocarbon (7). R-C-C-R Dihedral Angles (deg) are Given for the Optimized C_1 Geometries of the Ground States and C_2 Geometries of the Transition States.

	Ground State Energy (Symmetry Imposed)			Transition State Energy (Symmetry Imposed)		
Compound	E (C_1)	E (C_s)	∠ R-C-C-R[a]	E (C_2)	E (C_{2v})	∠ R-C-C-R[b]
1	0	0	—	14.94	14.94	—
2	0	1.28	2.0	10.99	15.83	26.7
3	0	—	4.8	9.99[c]	—	22.2
4[d]	0[e]	0.09	8.7	8.99	14.66	27.7
6	0	0	0	15.18	15.18	0
7	0	0.01	4.2	10.02	14.53	23.8

[a] C_1 geometry. [b] C_2 geometry. [c] Computed for C_1 geometry. [d] Diol model (see text) for 4. [e] E = 5.33 kcal/mol, relative to 3.

C_7 should not have a significant effect on the barrier for trimethylene bridge flipping. However, this supposition is obviously wrong, because the calculated barriers do not match the free energies of activation found experimentally.

Unlike the C_{2v} structures for 1 and 6, those for 2, for the model for 4, and for 7 were all found to have more than one negative eigenvalue. As shown in Table 2, reoptimization of these structures in C_2 symmetry, which allows the C-R bonds to be staggered in the transition states, as they are in the equilibrium geometries, leads to structures with very large dihedral angles between these bonds and much lower energies than the C_{2v} structures. Vibrational analyses confirmed that each of these C_2 structures has exactly one negative force constant and, thus, is a true transition state. A C_1 transition structure was located for 3 by optimizing a C_2 geometry, which was found to have two negative force constants; and then allowing the O-H groups to adopt a more favorable orientation by reoptimizing the C_2 structure in C_1 symmetry. As shown in Table 2, this transition state for trimethylene bridge flipping in 3, like the transition states for bridge flipping in 2, in our model for 4, and in 7, has a much larger dihedral angle between the C-O bonds than that in the equilibrium geometry.

The results of our MM3 calculations are in excellent agreement with experiment, and they reveal why the experimental free energy barriers to bridge flipping decrease in the order $1 \approx 5 > 2 > 3 \approx 4$. Twisting about the C_3-C_7 bond obviously lowers the barrier to trimethylene bridge flipping in the tricyclo[3.3.3.$0^{3,7}$]undecane ring system. The π bond in 1 prevents the alkene from twisting about this C-C bond, as does the three-membered ring in the $(Ph_3P)_2Pt$ complex (5) of 1 and in our cyclopropane model (6) for this metallocyclopropane.

The results in Table 2 show that preserving a plane of symmetry in the ground and transition states in both 2 and 4 gives almost exactly the same barriers to bridge flipping in each, respectively, 14.65 and 14.67 kcal/mol. When the plane of symmetry is removed, the calculated barrier to bridge flipping in 2 is higher than that in 4 by 2.00 kcal/mol. Puckering of the dioxolane ring stabilizes the ground state geometry of 2 by 1.19 kcal/mol more than twisting about the C_3-C_7 bond stabilizes the ground state geometry of 4; and, because the dioxolane ring in 2 is twisted in the preferred transition state geometry, when the plane of symmetry is removed, the transition state for bridge flipping is stabilized by 0.83 kcal/mol less in 2 than in 4.

The slightly higher free energy barrier, found by NMR, to bridge flipping in 3 than in 4 is mirrored in the MM3 calculations. As shown in Table 2, maintaining a favorable interaction between the OH groups in 3 results in a somewhat smaller O-C-C-O dihedral angle in the transition state for bridge flipping in 3 than in our model for 4.

The barrier to bridge flipping in the saturated hydrocarbon (7) is also computed to be slightly higher than that in our model for 4 and essentially the same as that in diol 3. The difference between the barrier heights calculated for 7 and our diol model for 4 results from the fact that deeclipsing of two hydrogens contributes less to facilitating twisting about the bond between C_3 and C_7 in 7 than does deeclipsing of the two oxygens in our model for 4. Calculations on ethane and ethylene glycol, with the OH bonds in the latter oriented as in our diol model for 4, find that going from an eclipsed geometry to one with a dihedral angle of 23.8° provides 0.99 kcal/mol less stabilization for the hydrocarbon than for the diol.

Our experimental values for the free energies required for trimethylene bridge flipping in the tricyclo[3.3.3.0^{3,7}]undecane ring system have relevance to the conformational dynamics of cyclooctane.[5] Trimethylene bridge flipping in 1 - 5 interchanges chair-boat (CB) and chair-chair (CC) conformations of the two eight-membered rings. CB and CC are the two lowest energy conformations of cyclooctane, and the barrier to conversion of the former to the latter has been measured to be $\Delta G^{\ddagger} = 11.2 \pm 0.4$ kcal/mol at 228 K by Anet and Basus.[6] Molecular mechanics calculations on the interconversion of the CB and CC conformations of cyclooctane predict that this process proceeds through twisted CB and CC conformations, which maintain a C_2 axis[7] or axes,[8] but not a plane of symmetry. Maintaining a plane of symmetry, so that twisting of the eight-membered ring is precluded, was calculated by Hendrickson to require passage over a substantially higher (about 8 kcal/mol) energy barrier.[8]

Our studies of trimethylene bridge flipping in the tricyclo[3.3.3.0^{3,7}]undecane ring system provide experimental confirmation of this qualitative prediction. Tricyclo[3.3.3.0^{3,7}]undecane derivatives 1 and 5 cannot rotate about the C_3-C_7 bond. Consequently, they must preserve a plane of symmetry while interchanging CB and CC conformations in the eight-membered rings that they contain; and this results in their having barriers to trimethylene bridge flipping that are about 5 kcal/mol higher than those in 2 - 4. The latter three molecules can rotate about the C_3 - C_7 bond and thus achieve twisted CB and CC geometries that allow them to undergo CB-CC interconversions with considerably lower free energy barriers than 1 and 5.[9]

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References and Notes

1. Smith, J. M.; Hrovat, D. A.; Borden, W. T.; Allan, M.; Asmis, K. R.; Bulliard, C.; Haselbach, E.; Meier, U. C. *J. Am. Chem. Soc.* **1993**, *115*, 3816.
2. Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.*, **1956**, *25*, 1228.
3. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551; Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566 and 8576.
4. Nicolaides, A.; Smith, J. M.; Borden, W. T. *J. Am. Chem. Soc.*, to be submitted; Nicolaides, A. Ph.D. thesis, University of Washington, 1992.
5. Review: Anet, F. A. L. *Top. Curr. Chem.* **1974**, *45*, 169.
6. Anet, F. A. L.; Basus, V. J. *J. Am. Chem. Soc.* **1973**, *95*, 4424.
7. Anet, F. A. L.; Krane, J. *Tetrahedron Lett.* **1973**, *14*, 5029.
8. Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7047.
9. The ability of the bicyclo[3.3.3]undecane ring system to twist is, presumably, responsible for the observation that the hydrocarbon[10] and the 1-aza derivative[11] both undergo a dynamic exchange between two sets of equivalent CB conformations for all three eight-membered rings with values of $\Delta G^{\ddagger}$ estimated[10] to be 11 ± 2 kcal/mol at 213 K.
10. Doyle, M.; Parker, W.; Gunn, P. A.; Martin, J.; MacNicol, D. D. *Tetrahedron Lett.* **1970**, *11*, 3619.
11. Coll, J. C.; Crist, D. R.; Barrio, M. C. G.; Leonard, N. J. *J. Am. Chem. Soc.* **1972**, *94*, 7092.

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