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Intramolecular Hydrogen Bonding and Conformational Behavior in Bicyclo[3.3.0]octane-Related and Tricyclic Propellane Diols: A Spectroscopic and Computational Study

Mahesh S. Khot,[†] Douglas A. Smith,[‡] Garnett R. McMillan,[†] and Chaim N. Sukenik*,[†]

Departments of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-7078, and University of Toledo, Toledo, Ohio 43606-3390

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The conformational flexibility and the intramolecular hydrogen bonding of a series of [*n*.3.3]propellanediols (and related model compounds) was explored. Evidence was obtained from an analysis of NMR coupling constants for solvent-dependent conformational changes related to intramolecular hydrogen bond formation. Gas-phase IR spectroscopy allowed direct observation of both hydrogen bonded and non-hydrogen bonded OH stretching. Molecular mechanics calculations helped identify the key structural features of these molecules. The calculated structures confirmed the possibility of the formation of excellent intramolecular hydrogen bonds (nearly linear, with oxygen–oxygen distances of about 2.8 Å) and allowed an assessment of the basis for the balance of conformations available to the bicyclo[3.3.0]octyl portion of the molecule as a function of the structure of the third propellane ring.

Introduction

In a study[1] of the structure and reactivity of [*n*.3.3] propellane diones, ketols, and diols, an interesting difference emerged between the *n* = 3 or 4 and the *n* = 10, 12, or 22 compounds. Stereoisomeric diols of each of these compounds were studied (Figure 1, X = CH_2, *n* = *m* + 2) and it was noted[1c] that the vicinal NMR coupling constants of the methylene adjacent to the OH-bearing carbon of the *n* = 10, 12, and 22 **AA** diols (X = CH_2, *m* = 8, 10, 20) were substantially altered by changing the NMR solvent from $CDCl_3$ to CD_3OD, while those of the *n* = 3 and 4 **AA** diols (as well as all of the **SS** diols) were invariant as a function of solvent.

This difference can be explained by noting that there is considerable flexibility in the bicyclo[3.3.0]octanediol system (Figure 2). Three general kinds of conformations can be envisioned: a down-down (**DD**) conformation (both OH bearing rings folded down, away from the nonfunctionalized ring); an up-down conformation (**UD**); and an up-up conformation (**UU**). Since only the **DD** conformation is conducive to intramolecular hydrogen bonding between the two OH groups, and since the coupling constants of the large ring **AA** diols in $CDCl_3$ are consistent[2] with the **DD** conformation, it was suggested[1c] that these **AA** diols exist predominantly in a hydrogen bonded **DD** form (**DDH**), while this conformer is less favorable for the corresponding small ring compounds. This explanation is also consistent with the observation that, based on normal-phase TLC R_f values, the **AA** diol is more polar than the **SS** diol for *n* = 3 and 4, while the reverse is true for *n* = 10, 12, and 22. The reduced molecular dipole expected of a **DDH** species is consistent with this behavior.[3] However, no direct observation of the intramolecular hydrogen bond was reported and no explanation was provided for the changing balance among available conformations.

We present herein both NMR and IR evidence in support of intramolecular hydrogen bonding in the larger ring propellane **AA** diols and in related bicyclo[3.3.0]octanediols. Through a molecular mechanics[4] study of various compounds (**1–7**) containing the bicyclo[3.3.0]octyl **AA** diol unit, the energetics and key structural features of the various conformations available to such molecules are considered. These data offer insight into the balance among [*n*.3.3] propellane conformations and allow us to address the question of whether the oxygen–oxygen distance of the [*n*.3.3] **AA** diols can be controlled by systematically varying *n*.

Experimental Section

General. Routine ^1H-NMR and ^{13}C-NMR spectra (reported in δ units) were determined in $CDCl_3$ at 200 MHz (referenced to $CHCl_3$ at 7.24 ppm) and at 50 MHz (referenced to $CDCl_3$ at 77.00 ppm). ^1H-NMR spectra in CD_3OD (Aldrich) are referenced to CH_3 at 3.3 ppm. Routine IR spectra were recorded in CCl_4 at a resolution of 4 cm^{-1}. HPLC used an IBM ODS (5 μm) 10.0-mm × 25-cm column and refractive index detection. TLC was done on aluminum-backed 0.2-mm 60F254 plates (EM Science) and visualized using phosphomolybdic acid. Flash column chromatography was done with silica gel (Aldrich, 230–400 mesh). Melting points are uncorrected. HPLC grade solvents (Fisher), dimethyl ketoglutarate (Aldrich), and biacetyl (Aldrich) were used as received. The synthesis, purification, and characterization of all the propellane ketols and diols have been described.[1]

Synthesis, Separation, and Characterization of *cis*-1,5-Dimethylbicyclo[3.3.0]octane-3,7-diols (2). *cis*-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione was prepared according to the procedure of Bertz et al.[5a] The tetramethyl ester was recrystallized from CH_3OH; its ^1H-NMR data agree with those reported in the literature;[5a] ^{13}C-NMR 18.04, 51.7, 52.22, 54.18, 58.14, 109.44, 169.34, 170.56, 170.87. After hydrolysis, the dione was purified by flash chromatography (20:80 EtOAc/hexane); its ^1H-NMR data agree with those in the literature.[5a] A mixture of diols[5b] was obtained by reduction of the dione (105 mg) with excess $NaBH_4$ (100 mg) in CH_3OH (25 mL) at rt for 3 h. The reaction was quenched with a small amount of glacial HOAc. The CH_3OH was removed on the rotary evaporator and the product was partitioned between EtOAc and H_2O. The EtOAc layer was separated and the aqueous layer was further extracted with 4 ×

[†] Case Western Reserve University.

[‡] University of Toledo.

[1] (a) Natrajan, A.; Ferrara, J. D.; Youngs, W. J.; Sukenik, C. N. *J. Am. Chem. Soc.* 1987, *109*, 7477. (b) Natrajan, A.; Sukenik, C. N. *J. Org. Chem.* 1988, *53*, 3559. (c) Natrajan, A.; Ferrara, J. D.; Hays, J.; Khot, M.; Colonell, J.; Youngs, W. J.; Sukenik, C. N. *J. Org. Chem.* 1990, *55*, 2164. (d) Anand Natrajan, Ph.D. Thesis, Case Western Reserve University, January 1988.

[2] *J* values were calculated using the generalized Karplus equation of Haasnoot et al. (Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* 1980, *36*, 2783) as implemented in the MacroModel program.

[3] Tierney, B.; Burden, P.; Hewer, A.; Ribeiro, O.; Walsh, C.; Rattle, H.; Grover, P. L.; Sims, P. *J. Chromatogr.* 1979, *176*, 329–335.

[4] Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph Series; American Chemical Society: Washington, DC, 1982.

[5] (a) Bertz, S. H.; Cook, J. M.; Gawish, A.; Weiss, U. *Org. Synth.* 1985, *64*, 27. (b) Reduction with $LiAlH_4$ has been reported by Askani et al. (Askani, R.; Kirsten, R.; Dugall, B. *Tetrahedron* 1981, *37*, 4437) and with $LiAlD_4$ by Baldwin and Kaplan (Baldwin, J. E.; Kaplan, M. S. *J. Am. Chem. Soc.* 1971, *93*, 3969).

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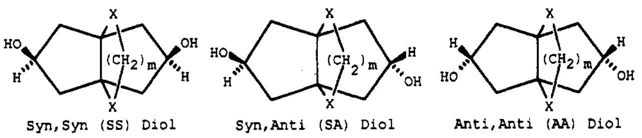


Syn,Syn (SS) Diol Syn,Anti (SA) Diol Anti,Anti (AA) Diol

1 X = H m = 0

2 X = CH_3 m = 0

3 no X m = 1

4 X = CH_2 m = 0

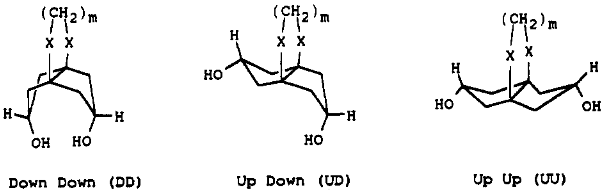
5 X = CH_2 m = 1

6 X = CH_2 m = 2

7 X = CH_2 m = 3

8 X = CH_2 m = 8

Figure 1. Stereoisomeric [*n*.3.3] diols.



Down Down (DD) Up Down (UD) Up Up (UU)

Figure 2. AA diol conformations.

25 mL of EtOAc and then continuously extracted with $CHCl_3$. The organic extracts were combined and dried (Na_2SO_4). The diol isomers can be partially purified by flash chromatography (5:95 CH_3OH/CCl_4) to yield the **AA** isomer (R_f = 0.04) and a mixture of the two other isomers (R_f = 0.06); a higher spot (R_f = 0.35) was discarded. The overall yield of the three isomers was 80%. The diol isomers were better purified by HPLC (flow 6 mL/min; CH_3OH/H_2O 40:60; retention times: 12.2 min (**AA** diol), 6.4 min (**SA** diol), 4.8 min (**SS** diol)). The characterization of the diol isomers and their stereochemical assignments (by analogy[1a]) are based on the following data. Anti,anti diol: mp 175–176 °C; ^{1}H-NMR ($CDCl_3$) 0.91 (s, 6 H), 1.87 (dd, 4 H, J_{vic} = 6.32 Hz), 2.03 (dd, 4 H, J_{vic} = 2.40 Hz, J_{gem} = 14.18 Hz), 4.31 (m, 2 H); ^{1}H-NMR (CD_3OD) 0.98 (s, 6 H), 1.81 (dd, 4 H, J_{vic} = 6.84 Hz), 1.98 (dd, 4 H, J_{vic} = 5.67 Hz, J_{gem} = 13.41 Hz), 4.29 (m, 2 H); ^{13}C-NMR 26.08, 50.54, 51.73, 73.66; IR 3624–3272, 2953, 1558, 1260, 1136, 1012. Syn,anti diol: mp 133–134 °C; ^{1}H-NMR ($CDCl_3$) 0.99 (s, 6 H), 1.40 (dd, 2 H, J_{vic} = 8.26 Hz), 1.59 (dd, 2 H, J_{vic} = 7.55 Hz), 1.84 (dd, 2 H, J_{vic} = 6.38 Hz), 2.11 (dd, 2 H, J_{vic} = 6.38 Hz, J_{gem} = 13.0 Hz), 4.2 (m, 1 H), 4.31 (m, 1 H); ^{13}C-NMR 25.50, 47.81, 50.91, 51.59, 70.85, 71.26; IR 3219, 2952, 1250, 1057, 1007. Syn,syn diol: mp 132–133 °C; ^{1}H-NMR ($CDCl_3$) 1.11 (s, 6 H), 1.48 (dd, 4 H, J_{vic} = 7.69 Hz), 1.89 (dd, 4 H, J_{vic} = 6.25 Hz, J_{gem} = 13.5 Hz), 4.2 (m, 2 H); ^{1}H-NMR (CD_3OD) 1.11 (s, 6 H), 1.47 (dd, 4 H, J_{vic} = 8.1 Hz), 1.85 (dd, 4 H, J_{vic} = 6.38 Hz, J_{gem} = 12.97 Hz), 4.12 (m, 2 H); ^{13}C-NMR 25.98, 47.98, 51.52, 71.50; IR 3629, 2943, 1552, 1057.

Gas-Phase IR Spectroscopy. HPLC purified samples[1] of ketols and diols were injected into a Hewlett Packard Model 5965B GC-IR instrument. GC column (HP-1, 8 m, 0.32-mm i.d.) and light pipe temperatures (isothermal) were adjusted to between 110 and 270 °C to accommodate the volatility of the various compounds, with no evidence of decomposition or significant change in the appearance of the IR spectra. Spectra (4 scans each; 8 cm^{-1} resolution) were collected over the width of the GC peak and used to verify sample homogeneity. Signal averaging over the top half of the peak gave the optimum signal-to-noise ratio. No peaks other than those reported in Table I were evident in the spectral region above 3510 cm^{-1}.

Molecular Mechanics Calculations. All computational work was done using the MacroModel and Batchmin programs (Version 3.1) of Still et al.[6] Versions of this program running on various platforms (VAX 785, SGI Personal Iris 4D/35, DECstation 3100) gave similar results. The global searches of conformational space were done as follows. Structure generation and minimization were run only on a DECstation 3100 running Ultrix 4.1. A systematic pseudo Monte Carlo search,[7] incorporating use-directed structure selection, geometric preoptimization of variable internal coordinates, torsional memory, and an energy cutoff of 40 kJ/mol for starting structures, was performed. With the exception of the two or three ring closure angles and their associated dependent torsions (two per ring closure) all torsions defined by carbon atoms in the rings and by the carbon to hydroxyl oxygen were allowed to vary with angular increments of between 0° and 180° in order to assure global searching. Between 1 and 5 torsion angles were varied in each step. Each starting structure thus generated was minimized using the truncated Newton conjugate gradient method[8] for 100 iterations. If the structure was not within 80 kJ/mol of the current global minimum by iteration 50 and 40 kJ/mol by iteration 100, the structure was discarded. Duplicate minima were eliminated if a least-squares superimposition of all the carbons, oxygens, and the hydroxyl hydrogens with their equivalent atoms in all previous unique minima were separated by less than 0.25 Å. In a subsequent minimization run, the initial set of structures was further minimized to a convergence of 0.05 kJ/mol; duplicates were eliminated as before and an energy window of 40 kJ/mol above the global minimum was enforced.

Analysis of the search results was done by editing standard MacroModel log files. The edited log files were imported into a spreadsheet program (Quattro Pro 3.0, Borland International Inc.) for ease of tabulation and analysis. The set of calculated structures were first sorted to remove redundancies and were then classified into sets which exhibited similar O–O atomic distances and X–C–C–X dihedral angles. These sets were arranged in order of increasing energy. The Boltzmann factor for each conformation was calculated using the formula $\exp(-E_i/RT)$, where E_i is the total energy of the *i*th conformer in kJ/mol, *R* is the gas constant (8.31×10^{-3} kJ K^{-1} mol^{-1}), and *T* is 293.15 K. Using the Boltzmann factors, the mole fraction of each conformer was calculated as an estimate of its percent contribution to the actual state of the molecule. Only conformers with energies within 21 kJ (5 kcal/mol) of the global minimum were included in the final data tabulation since only they made meaningful contributions to the overall conformer mix (see supplementary material).

For each of the conformers of the **AA** diols of **2**, **5**, and **6**, the vicinal coupling constants between the hydrogen on the OH bearing carbon and its neighboring CH_2 group were calculated.[2] The coupling constants for each of the four hydrogens on each face of the bicyclo[3.3.0]octyl unit were averaged and then multiplied by the mole fraction of that conformer. The weighted values of the coupling constants for the hydrogens on each face of each conformer were then summed to arrive at the weighted vicinal coupling constants, which were compared to the values obtained from NMR experiments.

Results and Discussion

To ascertain whether compounds without the constraints of the propellane structure show the same (albeit indirect) NMR evidence for hydrogen bonding as the larger ring propellanes, we synthesized the non-propellane model compound with methyl substituents in lieu of the third propellane ring (**2**). Chromatographic separation of the three diol isomers allowed complete characterization of these materials. The **SA** diol is distinguished by the lack of symmetry in its NMR spectrum and the assignment of **AA** vs **SS** is made by the relative chemical shift pattern previously established.[1a] As had been seen for the *n* = 10, 12, and 22 **AA** propellane diols, the vicinal NMR coupling constants of **2** change from 6.32 and 2.40 (in $CDCl_3$) to 6.84 and 5.67 (in CD_3OD). This is consistent with a dominant **DDH** form in $CDCl_3$ solvent, but not in protic solvents like CD_3OD where intermolecular hydrogen bonds to solvent are readily formed.

The most direct approach to the detection of intramolecular hydrogen bonds in **AA** diols is by IR spectroscopy. There is ample precedent for a substantial shift in the OH stretching frequency upon the formation of a hydrogen bond.[9] Since gas-phase IR offered the best way to elim-

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[6] Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. For a further description of how this program handles the various force field interactions and electrostatics, and for changes implemented in versions after 2.0, see the program documentation.

[7] (a) Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110. (b) Saunders, M. *J. Comput. Chem.* **1989**, *10*, 203. (c) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

[8] Ponder, J. W.; Richards, F. M. *J. Comput. Chem.* **1987**, *8*, 1016.

Table I. Vapor-Phase OH Stretching Frequencies

compound	OH stretch (cm^{-1})
cyclopentanol	3656.8[a]
3-methylcyclopentanol	3657.5[a]
6 anti ketol[b]	3654
8 anti ketol[b]	3655
8 syn ketol[b]	3655
8 SS diol	3655
8 SA diol	3656
8 AA diol	3654 3539
2 AA diol	3655 3537
5 AA diol	3656 3519
6 AA diol	3654 3521

[a] Aldrich/Nicolet Collection of Vapor Spectra. [b] Selected 3-keto, 7-hydroxy stereoisomers[1] were analyzed.

inate ambiguities that might arise from an inability to differentiate between intermolecular and intramolecular hydrogen bonding, we used GC-IR to examine selected diols and ketols. This approach confirmed the purity of each compound and allowed their IR spectra to be measured in the vapor phase. The OH stretching frequencies observed in this study are collected in Table I. Where two bands are reported for a single compound, they are baseline resolved.

Clearly, the peak between 3654 and 3657 cm^{-1} represents the free (non-hydrogen bonded) OH stretch. The second peak, at lower frequency, is indicative of hydrogen bond formation.[9] Interestingly, the [10.3.3] propellane **8** and non-propellane **2** show this second peak at 3538 cm^{-1} while propellanes **5** and **6** show it at 3520 cm^{-1}. A further difference among these spectra is that in compounds **2** and **8** the two OH stretches are of comparable relative intensity, whereas for **5** and **6** the peak at 3520 cm^{-1} is <20% of the intensity of the peak at 3655 cm^{-1}.

While both our IR and NMR data are consistent with intramolecular hydrogen bond formation, two questions remain. (1) Why do the **AA** diols of **2** and **8**, as well as those of the large ring propellanes, exhibit changes in NMR *J* values that suggest the presence (in aprotic solvent) of **DDH** conformations while the **AA** diols of **5** and **6** do not? (2) Why does the IR absorption indicative of hydrogen bonding have both an altered relative intensity and an altered position in going from the **AA** diols of compounds **2** and **8** to those of compounds **5** and **6**? Implicit in this second question is the possibility that the reduced intensity and lower frequency of the hydrogen bond signal in **5** and **6** are related to their lack of NMR evidence for a **DDH** conformation.

In an effort to develop some insight into these questions, we used the MacroModel[6] molecular mechanics[4,10] package and MM2(87) parameters[11] to explore the conformational potential energy hypersurface of the **AA** diols of compounds **1**–**7**. We found multiple occurrences of **DD**, **UD**, and **UU** conformations (Figure 2). In addition to the hydrogen bonded down-down form (**DDH**, Figure 3), MM2 located both a non-hydrogen bonded down-down conformer (**DDN**, where the oxygens are too far apart to allow hydrogen bonding) and a doubly hydrogen bonded conformer (**D2H**, where both oxygens act as hydrogen bond donors and acceptors). The complete results of these studies are available in the supplementary material.

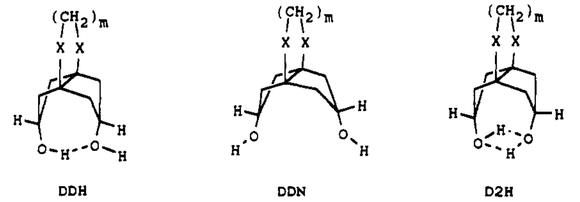

Figure 3. Variations within the **DD** conformers found by MM2.

Compounds **1** through **7** posed no significant difficulties in performing truly global searches. Multiple Monte Carlo runs starting from different conformations, followed by minimization, consistently led to identical results. In addition, we typically noted that no new structures were located in the 1000 step Monte Carlo structure generation after approximately step 700. For the [10.3.3] propellane (**8**) even studies involving 10 000 Monte Carlo steps did not produce a consistent set of structures.[12]

A summary of the number of local minima found for each **AA** diol, the distribution of conformers for each of these molecules, and the lowest energy found for each kind of conformer is presented in Table II. The percentages (which reflect both the number of contributing conformers and their relative energies) are calculated on the basis of the Boltzmann factor (at 20 °C) for each local minimum and then grouping them by conformational type and combining the weighting factors for all conformations of that type.

From our sampling of conformational space, it is clear that the preferred conformation of the bicyclo[3.3.0]octyl portion of these molecules is dependent on the nature of the polymethylene bridge. With no bridge (**1** and **2**) there is a preference for the **DDH** conformation along with a significant amount of **UD**. The lack of any alkyl substituent on the ring junction of **1** allows the **UU** conformation to also be a major contributor. Qualitatively, **7**, the compound with the largest and most flexible polymethylene bridge among the compounds we considered, resembles **1** and **2**; the **DDH** and **UD** forms dominate.

Compounds **3**, **4**, and **5** (with 1-, 2-, and 3-carbon bridges, respectively) are each strongly biased to a single conformer: **3** is **DDH**, **4** is **UU**, and **5** is **UD**. It is interesting to note the strong preference (≥83%) these systems each show for these different conformations. Also noteworthy is the effect of the 4-carbon bridge in **6** which defines a fused cyclohexane ring. The constraints of cyclohexane conformations yield a system that is almost exclusively (93%) in a **DD** form, but with a preference for an otherwise virtually unobserved **DDN** (non-hydrogen bonding) conformation.

Since the measured vicinal coupling constants between the hydrogens of the methylenes adjacent to the OH bearing carbon and the hydrogen on that carbon should reflect the overall population of conformations, we calcu-

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(9) See, for example: (a) Viteva, L.; Stefanovsky, J. *Izv. Khim.* **1975**, *8*, 84–92. (b) Fantazier, R. M. *Org. Magn. Reson.* **1973**, *5*, 77–81. (c) Busfield, W. K.; Ennis, M. P.; McEwen, I. J. *Spectrochim. Acta* **1973**, *29A*, 1259–1264.

(10) Some computational work on the *n* = 4 diols is reported (Kapon, M.; Ashkenazi, P.; Ginsburg, D. *Tetrahedron* **1986**, *42*, 2555) and a conformational analysis of the [2.3.3], [3.3.3], and [4.3.3] hydrocarbons can be found (Dodziuk, H. *J. Comput. Chem.* **1984**, *5*, 571). There is a also a recent publication that uses the [12.3.3] dione[1c] as a test substrate for the minimization of a large ring while leaving the conformation of another portion of a molecule untouched: Guarnieri, F.; Cui, W.; Wilson, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1542–1543. We find no discussion of hydrogen bonding in such systems.

(11) MacroModel uses the Kroon-Batenburg Lp-H parameter for nonbonded interactions whenever the donor and acceptor atoms are geometrically appropriate (separation ≤ 4 Å, angles ≥ 90°); Kroon-Batenburg, L. M. J.; Kanters, J. A. *J. Mol. Struc.* (*THEOCHEM*) **1983**, *105*, 417.

(12) These calculations were performed on both the Stardent Titan 3040 at the University of Toledo College of Arts and Sciences Instrumentation Center and the Cray Y-MP8/864 at the Ohio Supercomputer Center. Invariably, each Monte Carlo run on **8** yielded previously undiscovered structures and also missed some of the structures that had been found in other runs.

Table II. Number of Local Minimum Conformations of AA Diols, Their Percentage Distribution, and the Lowest Energy Version of Each

compd	no. conformers found	DDH % (kJ)	DDN % (kJ)	UD % (kJ)	UU % (kJ)	D2H % (kJ)
1	11	43 (91)		25 (95)	31 (94)	1 (100)
2	17	69 (105)	3 (115)	23 (110)	4 (114)	3 (113)
3	11	83 (126)		9 (134)	7 (134)	2 (135)
4	11	11 (209)		6 (213)	83 (206)	
5	18	7 (138)		87 (132)	6 (139)	<1 (145)
6	26	38 (138)	55 (138)	6 (144)	<1 (148)	<1 (149)
7	38	44 (160)		52 (160)	4 (167)	<1 (174)

Table III. Correlation between O–O Distance (Å) and Conformation

confrmtn	1	2	3	4	5	6	7	range
D2H	2.6	2.6			2.6	2.6	2.6	2.55–2.63
DDH	2.9	2.8	2.9	2.9	2.7	2.9	2.8	2.74–3.08
UD	4.6	4.4		4.5	4.3	4.3	4.2	4.05–4.77
DDN		5.3	5.2			5.0		4.88–5.65
UU	6.6	6.6	6.6	6.6	6.5	6.4	6.4	6.14–6.66

lated[2] the vicinal coupling constants for each of the individual conformers found in our conformational searches and compared the weighted average of each of their coupling constants to the three experimentally determined sets of coupling constants that were available. Since the range of calculated J values for a given vicinal interaction varied by up to 9 Hz, the agreement between these weighted averages and the observed values provides a good (independent) check of the calculated distribution of conformations. For **2** the calculated values were 6.2 and 2.9 Hz while the observed values were 6.3 and 2.4 Hz; for **5** calculation gave 5.8 Hz for both couplings and experiment showed 5.4 and 5.6 Hz; for **6** the calculated values were 8.1 and 3.6 Hz and the observed values were 7.9 and 4.4 Hz. In general, the agreement between calculation and experiment is excellent.

There are also a number of general structural patterns. There is a very narrow range of oxygen–oxygen distances observed for each kind of conformation (Table III); these ranges do not overlap. Secondly, all **UD** and virtually all **UU** conformers have X–C–C–X (Figure 2) dihedral angles <2°. Thirdly, while the **D2H** hydrogen bonds are all badly nonlinear (H–O–H angles of 100–107°), in all **DDH** forms the O–H–O angle of the hydrogen bond is a nearly linear 162–170°. Finally, there seems to be an interesting variation in the prominence of the **DDH** conformation for a particular **AA** diol and its X–C–C–X dihedral angle. For compounds **1** and **2**, where there is no conformational constraint imposed by a third polymethylene ring, this dihedral angle is 19.9 ± 0.3°, so too, in the relatively large ring case of **7**. In **4** (where the bridge is a cyclobutane) the angle is 17 ± 0.2°, in **5** (with a cyclopentane bridge) it is 11.2 ± 0.7°, and in **6** (a cyclohexane bridge) it is either 30.7 ± 1.4° or 16.4 ± 0.2°. In the **DDN** forms of **6** the dihedral is 42°. There is, of course, no X–C–C–X dihedral angle in **3** ($n = 1$).

Clearly, the **AA** diols in our study are capable of intramolecular hydrogen bonding. Such bonds prefer O–O distances of 2.75–2.80 Å and O–H–O angles of 165–170°. The propellane structure controls access to such bonding by the constraints imposed on the X–C–C–X dihedral angle. Acyclic, non-propellane systems (**1** and **2**) or large-ring systems (**7** and **8**) have ready access to the optimal 19.9° dihedral. The constraints of the 4-, 5-, and 6-membered ring bridges in **4**, **5**, and **6**, respectively, mitigate against such an angle. The relatively unusual cyclopropane bridge of **3** seems to favor a **DDH** conformer.

This suggests that the conformation of a 3,7-disubstituted bicyclo[3.3.0]octyl moiety can be controlled so that the distance between heteroatom (O, N, S) substituents could be precisely controlled by varying a remote structural feature (i.e. the third propellane ring). Moreover, elaboration of this third ring, as long as the length of the bridge did not change, could allow tethering of such a structure to other structural units without changing its conformation. Use of such structures as ligands with controlled chelating ability is an intriguing possibility. The ease of synthesis of such propellane skeletons[5a] further recommends exploration of such applications.

Our gas-phase IR study also has a number of interesting features. It is clear that a light pipe based GC-IR provides a convenient vehicle for the study of intramolecular hydrogen bonding. The normal OH stretch at 3655 cm^{-1} is easily seen in this way and such an approach allows for the easy elimination of interference by water. The hydrogen bonding interaction seen in **2** and **8** is clearly associated with a second, strong, OH stretch at 3538 cm^{-1} and this shift of 117 cm^{-1} is quite consistent with literature reports.[9] Moreover, analogs to the 8-membered ring formed by such an intramolecular hydrogen bond are documented for both intramolecular hydrogen bonding[9a] and intramolecular proton transfer.[13] These results clearly agree with the computational conclusion that such compounds should form excellent hydrogen bonds.

The spectroscopy of the **AA** diols of **5** and **6** deserves comment. The NMR analysis (lack of solvent-dependent change in J values) suggested the absence of **DDH** conformations and, by inference, the absence of intramolecular hydrogen bonding. This is consistent with the computational finding that **5** exists almost exclusively (87%) in an **UD** conformation. Since the contribution from its **DD** form is minor, our analysis is insensitive to its further reduction in protic solvent. For **6**, the computational finding that its **DDH** and **DDN** are so close in energy and that they together dominate (93%) its conformer mix, provides a basis for understanding the NMR behavior of this compound. In going from an aprotic to a protic solvent the conformational change is small and this change is not detected.

The IR spectra of **5** and **6** show a weak additional OH signal at 3520 cm^{-1}. Presumably, this is a reflection of the contribution of their **DDH** forms. Though the unique X–C–C–X dihedrals seen in the calculated geometries of the **DDH** forms of **5** and **6** might argue for distorted and thus weaker hydrogen bonding in these molecules, the observation of the signals for the hydrogen bonded OH at 3520 cm^{-1}, a shift of 135 cm^{-1}, rather than the 117 cm^{-1} difference between free and H-bonded OH seen in the unconstrained systems (e.g. **2**), suggests that the hydrogen bonds in **5** and **6** are stronger, not weaker. The hydrogen bonded conformers of **5** and **6** are energetically less accessible because of the distortion such a conformation causes in the fused cyclopentane or cyclohexane ring. However, to the extent that such conformations do form,

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(13) Gandour, R. D. *Tetrahedron Lett.* 1974, 295–298.

their hydrogen bonds are strong. Consistent with this, the value of the electrostatic stabilization term in the MM2 calculation for the only **DDH** form of **2** is −22.3 kJ/mol, while for two of the **DDH** forms of **5** (though only 7% contributors) it is −23.1 and −23.3 kJ/mol and for two of the **DDH** forms of **6** (12% contributors) it is −22.7 and −22.8 kJ/mol. Similarly, the structural parameters of the hydrogen bonds in **5** and **6** are as good (2.75-Å interoxygen distance and 163° bond angle) as those seen in the energetically more accessible **DDH** forms of **1** and **2**. Also, the shift of 135 cm^{-1} seen in the OH stretching frequency of **5** and **6** is still quite comparable to the 130 cm^{-1} shift seen for the 8-membered ring hydrogen bond in 1,5-pentanediol.[9c]

It is clear that intramolecular hydrogen bonding is a prominent feature in these compounds. Secondly, the constraints of the [*n*.3.3] propellane skeleton significantly affect the balance among available conformers. And, finally, strong intramolecular hydrogen bonding can be manifest even in those molecules whose **DDH** conformers show significant skeletal distortion.

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Supplementary Material Available: Tables of the conformers found in the MM2 calculations, including their energies, oxygen–oxygen distances, X–C–C–X dihedral angles, the O–H–O angles for the hydrogen bonds, and the percent probability for each conformer (5 pages). This material is contained in many 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.

Reactions of Enamines with Dehydro Aromatic Compounds

Henry L. Gingrich,* Qiurong Huang, Angel L. Morales, and Maitland Jones, Jr.*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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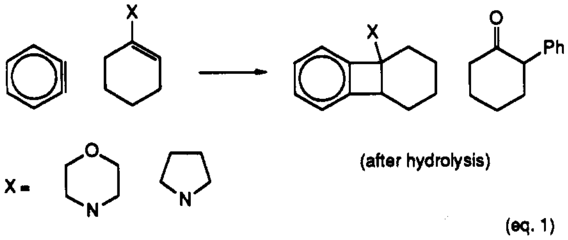
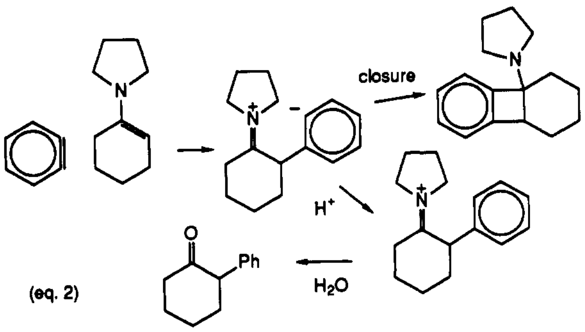
Benzyne reacts with enamines through a combination of ene and 2 + 2 cycloadditions. One of the two possible ene reactions is greatly favored. The three-dimensional intermediate, 1,2-dehydro-*o*-carborane,[1] eschews the 2 + 2 reaction in favor of the ene reaction that is less favored in the benzyne reactions. This preference is rationalized in terms of the different steric demands of the two intermediates.

Almost 30 years ago Martin Kuehne first described the reaction of benzyne with enamines. The reaction led, after hydrolysis, to 2-phenylcyclohexanone and compounds containing four-membered rings (eq 1).[2,3] Although the yields of the products depended upon reaction conditions and the method of benzyne generation, an overall mechanistic scheme was developed in which a dipolar intermediate partitioned between closure to give the aminocyclobutanes and protonation to give an iminium ion, the precursor to the ketone. This view was supported by the relative increase in cyclobutane formation when proton sources were reduced (eq 2).

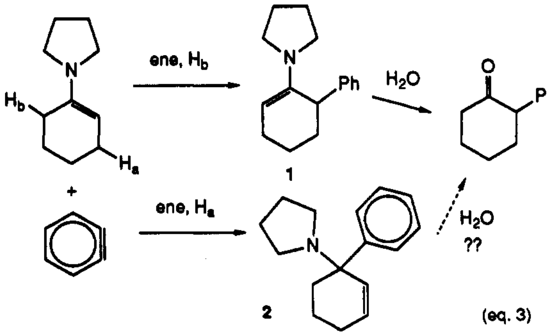


(eq. 1)



(eq. 2)

This scheme is sensible in the context of 1962, and even presages the requirements of the yet-to-be-developed theory of orbital symmetry control in its stepwise 2 + 2 reaction. However, even though at least one recent review accepts the mechanism,[4] there are other possibilities. For example, benzyne was known, even in 1962, to undergo the ene reaction with simple alkenes.[5] There are two possible ene reactions of benzyne and Kuehne's enamines. One of these, compound **1**, would surely lead to the ketone on hydrolysis, and the other, **2**, might (eq 3). Here we present evidence that the concerted[6] ene reaction and the nonconcerted 2 + 2 reaction[7] are in competition in this reaction



(eq. 3)

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[1] 1,2-Didehydro-*o*-carborane is the more correct name.

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[3] Keyton, D. J.; Griffin, G. W.; Kuehne, M. E.; Bayha, C. E. *Tetrahedron Lett.* **1969**, 4163.

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