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The Shapes and Cavities of the m-Xylylene Cholic Acid Host

by

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19. Abstract

Previous studies have dealt with the three-dimensional shapes of the cholic acid host systems created by using either a meta-or paraxylylene diamine spacer between two cholic acid molecules (report #1 entitled "The Cholic Acid Host System Shape" of 2/24/90). Due to the flexible geometry of the hosts with their sensitivity to minor bond rotations, cavities of different sizes and shapes had been obtained. Simple rotation of two dihedral angles in the flexible cholic acid side chain seemed to be critical for creating-either an overall "C" or "S" shape (report #2 entitled "The Cholic Acid Host System Shape" of 5/17/90).

The cholic acid host shapes which were previously created had not been correlated with their relative energies, and therefore, our recent studies have focused on conformation and energy. We have studied one host, the m-xylylene diamine cholic acid host (mCAH), and have used various strategies to generate a complete energy surface. Conformational analyses were performed by simultaneous rotation of 8 bonds (freezing 4 bonds in the diamine spacer) or 12 bonds; a calculation of energy and/or a preselected interatomic distance [O3(Arm A)--O3(Arm B)] was done for each conformation.

The results arising from the various conditions used in the conformational analyses have led to the development of a strategy which quickly generates several low-energy "C" shaped host conformations needed for sugar binding. In summary, we first generate a complete energy surface via simultaneous rotation of all 12 single bonds (each by 60 degrees) in the CAH. This involves evaluation of over 1/2 million states! However, the most accurate calculation for the global minimum energy structure is obtained at this grid resolution. We then uncover reasonable "C" shapes via a distance scanning procedure, i.e., we perform a conformational analysis of the 12 rotatable bonds using an interatomic distance constraint and presetting an absolute energy limit (a preselected L kcal value above the known absolute global minimum energy). The resulting conformations thus have an energy known to fall within a certain window (the preset L value) and have "C" shapes whose end-to-end distance is known. The $O_3(A) - O_3(B)$ distance serves as a qualitative measure to inferring the size of the host cavity.

Details of the Recent Studies

I. Partial Atomic Charges

We had previously calculated charges for mCAH via the AM1 and the AM1-Mulliken Population methods (report #4 entitled *"The Cholic Acid Host and Sugar Guest"* of 8/15/90). In order to decide which partial atomic chargeset to use, we calculated charges for the two independent fragments, the cholic acid host amide and the mxylylene diamine spacer, using the CNDO/2 method. The CNDO/2 charges would be compatible with the torsional functions of the Molecular Mechanics Force Field (MMFF, a modification of the MM2 program of N. L. Allinger) used in the conformational analysis utility of the CHEMLAB-II software¹. A comparison of the charge sets showed that the magnitude of the AM1 charges was greater overall, that the CNDO/2 charges were higher by +0.15 for C and N, about the same for O, and unpredictably different for H. All differences, however, were small. Thus the AM1 net charges were chosen for future use.

When the mCAH was assembled from the two fragments, the AM1-net partial atomic charges were adjusted accordingly.

II. Conformational analysis

<u>Approach 1</u>: Using the known conformational preferences of the m-xylylene diamine spacer as starting points for scanning of the 8 cholic acid bonds

Aproach 1 employed a logical substructure approach which first involved analysis of the m-xylylene diamine spacer conformations, by reasoning that these conformations if preferred in the spacer would also be found in the mCAH. The conformational analysis of the m-xylylene diamine spacer (4 bonds, by 30 degrees, Fig. 1) resulted in 5 unique local minima: 3 were "C" shapes and 2 were "S" shapes, with the global minimum at -25.15 kcal (details given in update report of 11/1/90).

The set of dihedral angles for each of the three "C" shapes was used to "lock-in" or freeze the cholic acid host. Conformational analysis of mCAH was done by evaluating 8 bonds (Fig. 2), while having the 4 m-xylylene spacer bonds frozen into each of the 3 "C" shapes above. Each starting point resulted in one global minimum energy structure at -161.48, -165.93, and -162.29 kcal. None of these minima were overall "C" shapes, but each was a twisted or helical structure (Fig. 3).

Earlier manually-derived conformations (obtained via the "eyeball" method) of mCAH had achieved the desired "C" shape. The energy for the m-xylylene portion of these conformations was calculated to be between -22.01 and -21.06 kcal (\geq 3 kcal from the global structure above). Therefore, the conformational analysis of the m-xylylene diamine spacer was refined (4 bonds by 15°), giving 13 local minima, with a global

minimum energy of -26.53 kcal. The eyeballed "C" shapes then became 4.5-5.5 kcal higher than this global minimum energy.

Two conclusions were drawn from Approach 1 Conformational Analysis:

Conclusion: The m-xylylene diamine spacer molecule is very flexible: the first scan had 5 unique local minima and their energies ranged from -23.8 to -25.1 kcal; the refined scan showed 13 local minima within the range of -25.6 to -26.5 kcal. The energies of the "C" shaped spacers made manually are about 5 kcal from the lowest energy minimum.

Conclusion: To give a properly shaped "C" clam, the m-xylylene spacer must not make the cholic acid arms parallel [like $\begin{pmatrix} H \\ 0 \end{pmatrix}$] but " $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ " shaped (Fig. 4), with the

 CH_2 to CH_2 distance not equal to 6.7 Å as with parallel $\frac{H}{2}$ mms but about 11 Å.

Conformational analysis of mCAH using the two "S" shaped m-xylylene diamine spacers of the original scan resulted in 1 local minimum each; the global minimum energies were -157.64 and -158.16 kcal. These conformations were "S" shaped overall but differed in the breadth of one arm from the aromatic ring (Fig. 5).

Conclusion: The "S" shaped m-xylylene spacers do not give "C" shaped mCAHs. To use Approach 1, only the "C" shaped m-xylylene diamine spacers can be used.

Approach 2: Conformational analysis of the 12 rotatable bonds in mCAH by energy

Conformational analysis of mCAH (12 bonds, by 60°, Fig. 6) evaluated 531,441 (over 1/2 million!) states by <u>energy</u> and resulted in 176 local minima, with energies ranging from -161.84 to -171.76 kcal (a 10 kcal range). The same conformational analysis by <u>energy</u> with O_3 (Arm A) to O_3 (Arm B) distance constrained to 12-20 Å resulted in 121 local minima, energies ranging from -161.86 to -171.76 kcal, with the distance in the global minimum energy structure equal to 14.78 Å. Conformational analysis by energy with O_3 to O_3 distance further constrained to the range of 13-17 Å gave 63 local minima, with a maximum energy of -161.86 kcal.

<u>Approach 3</u>: Conformational analysis of the 12 rotatable bonds in mCAH by interatomic pair distance

Conformational analysis of mCAH (12 bonds, by 60° , Fig. 6) by <u>distance</u>, using a wide O_3 to O_3 constraint of 12-20 Å and keeping conformations whose energy was less than -161.0 kcal, resulted in 146 conformations ranging from 12.05 to 19.98 Å. In a distance scan, energies are not specifically retained for each conformation; only the associated distance is kept (Fig. 7).

Breakdown by distance is:	13.13-13.96 Å	17 confs
•	14.02-14.91	19"
	15.01-15.99	24"
	16.01-16.97	<u>13 "</u>
		73 total

Conclusion: Conformational analysis by <u>distance</u> is a more expedient way to analyze the mCAH shapes <u>after</u> the global minimum energy conformation is known from an energy scan. This strategy efficiently generates low-energy "C" shaped host conformations needed for sugar binding.

Future studies:

- The reason for the discrepancy between the two methods (63 confs. vs. 73 confs.) needs to be determined.
- The overall shapes of the mCAH based on distances needs to be assessed in order to correlate O_3 -- O_3 distance with shape in the m-xylylene diamine spacer CAH.
- The p-xylylene diamine cholic acid host needs to be evaluated for conformation, energy, and shape, using the O_3 to O_3 interatomic distance as an index for inferring the shape/size of the host cavity.

¹ Allinger, N. L. Adv. Phys. Org. Chem. **1976**, 13, 1. Pearlstein, R. A. CHEMLAB-II Reference Manual **1988**, 6-42.





Contributions to energy:

Steric - Hopfinger 6-12 Potential Set

Electrostatic - CNDO/2 Charges

Torsional -- Bond **a** free rotation Bond **b** methylformamide Bond **c** HN-C=O fixed trans

Cl replaces CH₃ group, removes deg of freedom

Figure 2. Conformational Analysis Details for mCAH via Approach 1



8 rotatable bonds

4 * bonds frozen

Contributions to energy:

Steric -- Hopfinger 6-12 Potential Set

Electrostatic -- AM1 Net Charges

Torsional Fns. -- Bond a acetaldehyde Bonds b,c,d ethane

CI replaces CH₃ group, removes deg of freedom

Example of Twisted mCAH Shape from Approach 1 Relaxed stereo view, Heteroatoms labelled Figure 3.



Shape of m-xylylene diamine spacer required for creating the "C" shaped mCAH Figure 4.

Mono view, Heteroatoms labelled



Example of "S" Shaped mCAH from Approach 1 Relaxed stereo view, Heteroatoms labelled Figure 5.

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Figure 6. Conformational Analysis Details for mCAH via Approach 2



12 rotatable bonds

Contributions to energy:

Steric -- Hopfinger 6-12 Potential Set

Electrostatics -- AM1 Net Charges

Torsional Fns. -- Bond **a** free rotation Bond **b** methylformamide Bond **c** acetaldehyde Bonds **d,e,f** ethane