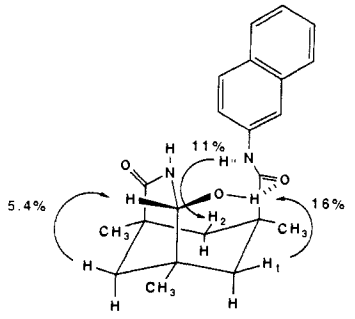
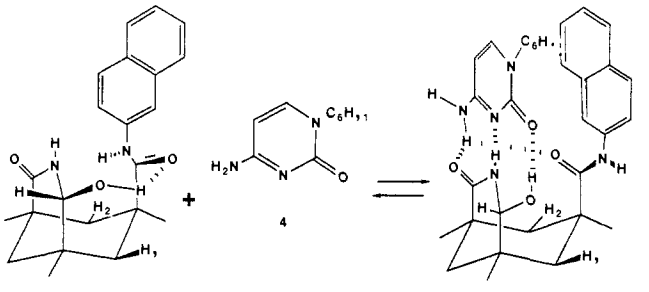
the tail of the arrow was irradiated and the percent enhancement was observed on the proton at the head of the arrow.)



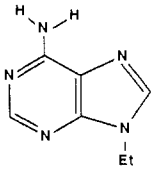

3a

Titration of either **3a**, **3b**, or **3c** with cyclohexyl cytosine[4] **4** in $CDCl_3$ gave changes consistent with simultaneous hydrogen bonding and stacking interactions as suggested in eq 3. Downfield



(3)

shifts of the lactam NH ($\delta$ 5.5 → $\delta$ 11.4) or the corresponding upfield shifts in the aromatic signals could be used to generate saturation curves. Association constants were obtained from Eadie plots.[5] The titration could even be followed by observing the change in coupling constant between the OH and methine proton which decreases from 13 to 3 Hz during the course of the complexation. For the naphthalene derivative **3a**, $K_a$ was observed to be 260 $M^{-1}$. For the phenyl derivative **3b** the corresponding value was 100 $M^{-1}$, while the anthracyl **3c** gave 290 $M^{-1}$. The naphthalene surface appears to offer all the aryl stacking interactions there are to be had in this system. Studies at various temperatures with **3a** gave $\Delta H = -8.65$ kcal/mol and $\Delta S = -18$ eu, figures which are in reasonable agreement with models for cytosine-guanine base pairing in organic solvents.[6] Parallel titration of **3a** with 9-ethyladenine **6** gave a value of $K_a \leq 25$ $M^{-1}$.



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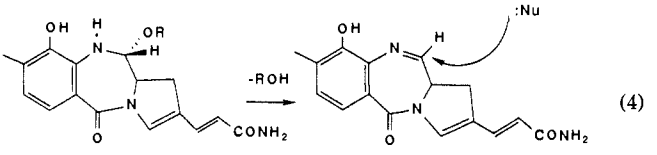
The selectivity of the new systems for cytosine over adenine is therefore at least 10-fold. For the binding shown in eq 1, $K_a$ = 220 $M^{-1}$ was observed,[1] but the (mismatched) interaction[7] of cytosine **4** with **1** shows $K_a < 10$ $M^{-1}$. The reversal of selectivities generated by altering a single hydrogen bonding site is quite satisfactory.

The structural details of the complex **5** were explored with NOE methods. Irradiation of the aryl N-H at 63% complex (37% free **3a**) gave enhancements of 8.5% at $H_1$ and 6.2% at $H_2$ (58:42). At 70% complex the corresponding values were 10% and 5.1% (66:34). Thus, complexation forces the rotation of the aryl carboxamide by ~180°, presumably because a bifurcated hydrogen bond can be formed with the amino group of cytosine. The net increase is two hydrogen bonds, since the intramolecular hydrogen bond of **3a** becomes broken on complexation. As a result the association constants are in the hundreds rather than the thousands that might be expected for three new hydrogen bonds.[8]

Finally, structures **3** incorporate the functional aspects of anthramycins **7**, agents that alkylate double-stranded DNA by way of their dehydration products (eq 4).[9] It should be possible to "tune" the new molecules for similar activity, and we are working toward this goal with suitable modifications.



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(4)

**Acknowledgment.** This work was supported by the National Science Foundation.

(4) Okano, T.; Goya, S.; Takahashi, T. *Yakugaku Zasshi* **1968**, *88*, 1112-1117 (*Chem. Abst.* **1969**, *70*, 37756x). See, also: Fox, J. J.; Van Praag, D.; Wempen, I.; Doerr, I. L.; Cheong, L.; Knoll, J. E.; Eidinoff, M. L.; Bendich, A.; Brown, G. B. *J. Am. Chem. Soc.* **1959**, *81*, 178-187.

(5) Eadie, G. S. *J. Biol. Chem.* **1942**, *146*, 85-93. Hofstee, B. H. J. *Nature (London)* **1959**, *184*, 1296-1298.

(6) Pohorille, A.; Burt, S. K.; MacElroy, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 402-409.

(7) For a similar mismatch see: Williams, L. D.; Shaw, B. R. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 1779-1783.

(8) Kyogoku, Y.; Lord, R. C.; Rich, A. *Science (Washington, D.C.)* **1966**, *154*, 518-520. Pitha, J.; Jones, R. N.; Pithova, P. *Can. J. Chem.* **1966**, *44*, 1045-1050.

(9) Barkley, M.; Cheatham, S.; Thurston, D. E.; Hurley, L. H. *Biochemistry* **1986**, *103*, 7629.

## Experimental Tests of Models To Predict Nucleophilic Addition Stereochemistries

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Many models have been proposed to explain the stereochemistries of nucleophilic additions, especially lithium aluminum hydride reductions, of both acyclic and cyclic carbonyl compounds.[4] While there are conceptual differences in these models, they rationalize the same body of experimental data, and consequently they have not been distinguishable by direct experimental tests. However, we have identified several new compounds for which different models predict different stereoselectivities in LAH reductions. We describe here these predictions and the experimental tests subsequently performed in our laboratories.

Various literature models for cyclohexanone reduction are summarized here with reference to cyclohexanones **1a-c**. LAH reduction of each of these compounds proceeds preferentially from the axial direction to give axial/equatorial attack ratios of 92:8, 83:17, and 53:47, respectively.[4] As generalized by Barton, axial attack of nucleophiles is favored when steric hindrance is negligible.[5] Dauben proposed that "product development control"

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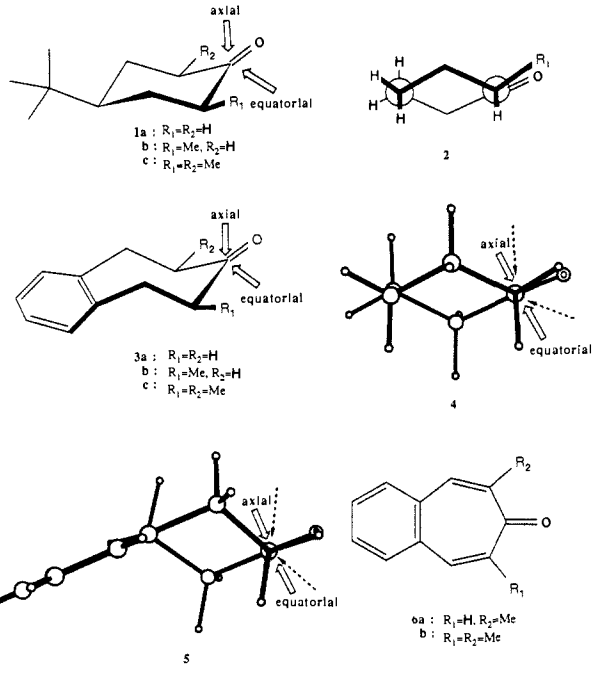
(4) Boone, J. R.; Ashby, E. C. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Vol. 11, p 53.

(5) Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027, footnote 23.




operates in unhindered cases, so that axial attack of the nucleophile produces the more stable equatorial alcohol in each case.[6] Felkin suggested that the preference for axial attack on unhindered cyclohexanones is due to the greater torsional strain which occurs in the transition state of equatorial attack,[7] as shown in **2**. Attack at any chosen trajectory on the carbonyl group of **2** is more eclipsed from the equatorial direction. This conformation is related to the Karabatsos model for nucleophilic attack on acyclic ketones,[8] but the preferred direction of attack is from the side of the larger out-of-plane substituent ($CH_2$) not on the side of the smaller group (H). Klein,[9] Anh,[10] Liotta,[11] Ashby,[12] and Hudec[13] suggested in various ways that axial attack stereoselectivity is the result of orbital distortion of the carbonyl $\pi$ and $\pi^*$ orbitals. That is, unequal distribution of electron or orbital density of the two faces of carbonyl group produces stereoselective attack. Anh and Eisenstein carried out model calculations which generally support the Felkin model, but these authors emphasized the importance of attack anti to a vicinal bond.[14] Wipke and Müller both developed force-field models which supported the notion that stereoselectivity arises from a combination of torsional and steric effects.[15,16]

In 1981, Cieplak suggested a new hypothesis: that nucleophilic attack occurs anti to the best electron-donor bond and that the electron-donor order is C–S > C–H > C–C > C–N > C–O.[17] In the transition state of axial attack there are two roughly antiperiplanar C–H bonds, while in that of equatorial attack there are two approximately antiperiplanar C–C bonds. The torsional effects cited by Felkin are considered unimportant: "it seems that the deviation of this order of magnitude would be unlikely to impede optimization of orbital interactions during the transition state".[17]

**Table I.** Predictions by the Modified MM2 Model[18] of the Stereoselectivities of LAH Reductions of Benzocycloheptenone Derivatives **3**

| $R_1$ | $R_2$ | $\Delta E$ (kcal/mol) (ax–eq) | equatorial/axial attack ratio 25 °C | 25 °C | −78 °C |
|---|---|---|---|---|---|
| Me | H | 0.22 | 60:40 | | 63:37 |
| *i*-Pr | H | 0.64 | 75:25 | | 83:17 |
| Me | Me | 0.57 | 73:27 | | 81:19 |
| *i*-Pr | *i*-Pr | 0.82 | 80:20 | | 89:11 |

Last year, we reported a quantitative calculational force-field model for the nucleophilic addition of LAH to both cyclic and acyclic ketones.[18] We concluded that axial attack on cyclohexanones is favored by the torsional effects pointed out first by Felkin.

In order to provide an experimental test which differentiates between these various models, we have designed several compounds which are predicted by different theories to give different major products. Derivatives of benzocycloheptenone **3** fulfill these requirements. By dynamic NMR studies, St. Jacques et al. found that **3a** exists predominantly in the chair conformation shown.[19] Our calculations with Allinger's MM2 force field[20] predict that the chairlike conformation is 2.1 kcal/mol more stable than the twist-boat conformation. Since **3a–c** are all sterically unhindered, it is predicted by Dauben's model that axial attack is preferred. The similarity of the local environment of **3** to **1** suggests that most models would predict a preference for axial attack. Axial attack is more or less anti to two CH bonds, while equatorial attack is anti to two CC bonds. According to the Cieplak model, axial attack is favored.[17] By contrast, our calculations using the previously reported MM2 method[18] predict that the transition structure for equatorial attack is 0.2 kcal/mol more stable than that for axial attack. The axial alcohol is 0.3 kcal/mol less stable than the equatorial by MM2.[20] Once the ground-state conformation is known, Felkin's model also predicts that the equatorial attack is favored, because the staggering in the transition state of equatorial attack is better. Structures **4** and **5** demonstrate the more staggered approach from the axial direction in cyclohexanone, **4**, but better equatorial approach in benzocycloheptenone, **5**. The arrows drawn with dashed lines show the Cieplak modes of attack, anti to CH in both **4** and **5**—which occurs upon axial attack, and anti to CC—which occurs upon equatorial attack.

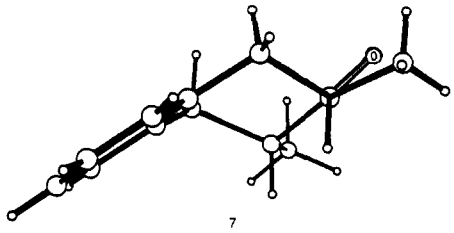
Table I gives the MM2 predictions about the stereoselectivities of reactions of several derivatives of **3**. It is predicted that the preference for equatorial attack increases from monosubstituted cases to disubstituted cases and upon increasing the size of substituents.

In order to test these predictions, compounds **3b** and **3c** were synthesized by the following techniques. Condensation of phthalaldehyde with 2-butanone (2 N NaOH, 0 °C) or 3-pentanone (NaOEt, EtOH, 25 °C) gave the substituted benzotropones **6a** (71%, mp 68–69 °C) and **6b** (66%, mp 85–86 °C), respectively. Catalytic hydrogenation (5% Pd–C, EtOH, 25 °C) gave **3b** (80%, mp 53–54 °C) from **6a** and a mixture of *cis*- and *trans*-**3c** from **6b**. Preparative TLC separation of the latter mixture gave a solid isomer, *cis*-**3c** (mp 55–56 °C). Compounds **3b** and *cis*- and *trans*-**3c** were reduced with LAH at −78 °C in ether solution. In each case the ketone was added to the cold solution of excess reductant. Workup gave the alcohol products, which were analyzed by 500 MHz NMR. The alcohols were also converted into the acetates for independent analysis.

The product structures were clearly indicated by both coupling constants and chemical shifts, which correspond closely to those observed in the corresponding cyclohexanols.[21] The results not

(6) Dauben, W. C.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.
(7) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205; **1971**, 383. Cherest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1971**, 379.
(8) Karabatsos, G. T. *J. Am. Chem. Soc.* **1967**, *89*, 1367.
(9) Klein, J. *Tetrahedron Lett.* **1973**, 4307.
(10) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Trân Huu Dâu, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146.
(11) Liotta, C. L. *Tetrahedron Lett.* **1975**, *519*, 523. Liotta, C. L.; Burgess, E. M.; Eberhardt, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 4849.
(12) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890.
(13) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459.
(14) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Anh, N. T. *Fortschr. Chem. Forschung.* **1980**, *88*, 145.
(15) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107.
(16) Perlburger, J.-C.; Müller, P. *J. Am. Chem. Soc.* **1977**, *99*, 6316.
(17) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(18) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.
(19) Bodennee, G.; St. Jacques, M. *Can. J. Chem.* **1977**, *55*, 1299.
(20) Allinger, N. L.; Yuh, Y. *QCPE* **1980**, *12*, 395. Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

only prove the structure but show the similarity of conformation to those of the six-membered analogues. In the case of **3c** and the acetate derived from the major reduction product, X-ray crystal structures were also determined. The products resulting from equatorial attack are favored upon reduction of both **3b** and **3c**. From **3b**, the ratio of equatorial/axial attack is 60:40, just as predicted, while only the product of equatorial attack can be detected by 500 MHz NMR spectra of the alcohol or derived acetate formed from **3c**. As shown by the Newman projection, **7**, of the crystal structure of **3c**, equatorial attack can clearly occur with less eclipsing than axial attack.



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In general, flattened cyclic ketones such as cyclohexanone itself give axial attack, while puckered ones such as **3**, or dithia analogues of **1** give equatorial attack. This has been summarized as Anh's "flattening rule".[14b,22] Equatorial substituents $\alpha$ to the carbonyl group of **1** or **3** flatten the ring and promote equatorial attack, even though this attack occurs near the substituents. Electronic effects are of minor significance in LAH reductions of cyclic ketones.[23]

In summary, we have demonstrated that the stereoselectivity of LAH reductions of benzocycloheptenones can be correctly predicted by our quantitative calculational model and by Felkin's torsional strain model but not by other models.

**Acknowledgment.** We are grateful to the National Institutes of Health for financial support of this research.

(21) Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day, Inc.: San Francisco, CA, 1964.
(22) Huet, J.; Maroni-Barnand, Y.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1976**, 159.
(23) Kobayashi, Y. M.; Lambrecht, J.; Jochims, J. C.; Burkert, U. *Chem. Ber.* **1978**, *11*, 3442.

## Formation and Autocatalytic Destruction of the Quinone Methide from Reductive Cleavage of Menogaril[1]

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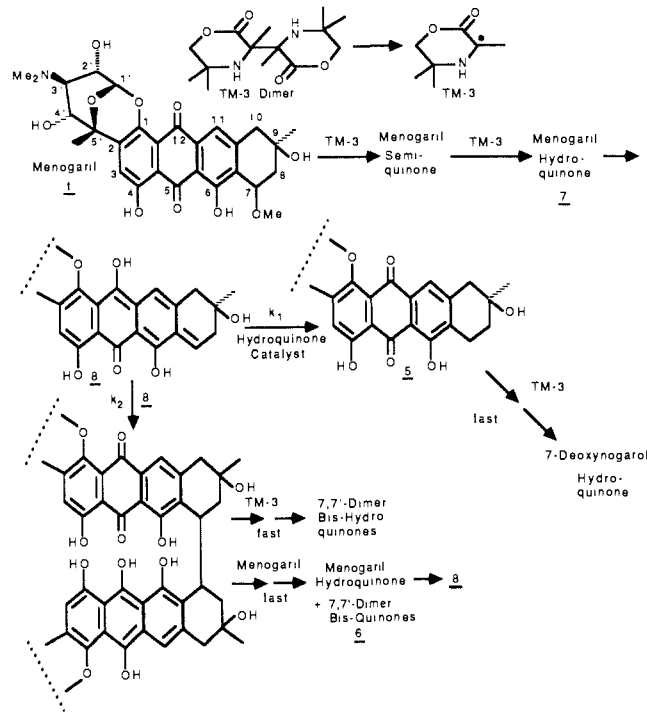
Menogaril, 7-*con*-*O*-methylnogarol (**1**), is a semisynthetic antitumor drug of the anthracycline class presently in clinical trials.[3] It is formed from nogalamycin, a product of the organism *Streptomyces nogalater*.[4] Because of the oxygen substitution

Scheme I




pattern, in particular the presence of an alkoxy substituent at the 7-position and the absence of a hydroxyl substituent at the 11-position, menogaril has the potential for bioreductive activation[5] analogous to that of aclacinomycin A (**2**)[6] and 11-deoxydaunomycin (**3**).[7] We[6,7] and others[8,9] have demonstrated that reduction of **2** and **3** yields the respective 7-deoxyaglycons, 7-substituted aglycons, and 7,7'-dimers of the 7-deoxyaglycons via glycosidic cleavage at the hydroquinone states to form transient quinone methides. 7-Deoxyaglycons result from tautomerization, 7-substituted aglycons from nucleophilic addition, and 7,7'-deoxydimers from combination, one quinone methide serving as a nucleophile and one as an electrophile.[6-9]

Fisher and co-workers have reported that reduction of menogaril with spinach ferrodoxin–$NADP^+$ reductase gives 7-deoxynogarol with only the hydroquinone as an observable transient.[8] We report here that reduction of menogaril with *dl*-bi(3,5,5-trimethyl-2-oxomorpholin-3-yl)(TM-3 dimer)[10] gives 7-deoxynogarol (**5**) and stereoisomers of bi(7-deoxynogarol-7-yl) (**6**) via the observable quinone methide state. Surprisingly, formation of **5** was catalyzed by the presence of hydroquinones including its own hydroquinone and did not occur to any significant extent in the absence of hydroquinones at an apparent pH of 8.

Anaerobic reduction of $1.0 \times 10^{-4}$ M **1** with 2 or more equiv of TM-3 dimer in apparent pH 8 methanol buffered with tris(hydroxymethyl)aminomethane/tris(hydroxymethyl)aminomethane hydrochloride at ambient temperature gave 85% **5** and 15% **6**. Similar reduction with 0.5 equiv of TM-3 dimer gave 30% **5**, 40% **6**, and 30% recovered **1**. The products, **5** and **6**, were isolated by reverse phase, flash chromatography and characterized from spectroscopic data[11] and in the case of **5** by comparison with

(1) Facilitated by PHS Grant no. CA-24665 and gifts of menogaril and 7-deoxynogarol from Dr. Paul Wiley of the Upjohn Co. We wish to thank Professors Edward King and Stanley Gill and Dr. Timothy Dietz for assistance.
(2) On sabbatical leave from American University of Beirut, Beirut, Lebanon.
(3) Young, C. W.; Raymond, V. *Cancer Treatment Rep.* **1986**, *70*, 51.
(4) Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Krueger, W. C.; Moscowitz, A. *J. Org. Chem.* **1979**, *44*, 4030. Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Richard, F. A. *J. Med. Chem.* **1982**, *25*, 560.
(5) Moore, H. W. *Science (Washington, D. C.)* **1977**, *197*, 527. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.
(6) Kleyer, D. L.; Gaudiano, G.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 1105.
(7) Boldt, M.; Gaudiano, G.; Koch, T. H. *J. Org. Chem.* **1987**, *52*, 2146.
(8) Fisher, J.; Abdella, B. R. J.; McLane, K. *Biochemistry* **1985**, *24*, 3562. Abdella, B. R. J.; Fisher, J. *Environ. Health Perspect.* **1985**, *64*, 3.
(9) Ramakrishnan, K.; Fisher, J. *J. Med. Chem.* **1986**, *29*, 1215.
(10) Burns, J. M.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 849. Olson, J. B.; Koch, T. H. *Ibid.* **1986**, *108*, 756.

0002-7863/88/1510-3330$01.50/0 