correction for solvent effect, have often given useful insights into molecular behavior in solution.

Although the calculated energy differences are small (2-7 kcal), we note that the actual energy differences are also small. Furthermore we make the usual assumption[21] that, when only small perturbations (such as addition of a methyl group) are made to the system, errors of the CNDO/2 method will tend to cancel.

For linear polypeptides, then, N-alkylation enhances epimerization because of a higher concentration of cis peptide (effect b), which is more easily deprotonated (effect a), and because of hyperconjugative stabilization of the β carbanion (effect c).[22] For diketopiperazines, the incipient carbanion is held in the more favorable transoid conformation (effect a), as shown by the outline in **8**. N-Alkylation of diketopiperazine speeds epimerization further by hyperconjugation (effect c).

Diketopiperazine carbanions are calculated to be substantially more easily formed than those from the peptide models **1-7**. This is primarily due to carbanion stabilization by the C_α substituent, as shown by the comparable deprotonation energy computed for a representative conformation of the N-methylalanine derivative (**9**).

In conclusion, it appears that CNDO/2 calculations not only reproduce the observed relative ease of epimerization of N-alkylated polypeptides and cyclic dipeptides, but also help identify some effects which govern this reaction.

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(8) Adjacent electronegative heteroatom substituents raise the inversion barrier of CH_3^- and NH_3; see review by A. Veillard in "Quantum Mechanics of Molecular Conformations", B. Pullman, Ed., Wiley, London, 1976, p 1 (see especially p 69).

(9) For example, CNDO/2 gives 16.2 kcal for inversion of CH_3^- vs. actual value of ~1 kcal (ref 8, p 60).

(10) The carbanion conformation chosen for each of the linear models was that formed by deprotonation of a planar polypeptide—i.e., the carbanionic lone pair of electrons formed an angle of 60° with a plane containing the C_α–N–CO grouping. The minimum energy carbanion conformation in all cases had the lone pair in that plane (angle of 0°), but this is unlikely to resemble the transition state for deprotonation. In any case, the conformation chosen was consistently 2–3 kcal above the minimum energy conformation, and the arguments presented are not affected by this choice.

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(19) Interestingly, for carbanions derived from the better polypeptide models, **5** and **7**, N-methylation actually slightly destabilizes the HOMO (of π character, centered on the carbanion) by 1.0 kcal, but stabilizes the third highest occupied MO (which is the next highest orbital of π character, but has a small amplitude at the carbanionic center) by 3.3 kcal. This ordering of energy levels is subject to the usual uncertainties of the CNDO method.

(20) For reviews, see ref 8 and J. I. Fernández-Alonso in "Quantum Mechanics of Molecular Conformations", B. Pullman, Ed., Wiley, London, 1976, p 117.

(21) For example, see the discussion of approximations in the calculations of molecular conformations: ref 8, p 14.

(22) It should not be overlooked that, as demonstrated for **8** in Chart I, deprotonation at nitrogen is always easier than at carbon. However, these compounds should mostly be un-ionized in dilute aqueous base; so it is unlikely, as proposed by McDermott and Benoiton,[1b] that the major effect of N-methylation is to promote epimerization by preventing formation of the N anion.

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Received September 11, 1978

Conformations of Cyclododecyne. Evidence from Dynamic Nuclear Magnetic Resonance Spectroscopy and Iterative Force-Field Calculations

Sir:

The structural and conformational information available on cyclic acetylenes and their derivatives is rather limited,[1-3] and in the homologous cycloalkynes only the structure of cyclooctyne is known.[2] We now show that the major conformational features of cyclododecyne (I) can be determined by dynamic nuclear magnetic resonance spectroscopy and iterative force-field calculations.

The α-CH_2 resonance in the 251-MHz ^1H NMR spectrum[4,5] of I broadens strongly below about −100 °C and is observed as a complex pattern spread over at least 160 Hz below −140 °C. Since all proton-proton coupling constants should be <20 Hz, this pattern must represent more than two chemical shifts. The "coalescence temperature" is about −107 °C and thus some conformational process with a $\Delta G^{\ddagger}$ of ~7.8 ± 0.3 kcal/mol must be present.[6]

In the ^{13}C NMR spectra[4] of I, the acetylenic carbon resonance, which is a sharp single line above about −60 °C, broadens as the temperature is lowered, reaches a maximum broadening at about −95 °C, and finally gives rise to three sharp lines with intensity ratios of ~1:4:1.2 at −133 °C.[7] These results can be rationalized in terms of two conformations, one symmetrical and the other unsymmetrical (idealized intensity ratio for the acetylenic carbons of 1:4:1 for a conformational ratio of 2:1; i.e., $\Delta G° \simeq 0.2$ kcal/mol at −133 °C). The major conformation is symmetrical and is immediately consistent with a $[3_{yne}333]$[8] structure (Figure 1), which can be thought of as derived from the lowest energy conformation of cyclododecane, i.e., the [3333] or "square" conformation.[9] The minor conformation of I lacks symmetry and is difficult to identify without further information such as that provided by force-field calculations.

Boyd's iterative force-field program,[10] with modified parameters,[3b] has been used to calculate the strain energies and geometries of the conformations of I shown in Table I. The initial geometries required for the calculations have been obtained by replacing CH_2CH_2 by C≡C groups in molecular models of the known low-energy conformations of cyclododecane.[9] Because of its linear (or nearly linear) geometry, the acetylenic unit (-C≡C-) cannot reside at corner positions, and this greatly limits the number of available conformations. Vibrational frequencies have been calculated in all cases to

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Table I. Experimental Free Energies and Calculated Strain Energies[a] of Various Conformations of Cyclododecyne

conformation[b]	symmetry	ΔSE[c]	$\Delta G°$ [d]
[4_{yne}332][e]	C_1	0.0	0.2
[3_{yne}333][e]	C_2	0.8	0
[3_{yne}243]	C_1	1.4	
[3_{yne}234]	C_1	1.9	
[4_{yne}233]	C_1	2.1	
[4_{yne}323]	C_1	2.3	
[3_{yne}324]	C_1	3.5	

[a] In kilocalories per mole. [b] See note 8 for nomenclature; the acetylene units in these conformations are slightly bent (e.g., internal angles of 177 and 179° for [4_{yne}332]), and this allows Boyd's program,[10] which fails for $\theta = 180°$, to be used. [c] Strain energy relative to that of the [4_{yne}332] whose total (force-field) strain energy is 7 kcal/mol (the contributions to angle bending, torsional, and nonbonded strains are 2.0, 1.4, and 3.0 kcal/mol, respectively). [d] Free energy relative to that of the [3_{yne}333] at −133 °C. [e] See Figure 1 for torsional angles.

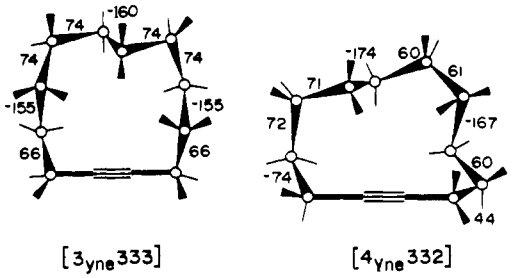

Figure 1. Calculated torsional angles in the [3_{yne}333] and [4_{yne}332] conformations of cyclododecyne.

verify that true (local) energy minima have been obtained.[11]

Of the two lowest energy conformations, one is symmetrical and the other is unsymmetrical (Figure 1), in agreement with the NMR data. The calculated order of these conformations is inverted (Table I), but this is not very significant, given the small energy differences and the expected accuracy (within 1 kcal/mol) of the force-field calculations. The next four conformations (Table I) are not observed at low temperatures, but, because of their fairly low relative strain energies (1.4-2.3 kcal/mol), they may become slightly populated at higher temperatures.[12]

On the assumption that the only mechanism of exchange is the interconversion of the [3_{yne}333] and [4_{yne}332], the ^{13}C NMR data gives[13] a conformational energy barrier of 7.9 ± 0.3 kcal/mol at −95 °C, in agreement with the barrier estimated from the ^1H NMR data. However, the above simple interconversion leads only to a C_2 time-averaged symmetry, whereas the high temperature (>−80 °C) ^1H spectrum of 1 corresponds to a C_{2v} time-averaged symmetry. Thus, a second conformational process must exist in 1, and its barrier must be of the order of 8 kcal/mol in order to accommodate the ^1H NMR data.

It is planned to investigate the conformational properties of other cycloalkynes by the methods described above.

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

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(4) All spectra were measured on a superconducting solenoid NMR spectrometer operating at 59 kG; $CHCl_2F$ was used as a solvent and tetramethylsilane as an internal reference. ^1H NMR spectra were obtained in a frequency sweep mode, while ^{13}C spectra were obtained by the Fourier transform technique with protons noise decoupled. In both ^1H and ^{13}C spectra an ^{19}F line of the solvent was employed for lock purposes.
(5) The ^1H NMR spectrum of I at −5 °C has bands having the following chemical shifts: δ 1.44 (8 H), 1.56 (8 H), 2.18 (α-CH_2, 4 H).
(6) If an average chemical-shift difference of 80 Hz is used, $k \simeq 180$ Hz (with $k = \pi\Delta\nu/\sqrt{2}$) and $\Delta G^{\ddagger}$ follows from absolute rate theory with a transmission coefficient of 1. If k is in error by a factor of 2, the error in $\Delta G^{\ddagger}$ is 0.2 kcal/mol.
(7) The ^{13}C NMR spectrum of I at −50 °C shows the following chemical shifts, δ 18.8, 24.4, 24.6, 25.8, 26.1, and 82.1 (acetylenic carbon), in reasonable agreement with a recently published NMR spectrum of I in $CDCl_3$ at room temperature; see P. A. Bartlett, F. R. Green, and E. H. Rose, *J. Am. Chem. Soc.*, **100**, 4852 (1978). At −133 °C, lines of approximately equal intensities at δ 19.3, 23.2, 23.6, 26.5, 27.2, and 82.1 are assigned to the [3_{yne}333] conformation, while weaker lines at 16.5, 20.9, 24.1 (two overlapped lines), 30.7, 78.8, and 84.9 are assigned to the [4_{yne}332] conformation. The remaining lines of the latter conformation are apparently obscured by the stronger lines of the major conformation.
(8) The nomenclature used to describe the various conformations of cyclododecyne is an extension of the shorthand notation proposed by Dale[1] for the conformations of the cycloalkanes. The number of bonds on consecutive sides of a conformation are concentrated and placed in square brackets, starting with the side containing the acetylenic linkage. The direction of numbering around the ring is then dictated by the position of the triple bond and starts at the corner position nearest this bond. In cases where the acetylenic function is symmetrically situated on a side, the direction around the ring is so chosen that the second number is the smallest possible, e.g., [3_{yne}234] not [3_{yne}432]. This nomenclature can be applied to a variety of systems including unsaturated and heterocyclic rings where a subscript can be used to designate the functional group present.
(9) The low-energy conformations of cyclododecane in order of increasing energy are calculated to be the [3333], [2334], and [2343]. Experimentally, there is no evidence for population of any conformation except the [3333] (F. A. L. Anet and T. N. Rawdah, *J. Am. Chem. Soc.*, **100**, 7166 (1978); J. Dale, *Acta Chem. Scand.*, **27**, 1115, 1130 (1973)).
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(12) In view of possible errors in the force-field calculations, it is conceivable that the [3_{yne}243] conformation is actually of lower energy than the [4_{yne}332], but this is not considered likely.
(13) Because of the small solubility of I at low temperature, the signal-to-noise ratio of the ^{13}C lines at intermediate rate of exchange is low and this has prevented an analysis of the exchange mechanism to be made. It is planned to prepare a suitably ^{13}C-labeled cyclododecyne for line-shape analysis.

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^{13}C NMR Studies of Marine Natural Products. 1. Use of the SESFORD Technique in the Total ^{13}C NMR Assignment of Crassin Acetate

Sir:

The antineoplastic and cytotoxic marine cembranolide, crassin acetate (**1a**),[1] is representative of the burgeoning number of cembrane diterpenes steadily being reported from marine organisms of the coelenerate phylum, as well as from terrestrial plant sources such as tobacco and pines.[2]

Unambiguous ^{13}C NMR spectral assignment has not yet appeared for any member of this interesting group of 14-membered carbocyclic compounds. We now report the complete assignment of the ^{13}C NMR spectra of the naturally occurring crassin acetate (**1a**), and its derivatives crassin (**1b**) and crassin diacetate (**1c**), based largely on the use of the newly developed technique of selective excitation with single fre-

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