Figure 3. AJCP ^{15}N spectrum of an equivolume mixture of formamide, *N*-methylformamide, and *N,N*-dimethylformamide. Though the values of J_{NH} differ (89, 94, and 15 Hz, respectively), AJCP produces the expected signal enhancement for the first two and about 65% for the last. The discrepancy for *N,N*-dimethylformamide is attributed to nonadiabatic conditions in violation of eq 7 (see text).

dependence for coherent cross-polarization using the Hartmann–Hahn sequence is far more severe.[12]

Figure 3 shows the natural abundance ^{15}N spectrum obtained from an equivolume mixture of formamide, *N*-methylformamide, and *N,N*-dimethylformamide. The dominant J_{NH} couplings are 89, 94, and 15 Hz, respectively. The fields were ramped in 400 ms, the proton rf decreasing from 800 to 650 Hz, and the nitrogen rf rising from 650 to 800 Hz. A 5-mm sample tube was used in a static field of 2.34 T, the pulse sequence was repeated at 10-s intervals, and 0.5-Hz line broadening was applied. The dominant peak in Figure 3 shows a 22:1 signal-to-noise ratio after 256 accumulations. The three resonances are observed in the ratios 1.0:0.63:0.33, whereas on the basis of composition the expected ratios are 1.0:0.68:0.51.

We attribute the discrepancy in the *N,N*-dimethylformamide intensity to nonadiabatic conditions in violation of eq 9. The crossing rate is approximately $2\pi \times 300 \text{ Hz}/400 \text{ ms} = 4.7 \times 10^3 \text{ s}^{-2}$, whereas $J^2 = (2\pi \times 15 \text{ Hz})^2 = 8.9 \times 10^3 \text{ s}^{-2}$.

Conclusions

Spectrometer requirements for AJCP are rather modest. In principle, separate A and X transmitter coils can be used, whereas rotating frame coherent transfer methods are essentially restricted to probes with common transmitter coils. There is no critical requirement for setting the rf fields. The details of the rf amplitude sweep are constrained only by the adiabatic requirement; in particular, the sweep need not be linear and many rf imperfections are tolerated. The AJCP sequence is relatively insensitive to resonance offset and will work equally well on any coupled spin system having sufficiently long relaxation times to allow the adiabatic transfer. A related adiabatic method[13] transfers polarization through an intermediate state of *J* order; in contrast to AJCP, however, this method is particularly sensitive to resonance offset.

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# Ring Inversion in 1,4,7-Cyclononatriene (Trishomobenzene). Force-Field Calculations for Abnormally Large Bond Angles

Frank A. L. Anet* and Mehran Ghiaci

Contribution from the Department of Chemistry, University of California—Los Angeles, Los Angeles, California 90024. Received June 21, 1979

Abstract: The barrier to ring inversion in 1,4,7-cyclononatriene has been measured by ^1H dynamic NMR spectroscopy in tetrachloroethylene, 1,1,2,2-tetrachloroethane, and toluene-d_8 as solvents. Values of $\Delta G^{\pm}$ near room temperature vary from 14.5 $\pm$ 0.1 to 14.8 $\pm$ 0.1 kcal/mol. Values of $\Delta S^{\pm}$ vary from -2.2 ± 2 to -4.9 ± 2 eu, and are not strongly negative (-18.2 ± 0.1 eu in CDCl$_3$), as previously reported. Values of $\Delta H^{\pm}$ vary from 13.1 $\pm$ 0.5 to 14.1 $\pm$ 0.5 kcal/mol. Calculations with the Boyd force field show that the strain energy of the crown conformation is 4.6 kcal/mol lower than that of the saddle conformation. The barrier for ring inversion is not well reproduced by the calculations, and possible reasons for this are discussed.

cis,cis,cis-1,4,7-Cyclononatriene (I)[1-7] and related compounds[8-10] show some unusual conformational properties. The ring system can exist in either a crown (I-C) which is rigid and has C_{3v} symmetry for the parent hydrocarbon or as a saddle conformation (I-S), which is more or less flexible. Both types of conformations have been observed in the cyclotriveratrylene

series,[9] and are separated by relatively high barriers ($\simeq 25$ kcal/mol), thus giving rise to atropisomers. The parent compound, however, exists entirely in the crown conformation and can be considered formally to be a trishomobenzene, although the delocalization energy, as calculated by simple MO methods, is actually negligible.[1,3]
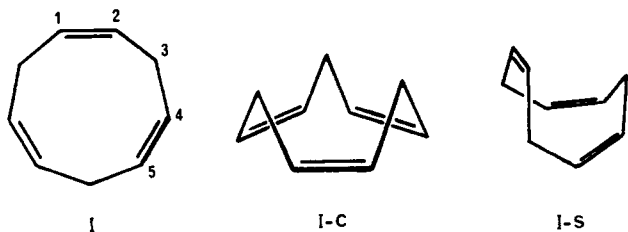
Ring inversion in I has been studied by dynamic NMR methods.[1,3,4] Although there seems little doubt about the value (14.6 kcal/mol) of the free energy of activation ($\Delta G^{\ddagger}$) for this process, the strongly negative (-18.2 ± 0.1 eu) value reported[3] for the entropy of activation ($\Delta S^{\ddagger}$) appears to be unreasonable for a simple conformational process,[1] and indeed the reliability of this parameter has been questioned.[11] In view of this we have reinvestigated the dynamic ¹H NMR spectrum of I, and we have also carried out iterative force field calculations to delineate the ring-inversion path in this molecule.

Experimental Section

Compound I was prepared from 1,5-cyclooctadiene by the procedure described by Detty and Paquette.[6] Sublimation (25 mm) gave white needles: mp 50–52 °C (lit.[2] 51 °C); NMR (CDCl₃, 200 MHz) δ 2.15 and 3.57 (broad, CH₂), 5.4 (m, -CH=CH-). The spectra were measured on a superconducting solenoid spectrometer operating at 47 kG (Bruker WP-200), and are Fourier transforms of accumulated free induction decays obtained under the following conditions: 45° pulse angle, 16K data points, 2000-Hz spectrum width, and a broadening of 0.1 Hz. The lock signal was obtained either from the solvent or from a small amount of added benzene-d_6. Tetramethylsilane was used as an internal reference.

Temperatures were measured and controlled with the Bruker variable-temperature accessory, which uses a copper–constantan thermocouple situated 2–3 cm below the sample tube in the probe. The temperature readings were checked at 0 and 85 °C by observing the reappearance of the free induction signal of the liquid phase upon very slow melting of water and 4,6-dinitro-*o*-cresol, respectively. The calibration samples were in thin-wall capillaries placed in a regular NMR tube containing either CDCl₃ or C₂Cl₄. The 0 °C reading was correct within ±0.2 °C; the reading at 85 °C was correct to within 1 °C, the melting range of the compound. Force-field calculations were carried out on the IBM-360/91 computer of the Office of Academic Computing at the University of California, Los Angeles.

Results and Discussion

NMR Data. The ¹H NMR spectrum of I at −20 °C or lower shows different chemical shifts for the inside and outside protons of the methylene groups. Although the chemical-shift difference between these protons is relatively large (1.5 ppm), the spectrum is complex and is not close to first order, even at high magnetic fields. This follows, for example, from the fact that the two protons on any of the double bonds of I are not completely magnetically equivalent. A much simpler spectrum can be obtained by decoupling the olefinic proton.[7] Even here, the methylene spectrum is not strictly an AB system, since small (0–2 Hz) long-range (^5J) couplings are expected to exist.[12] Since the decoupled spectrum appears as a slightly broadened quartet which does not show resolved splittings, other than those due to J_{gem}, it is impossible to extract the long-range coupling constants by an analysis of the six-spin system. We have chosen to include the effects of the long-range couplings into an effective T_2 value and to treat the system at higher temperatures as a simple mutually exchanging AB system.

In order to obtain reasonably accurate values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, the rate constant must be measured over a wide temperature range. We have chosen to measure the rate constant for inversion in I in the vicinity of 15 °C and at either 95 or 105 °C. At these temperatures the observed broadenings are very much larger than the line widths in the absence of exchange,

and thus the rate constants are only slightly affected by incorrect values of the latter parameters.

Common NMR solvents, such as CDCl₃, CCl₄, and CS₂, are not very suitable for the present work, because of their low boiling points. We have chosen to measure rate constants for ring inversion in I in three rather different high-boiling solvents, namely, tetrachloroethylene (C₂Cl₄), tetrachloroethane (C₂H₂Cl₄), and perdeuterated toluene (C₆D₅CD₃). Although the second solvent contains protons, these did not interfere with the resonances of I. All of the solvents are liquid and mobile at −20 °C, and this allows measurements of the spectra in I under conditions where ring inversion is very slow and no longer affects the line widths.

The line width in the absence of exchange at 95 or 105 °C was estimated in the following considerations. The contribution to the line width arising from dipole–dipole or other relaxation effects should be very small. The contribution of long-range coupling effects can be ignored since this coupling is between exchanging nuclei and it will therefore be negligible when the rate constant is large.[13] Contributions from imperfect decoupling of the olefinic protons and from magnetic-field inhomogeneities are estimated to be 1 Hz. Since the observed line width at these temperatures is at least 10 Hz the correction to be applied amounts to no more than 10% of this width, and therefore the actual correction does not need to be known to an accuracy of better than ±50% in order for the contributing error to the rate constant to be less than 5%.

The line-width correction required at 15 °C is complicated by unresolved long-range coupling. However, this effect should be quite small since the coupling constants should be of the order of 0–2 Hz.[12] The broadening due to dipole–dipole relaxation should also be small, because molecules of similar molecular weights and volumes are known in our experience to give sharp lines even at 0 °C or below. Also, since the line width at −20 °C is 2.7 Hz, this must be the maximum possible nonexchanging line width at higher temperatures. We have used 1.8 Hz as the best estimate of the nonexchanging line width at 15 °C. This value reflects contributions from long-range coupling and possible incomplete decoupling.

Line shapes generated by a computer program for an exchanging AB system were obtained for a variety of rate constants for comparison with the spectra measured at 15 °C. The chemical-shift difference and the coupling constants (12.8 Hz) used were those obtained at −20 °C. That chemical-shift differences are essentially independent of temperatures between −20 and 15 °C (at least) is shown by the fact that the observed peak separation at 15 °C is the same as that calculated with the chemical-shift difference obtained at −20 °C and a rate constant chosen to reproduce the observed line broadening at 15 °C. Dynamic NMR measurements on I in three different solvents were made and treated by the procedure described above. The results are given in Tables I and II. The values of $\Delta G^{\ddagger}$ given in these tables refer to the overall (crown to crown) ring inversion process in I. The values of $\Delta G^{\ddagger}$ at room temperature vary only slightly with different solvents and are close to the value (14.6 kcal/mol) reported previously for chloroform solutions.

From the temperature dependence of $\Delta G^{\ddagger}$, values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be obtained and are given in Table II. The values of $\Delta S^{\ddagger}$ vary, depending on solvent, from −2 to −5 eu. On theoretical grounds, a $\Delta S^{\ddagger}$ of +0.9 eu would be predicted. The discrepancy may be due to unsuspected systematic errors in our results. However, there may be some weak complexing between the solvent and the triene and this might change on going to the transition state for ring inversion, giving rise to an entropy change. The differences in solvent complexation between the triene and the transition state for ring inversion are probably not very great since rather different solvents give very similar values of $\Delta G^{\ddagger}$. Additionally, ¹H NMR measurements

Table I. Dynamic NMR Parameters in I

solvent	chemical shift, Hz	temp, °C	width at half-height, Hz	rate constant, s^{-1}	$\Delta G^{\ddagger}$,[b] kcal/mol
$C_2H_2Cl_4$	303	−20	2.8		
	303	+15	26.7	34	14.8
	303[a]	+95	16.0	9600	14.9
$C_6D_5CD_3$	318	−20	2.7		
	318	+15	31.6	54	14.5
	318[a]	+105	10.0	17 600	14.9
C_2Cl_4	316	−20	2.8		
	316	+15	31.8	55	14.5
	316[a]	+95	16.1	10 400	14.9

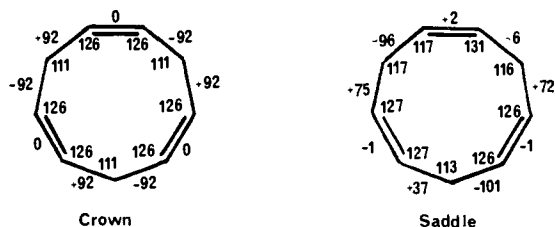[a] Assumed. [b] Overall ring inversion at temperature shown.

Figure 1. Calculated torsional and internal angles for the crown and saddle conformations of 1,4,7-cyclononatriene.

on I at a single temperature (15 °C) were carried out for a number of solvents (cycloheptane, deuterated acetonitrile, and pyridine), but the differences observed in the values of $\Delta G^{\ddagger}$ were quite small (±0.2 kcal/mol).

Irrespective of the precise reason for the apparently slightly negative value of $\Delta S^{\ddagger}$, it is established that $\Delta S^{\ddagger}$ is certainly not as negative as −18.2 ± 0.1 eu, as was earlier reported. The previous determination of $\Delta S^{\ddagger}$ is in error probably because of the following factors: (1) The temperature range for which k was determined was only 25 °C, vs. 80 °C in the present measurements, (2) The determination of the rate constant for ring inversion was carried out using the peak separation method with neglect of all coupling constants, and at a magnetic field much lower than that used in the current work. The unsymmetrical nature of the lines appearing in the moderately slow exchange region makes very difficult a reliable measure of the "peak separation". Furthermore, the peak separation method is notoriously sensitive to systematic errors, even when applied to the simplest systems.[14,15]

Force-Field Calculations. Force-field calculations were carried out with Boyd's program[16,17] on the crown and saddle conformations of I and the results are given in Figure 1 and Table III. The strain energy of the crown is 4.6 kcal/mol less than that of the saddle conformation, and thus only the crown is expected to be populated significantly, in agreement with all experimental data. The saddle conformation is flexible when built with molecular models, and the calculated strain energy varies only 1 kcal/mol during pseudorotation of this conformation. The crown conformation suffers from a considerable amount of torsional strain and from nonbonded interactions of the three inward-pointing methylene protons which are separated by 2.17 Å. The latter effect does not cause any increase in the C–CH₂–C bond angle from its unstrained value (111°), but rather it reduces the H–C–H angle to 105° from its normal 108° value.

The structure of I in the crystal at −35 °C has been determined previously to be a crown by an X-ray diffraction analysis. Only 86 independent reflections were observed and the reliability index was 12%; no attempts to locate hydrogens were made. The C–CH₂–C bond angle is 108°, but it is likely that the parameters obtained in this work are not very accurate and

Table II. Ring Inversion Parameters in I

solvent	$\Delta G^{\ddagger}$, kcal/mol[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/K·mol (eu)
$C_2H_2Cl_4$	14.8 ± 0.1	14.1 ± 0.5	−2.2 ± 2
$C_6D_5CD_3$	14.5 ± 0.1	13.2 ± 0.5	−4.4 ± 2
C_2Cl_4	14.5 ± 0.1	13.1 ± 0.5	−4.9 ± 2

[a] At room temperature.

Table III. Calculated Strain Energy Contributions (kcal/mol) in 1,4,7-Cyclononatriene (I)

strain-energy contributions	crown	saddle
bond stretching	0.200	0.300
bond-angle bending	1.496	3.722
out-of-plane bending	0.004	0.006
torsional strain	5.045	5.845
nonbonded interactions	2.054	3.489
total strain energy	8.80	13.36

Table IV. Crown to Saddle Paths

mechanism	angle driven	rel strain energy[a] of energy max
symmetrical methylene local inversion	ω_1 and ω_2	25.0
unsymmetrical methylene local inversion	ω_1	24.2
symmetrical double bond local inversion	ω_1 and ω_8	>27

[a] Relative to strain energy of the crown.

that differences between them and those calculated by the force-field method are probably not significant.

The saddle has more nonbonded and angle bending strain than does the crown, and this causes it to be 4.6 kcal/mol less stable than the crown. Because of its rigidity and the presence of a threefold real symmetry axis, the crown should have a lower entropy than the saddle by about 4 eu. However, these entropy effects are sufficiently small so that the crown should be strongly favored in its equilibrium with the saddle, at least up to moderately high temperatures.[18]

In order to obtain the strain-energy profile for ring inversion in the crown, it is sufficient to have the profile for the crown to saddle change, since there is no reasonable crown inversion mechanism which does not have the saddle as an intermediate. Three different procedures were used to drive the crown to the saddle, and vice versa, as shown in Table IV.

The two symmetrical processes, which require that two torsional angles be driven simultaneously as shown in Table IV, have been discussed qualitatively by Dale.[11] Neither of these paths gives rise to a true transition state, since the max-

Table V. Strain Energy in the Transition State for Ring Inversion in 1,4,7-Cyclononatriene

angle bending parameters $(K)^a$		internal angles $C-^1CH-^2CH-^3CH_2-^4CH-^5CH-C$					strain energy
$C-CH_2-C$ ($\theta_0 = 111°$)	$C-CH=CH$ ($\theta_0 = 124.7°$)	θ_1	θ_2	θ_3	θ_4	θ_5	rel to crown
0.80	0.62	137	144	130	138	129	24.2
0.40	0.62	134	140	138	137	129	19.6
0.30	0.62	133	139	140	136	129	17.9
0.20	0.62	132	137	143	135	129	15.9
0.40	0.40	136	142	134	137	129	17.0

^{a} K is the force constant in mdyn·Å/rad^2, θ_0 is the unstrained bond angle in degrees, and the strain energy for angle bending (kcal/mol) is given by $E = 72K(\theta - \theta_0)^2$, where the θ's are in radians.

imum energy structures are calculated to have two imaginary frequencies, rather than just one.[19]

If only one torsional angle is driven, the crown becomes unsymmetrical and is converted to the saddle via a true transition state. The strain energy of this transition state relative to that of the crown is 24.2 kcal/mol, a value which is in striking disagreement with the observed NMR barrier ($\Delta H^{\ddagger}$) of 14.6 kcal/mol. We have carefully examined the crown to saddle interconversion process to see whether other paths would be possible, but we have been unable to find any reasonable alternative to the paths shown in Table IV. Because of the high symmetry of the crown, the possibilities for distorting this conformation are very limited. We are thus quite confident that the unsymmetrical path given in Table IV is in fact the best path.[20]

As was pointed out in the previous section, the NMR data on I is on very firm grounds, and thus the discrepancy of about 11 kcal/mol cannot be ascribed to experimental error, in our opinion. The only reasonable conclusion is that the force-field calculations fail badly in this instance. Our previous experience,[16,17] however, and that of others, has been that such calculations are very successful in reproducing heats of formation, conformational energy differences, barriers in conformational processes, and molecular geometries. Thus, there should be a good reason why the calculations fail in the present instance. An examination of the geometry of the transition state shows the presence of some extraordinarily large bond angles, and this suggests itself as a possible cause for the very high calculated strain energy. One $C-CH_2-C$ angle in the transition state has the value of 130° vs. an unstrained value of 111°. Several olefinic bond angles are also very large, e.g., 144, 137, and 138° vs. an unstrained value of 124°.

Unfortunately, the force-field parameters which we are using have not been tested in molecules with such large distortions. Furthermore, force fields used by different workers can have substantially different parameters. For C-C-C angle bending at a CH_2 group, force constants which have been used are as follows: 0.8 (Boyd),[16] 0.7 (Ermer and Lifson),[21] 0.38-0.4 (Allinger).[22] Thus, the Boyd force field uses very stiff C-C-C bond angles. The force constants for C-C-H and H-C-H angle bending used by Boyd are also higher than those of Schleyer and Allinger, but somewhat smaller than those of Ermer and Lifson. Boyd's force constant for C-C-C angle bending at an olefinic carbon is also somewhat higher than the values used by other workers. To determine the effects of the angle bending force constants on the barrier to ring inversion in I, the calculations shown in Table V were carried out.[23]

Even with quite low force constants for bending at the $C-CH_2-C$ angle, the relative strain energy of the transition state is still considerably higher than the experimental enthalpy of activation. It seems that low bending force constants may be needed at both the sp^3 and sp^2 carbons to even approach the experimental value. Lowering the force constants naturally results in increased bond angles, which reach values of 134 ($C-CH_2-C$) and 142° ($CH_2-CH=CH$) when both force constants have the value of 0.4 mdyn·Å/rad^2. Even then, the

calculated relative strain energy is still too high by about 2.5 kcal/mol. Comparatively little is known about the strain in molecules with enlarged bond angles.[24] Such angles occur in some medium-ring compounds containing eight, nine, or ten members.[25,26] One molecule which has quite a large $C-CH_2-C$ angle (121°) is II.[26] The conformational transition state in II

II
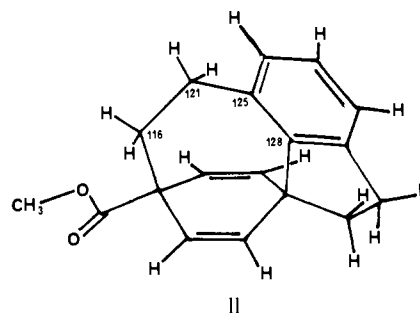
which leads to a time-averaged structure having a plane of symmetry undoubtedly contains an even larger angle. Significantly, the barrier calculated for II is 2.3 kcal/mol too high,[26] and this is in qualitative agreement with the results on I. Unfortunately, the $C-CH_2-C$ angle in the transition state is not given in the paper, but it must be significantly larger than 121°.

Di-*tert*-butylmethane and related compounds (e.g., polyisobutylene) have very strained structures containing $C-CH_2-C$ bond angles which are of the order of 126°.[27] Calculations on di-*tert*-butylmethane with several different force fields have been reported recently,[28] and give $C-CH_2-C$ bond angles of 126.9-128.6 (Allinger[22] and Schleyer[29] force fields) and 122.6° (Bartell,[30] MUB-2 force field). We find that the Boyd force field gives a value of 121.9° for this angle, and thus it is clear that the force constant for angle bending in this force field is too stiff, at least when the angle distortion becomes very large. If the Boyd force constant for the $C-CH_2-C$ angle only is reduced by a factor of 2 from its normal value, this angle in di-*tert*-butylmethane becomes 125.5°, whereas if all the C-C-C angles are relaxed in that way the $C-CH_2-C$ angle becomes 123.6°.

Other molecules which have unusually large bond angles, although not involving a methylene group, include tantalum carbene complexes.[31,32] In complexes where the tantalum atom is electron deficient, the $Ta=CH-C$ angle is much larger than 120°. In one complex, which has two *tert*-butylcarbene moieties bonded to tantalum, the Ta-C-C angles in the $Ta=CH$ *tert*-butyl groups are 155 and 165°.[32] Also, the $Ta=C-H$ angle and the tantalum-carbon distance in these complexes are abnormally small. This is consistent with a carbon whose hybridization is between sp^2 and sp, and where there is enhanced hyperconjugation involving the C-H bond and an empty tantalum orbital. Thus, the $Ta=CH-C$ bond angle can become very large in order to accommodate the bulky *tert*-butyl groups.

The association of large bond angles at carbons which are involved in strong hyperconjugative interactions, as in the

tantalum carbene complexes, suggests that angle opening in other systems may become easier if such interactions are present. The hyperconjugation does not have to be a large effect in the undistorted molecule, provided that it increases substantially as the molecule distorts.

Although the energy required to change the geometry of a carbon atom from tetrahedral to square planar or to trigonal pyramidal in various molecular environments has been studied by quantum-mechanical calculations,[33-35] the effect of the kind of distortion required for ring inversion in I has apparently not been investigated theoretically, Opening of a C–CH$_2$–C angle ultimately results in a linear carbon arrangement (disphenoid shape)[36] and the orbitals in this extreme geometry are easy to visualize. The central carbon should become sp hybridized and the C–H bonds should make use of pure p orbitals on carbon, so that the H–C–H bond angle should be 90°, This agrees with the rule that a decrease in C–CH$_2$–C bond angle is accompanied by an increase in the H–C–H bond angle (as in cyclopropane) and vice versa. The effect of an adjacent π system should be to stabilize the linear state more than the tetrahedral state because of increased hyperconjugation. Thus, the energy required to distort a tetracoordinate carbon from tetrahedral to linear should be lowered by the presence of adjacent π orbitals. An energy-lowering effect should also operate for geometries between tetrahedral and linear, but the stabilization should gradually decrease as the geometry becomes closer to tetrahedral.

In the transition state for ring inversion in I, the two adjacent double bonds have an ideal geometry for hyperconjugation with the methylene group, as shown in Table III. Thus, the energy for opening the C–CH$_2$–C bond angle in III may be less than

III
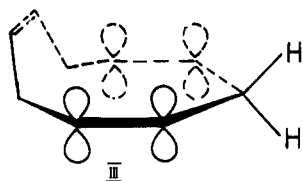
that predicted by ordinary force-field calculations. It is not clear whether the presence of a distorted CH$_2$ atom will lower the force constant for in-plane bending of an adjacent olefinic carbon; if this occurred, it would further help in explaining the low barrier in I. Ab initio quantum mechanical calculations may be able to throw some light on these problems.

Conclusions

Ring inversion in compounds such as 1,4,7-cyclononatriene can provide valuable information about force fields, both from the point of view of testing parameters and of bringing to light unexpected bonding effects, such as the possible presence of hyperconjugation, Although the Boyd force field reproduces energies and geometries quite well for molecules without a great deal of angle strain, it performs poorly in cases where the angle distortion is extremely large. This discrepancy is decreased if smaller angle bending force constants, as have been used by some other workers, are employed in the force field. The presence of p orbitals flanking a strongly distorted methylene group, as occurs in the transition state for ring inversion in I, may also be of importance in causing the force constant for angle bending at the methylene group to be abnormally low.

Although force-field calculations, being empirical in nature, may not reproduce well experimental data when applied to structures which contain unusual structural features, such calculations can provide a base or "classical" value of the energy or geometry and may reveal effects which are not necessarily obvious in quantum-mechanical calculations,

For example, the bond lengths calculated by force-field

methods in certain strained compounds do not agree with experimental values, and this has been ascribed to the presence of hyperconjugative or rehybridization effects which have not been included in the force-field calculations.[37,38] In a similar fashion, the abnormally low barrier for ring inversion in I may reflect the presence of an enhanced hyperconjugation in the strongly distorted conformational transition state.

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Torsion Angles in the Cystine Bridge of Oxytocin in Aqueous Solution. Measurements of Circumjacent Vicinal Couplings between ^1H, ^{13}C, and ^{15}N[1a]

Alan J. Fischman, David H. Live, Herman R. Wyssbrod,[1b] William C. Agosta, and David Cowburn*

Contribution from The Rockefeller University, New York, New York 10021.
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Abstract: The six couplings from $^1H^\alpha$, $^{13}C'$, and $^{15}N'$ to the two β protons have been measured for the two half-cystyl residues in oxytocin, using a series of specifically designed and synthesized isotopic isomers. In the case of half-cystyl 1, the observed couplings strongly suggest that the torsion angle χ^1 (N'–C^α–C^β–S) has the eclipsed value of $-120°$. The value for this angle in the half-cystyl residue 6 is less clearly defined, but is probably also fixed. Using the same analysis as for χ_1^1, χ_6^1 is approximately $+120°$. The stereochemical assignments of the β protons of the two residues have been confirmed by stereoselective deuteration.

A substantial number of observations suggest that the conformation of the peptide hormone oxytocin is relatively flexible in aqueous solution and that the number of conformers contributing to this dynamic equilibrium is small.[2] Such

Cys^1–Tyr^2
S   Ile^3
S   Gln^4
Cys^6–Asn^5
Pro^7
Leu^8–Gly^9–NH$_2$
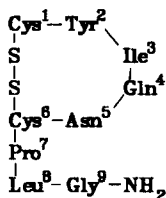
flexibility may be significant in activation of the hormonal receptor upon binding, and it has been suggested that inhibition by binding without activation, as, for example, by [1-penicillamine]oxytocin, is a result of the more rigid conformation of such an inhibitor.[3]

In an effort to understand this dynamic conformation we are currently investigating torsion angles in the molecule by measurement of homo- and heteronuclear vicinal coupling constants in specifically designed and synthesized isotopic isomers of oxytocin.[4] As part of this program we have been interested in the torsion angles about the α and β carbons of half-cystyl residues 1 and 6, χ_1^1 and χ_6^1. These angles are important since, along with the other angles of the disulfide bridge of cystine (χ_1^2, χ^{SS}, χ_6^2), they are torsion angles of the 20-atom ring of oxytocin and thus are involved in the stereoisomerism of this ring in solution.

In the synthetic isotopic isomers described here, deuterium substitution of protons has been used to remove overlapping resonance patterns of similar chemical shifts, to simplify spin systems in which the participating nuclei are either so numerous or so close in chemical shift that analysis of the spectra of the natural material is impossible, or to identify stereospecifically particular protons. In addition, substitutions of ^{13}C for ^{12}C and of ^{15}N for ^{14}N have been used so that the vicinal heteronuclear coupling constants between ^{13}C or ^{15}N and protons can be directly observed in the proton spectrum of the molecule.[5]

It has previously been demonstrated[6] that in a free amino acid it is feasible using similar strategies of isotopic substitution

to determine the six homo- and heteronuclear couplings between two β protons and the three α-carbon substituents $^1H^\alpha$, $^{13}C'$, and $^{15}N'$. In that case,[6] it was shown that those couplings were consistent with averaging among staggered rotamers about the C^α–C^β bond, that stereochemical assignments could be made, and that it might be possible to describe the torsion angle and its distribution with time by the use of these multiple vicinal couplings without resort to the usual assumption either of the exclusive presence of rotamers or of a single fixed angle,

This report is concerned with NMR studies of a series of isotopic isomers of oxytocin designed to permit measurements of the heteronuclear coupling constants about the C^α–C^β bonds of the two half-cystyl residues in order to determine unequivocally the torsion angle and its distribution with time. The homonuclear vicinal proton coupling constants have been previously reported.[2]

Experimental Section

Five isotopic isomers of oxytocin, from a larger set, were used in deriving the results described here. The methods of peptide synthesis and characterization used have been previously described.[4] The composition of some of the isotopic isomers[4,7] and outlines of some syntheses of amino acids have been presented elsewhere.[6,7] The isotopic substitutions in these peptides are summarized in Table I.

Syntheses of Amino Acids. All amino acids described are the L stereoisomer, unless otherwise indicated. Syntheses described here are for the L stereoisomers of the *S-p*-methylbenzyl (MeBzl) derivative of [$^{15}N',\alpha$-^2H], [$^{13}C',\alpha$-^2H], [$\beta2,\beta3$-$^2H_2$], and [$\alpha,\beta3$-$^2H_2$] isotopic isomers of cysteine.

S-p-Methylbenzyl[$\beta2,\beta3$-$^2H_2$]cysteine (**1**)[8] was synthesized by the addition of *S-p*-methylbenzyl chloro[$^2H_2$]methyl sulfide (**2**)[9] to diethyl α-acetamidomalonate.[10]

S-p-**Methylbenzyl Chloro[$^2H_2$]methyl Sulfide (2).** A 48.7-g portion of *p*-methylbenzyl mercaptan (Parrish) was placed in a flask with 15.0 g of [$^2H_2$]paraformaldehyde (Merck Sharp and Dohme). The mixture was cooled in an ice bath and saturated with dry hydrogen chloride; during the saturation process the mixture became quite viscous and 10 mL of dry benzene was added. A 9.0-g portion of anhydrous calcium chloride was then added and the mixture stirred at room temperature for 24 h. The solid material was removed by filtration and washed thoroughly with anhydrous ether. The resulting solution was freed of solvent and the residual liquid distilled at reduced pressure