The linear free-energy relationships in Figures 1 and 2 clearly demonstrate a fundamental control of positional orientation by the strength of oxyanion bases. However, for certain outsized bases, such as 2,6-di-*tert*-butylphenoxide (system 7), but not *tert*-butoxide (system 13), steric effects become important in determining positional orientation.

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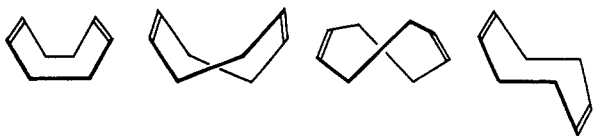
Determination of Conformational Barriers in 1,5-Cyclooctadiene by Proton and ^{13}C Nuclear Magnetic Resonance

Sir:

There has been much interest in the conformation of *cis,cis*-1,5-cyclooctadiene (I) and its derivatives, but certain aspects, including the flexibility of this ring system, have remained unclear. The dipole moment of 1,6-dichloro-1,5-cyclooctadiene is consistent with a predominant boat form.[1] An electron diffraction study of I in the gas phase has shown the presence of a twist-boat form (I-*TB*) with possible minor amounts of the chair form (I-*C*).[2] Two recent X-ray studies of derivatives of I have revealed twist-boat conformations,[3] in contrast to dibenzo-1,5-cyclooctadiene which is centrosymmetrical in the crystalline phase and hence must be a chair.[4] Several strain-energy calculations on I have been carried out,[1,5] and the nature of the flexibility of the boat (I-*B*), twist-boat, and skew forms (I-*S*), in contrast to the rigidity of the chair form, has



I-*B* boat | I-*TB* twist boat | I-*S* skew | I-*C* chair

been discussed from a restricted geometric point of view.[6] The 60-MHz ^1H nmr spectrum of I has been found to be temperature independent down to $-150°$, indicating either very low conformational barriers, or possibly very small chemical-shift differences between nonequivalent methylene protons.[7]

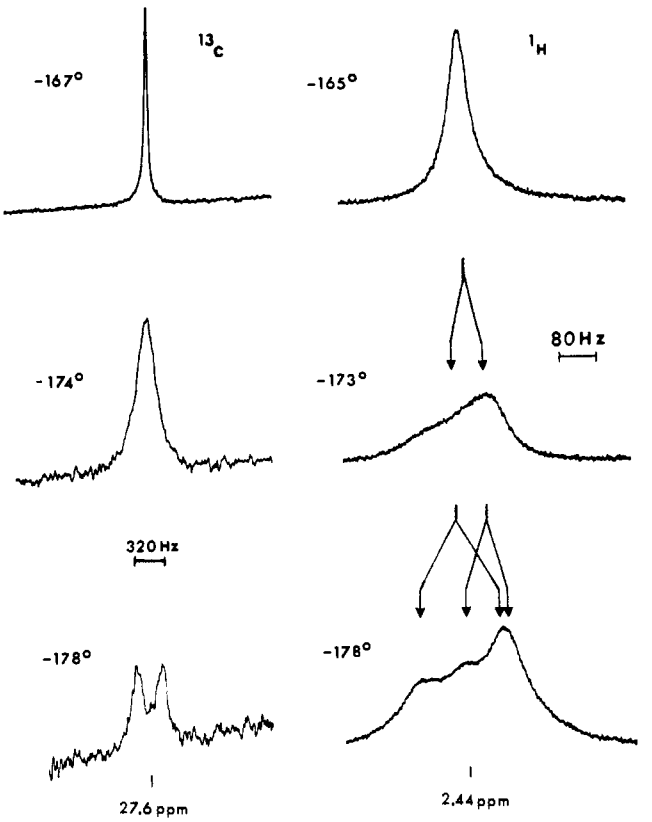


Figure 1. Variable temperature nmr spectra of the methylene groups of *cis,cis*-1,5-cyclooctadiene (*ca.* 3% solution in a 2:3 mixture of $CHCl_2F$ and $CHClF_2$). The ^{13}C spectra (protons decoupled) represent Fourier transforms of free induction decays accumulated after 250 pulses. The ^1H spectra were obtained in the frequency sweep mode in single scans. The frequency scale is in ppm downfield from tetramethylsilane nuclei in both cases.

We have now reinvestigated the nmr spectra of I, using temperatures lower than $-150°$, with both ^1H and ^{13}C nmr at a magnetic field of 59 kG.[8] Figure 1 shows that the methylene carbon resonance in the 63.1-MHz cmr spectra of I changes from a single line at high temperatures to a 1:1 doublet below $-176°$. The olefinic carbon resonance of I broadens at low temperatures, but is not resolved into a doublet, presumably because the chemical-shift difference is too small. The cmr results are consistent with a twist boat of C_2 symmetry, which undergoes a spectral process, labeled A, with a $\Delta G^{\ddagger}$ at $-176°$ of 4.2 ± 0.2 kcal/mol.[9]

Figure 1 also shows 251-MHz pmr spectra of the methylene protons of I at various temperatures. The methylene band, which is relatively sharp at high temperatures, is already quite broad at $-165°$, and below $-168°$, it splits into an approximately equal intensity doublet, with the low-field component much broader than the high-field component. At still lower temperatures (*ca.* $-175°$), each of these resonances splits into two, with the low-field component giving rise to the larger splitting, as shown diagrammatically in Figure 1. The above splittings are of the order of 100 Hz and must result from chemical-shift differences.[10] The

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(8) The spectra were obtained on a superconducting solenoid nmr spectrometer.
(9) The uncertainties in $\Delta G^{\ddagger}$ arise entirely from difficulties in obtaining accurate temperatures in ^{13}C spectra obtained with proton decoupling.
(10) The lowest field proton line at $-178°$ probably originates from the two most inside protons in I-*TB*.

pmr results clearly show the presence of two spectral processes: one (B) with a $\Delta G^{\ddagger}$ of 4.4 ± 0.1 kcal/mol (at −177°) and the other (C) with a $\Delta G^{\ddagger}$ of 4.9 ± 0.1 kcal/mol at −168°. At −165°, k_B/k_C is about 15.[11]

The detection of one spectral process in the ^{13}C spectrum, and two processes in the ^{1}H spectrum, is consistent with the twist boat as the ground conformation of I. It rules out the boat, chair, and skew forms as sole conformations, as well as 1:1 mixtures of a chair (or skew form) and a boat (or twist boat). It does not exclude the presence of small concentrations (<10% at low temperatures) of conformations other than the twist boat.

The likely degenerate interconversion paths for the twist boat are as follows: (1) pseudorotation *via* the boat, (2) pseudorotation *via* the skew form, and (3) interconversion of the boat, as obtained in path 1, into the chair.[12] It will be assumed in the following discussion that the boat, the skew form, and the chair are present in unobservable concentrations at low temperatures. Spectral process B cannot correspond to path 3, since this leads to a complete averaging, in disagreement with experiment. If B corresponds to path 1, C can be path 2 or 3, and this statement remains true if 1 and 2 are interchanged. In either case, process A observed in the ^{13}C spectrum is not simple, but corresponds to the sum of processes B and C seen in the ^{1}H spectrum. However, since $k_B \gg k_C$, processes A and B should have about the same free energies of activation, as found experimentally. Whether process B involves path 1 or 2 can in principle be determined experimentally or by accurate strain-energy calculations.

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(11) No attempt has been made at precise line-shape analysis of these spectra because of the very rapid increase in the line width resulting from dipole–dipole relaxation in the temperature range −165 to −178°. Nevertheless, the changes in line shapes are qualitatively in agreement with the scheme shown in Figure 1. It is planned to carry out a line-shape analysis on suitably deuterated derivatives of I, which should give much sharper lines than I itself.

(12) Although path 3 suffers from rather large internal angle strains,[1] it has very little eclipsing strain, and thus cannot be dismissed, in the absence of quantitative calculations, for process C.

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Erratum. Tautomerism of Nucleic Acid Bases

Sir:

Recently several papers from this laboratory indicated that cytosine and guanine exist in their minor tautomeric forms to the extent of 15% at room temperature in neutral aqueous solution.[1-4] This conclusion was based on a detailed analysis of the unusual selective line broadening observed for the cytosine H_5 and guanine H_8 nuclear magnetic resonance signals.

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In view of the important implications of the above findings, we felt compelled to confirm these observations. Unfortunately, we have found it impossible to duplicate the basic experimental data reported earlier, even though identical methods were used to purify the samples. The purification of the nucleotide derivatives was essential to this work since many of the compounds were known to be contaminated with paramagnetic impurities, which could lead to the observed line broadening. Subsequently we have found that a number of samples, whose data were reported, were not purified as stated in the earlier publications, and, in addition, that some of the control experiments were carried out incorrectly.

The following additional experiments were undertaken in light of the above observations. (a) Guanine and cytosine derivatives were purified using both Dowex 50W-8X and Chelex-100 cation exchange resins. (b) Cytidine was purified by recrystallization from ethanol–water mixtures. Both the recrystallized samples and those purified using the chelating resin Chelex-100 gave sharp nuclear magnetic resonance signals.

Under certain conditions, however, broad guanine H_8 and cytosine H_5 proton line widths were obtained for samples passed through Dowex 50W-8X columns. In the case of 2′-GMP at pD 6.0, a temperatue of 18°, and at 220 MHz this residual line width was 5.5 Hz. The addition of 4×10^{-6} *M* EDTA to a 0.03 *M* solution sharpened the resonance. Since it was initially suggested that EDTA caused line narrowing by catalysis of the exchange between tautomeric structures, the line narrowing should depend only on the EDTA concentration and should be independent of the nucleotide concentration. This was not observed. Instead it was found that the amount of EDTA required to sharpen the line depended on the nucleotide concentration. This immediately suggested that the line broadening was induced by a paramagnetic impurity. Cu^{2+} is the most likely candidate, as suspected earlier by us.[1] More recently, in fact, Kearns, *et al.*, have shown that all the experimental data can be reproduced by adding 10^{-5}–10^{-6} *M* Cu^{2+} to 0.05 *M* solutions of 2′-GMP and 5′-CMP.[5]

In summary, then, it appears that the line broadening previously attributed to tautomerism can be traced to the presence of paramagnetic impurities in the samples, the most likely being Cu^{2+}.

One of us (S. I. C.) would like to apologize to the scientific community for permitting this fiasco.

(5) Y. P. Wong, K. L. Wong, and D. R. Kearns, *Biochem. Biophys. Res. Commun.*, in press.

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Chemistry of Metalated Heterocycles. Rearrangement and Dimerization of Lithiothiazoles, Thiadiazoles, and Oxadiazoles

Sir:

We wish to report a remarkable property of metalated aromatic heterocycles bearing the structural feature A.