than the more compact cyclooctyl ring which closely approximates *n*-butyl in length. Now the conformational versatility or flexibility of the alkyl substituents increases with chain length, but in the constrained cycloalkyl series it increases much less from cyclobutyl to cyclohexyl than from the latter to larger rings which can assume many more conformations and exhibit pseudorotation.[26] Hence, the reversal of the respective trends of α values in the two series may well have different origins: in the alkyl series it may be related to protein penetration by long-chain substituents whereas in the cycloalkyl series it may coincide with a sudden departure from the conformational constraints of small rings. The free energies of binding *vs.* volumes are uninformative in this regard since they do not correlate with the volume effects on α (Figure 3). However, the van't Hoff enthalpies *vs.* volume yield some valuable information (Figure 4): first, ΔH becomes increasingly positive up to pentyl-TMA, but then virtually levels off at the peak of acceleration. The average $\delta\Delta H/\delta\Delta S$ ratio for the binding of the short-chain alkyls up to hexyl or heptyl is 250–288°K,[6,15] but for the longer chain members it falls to about 50°K. The transfer of alkanes from an apolar to an aqueous phase is characterized by a ratio of 50–150°K.[27] The nearly athermal binding of the longer chain alkyl substituents is therefore suggestive of chain penetration of an apolar region,[28] presumably at the periphery of the cleft. One consequence may be that a distorted conformation of the enzyme is induced. This could explain the decline in α values as the chain is elongated.

In the case of the cycloalkyl series, again no correlation is found between volume effects on α and ΔG binding, respectively (Figure 5). However, a fairly good correlation between volume effects on α and ΔH binding, respectively, is found (Figure 6). Since the $\delta\Delta H/\delta\Delta S$ ratio for the binding of *all members* of the series averages 288°K, it seems to follow that the decline in the α values may not be caused by a shift of interaction mechanism such as penetration of the larger rings into the interior of apolar regions. It appears, then, that the volume effects on α would be primarily a measure of an important property of the protein which is detectable in enthalpies and entropies of binding, but as a consequence of enthalpy–entropy compensation, not clearly indicated by the free-energy changes in binding.

As already pointed out in the introductory statement, a ligand-induced change of conformation may be defined as a stereotyped alteration in the balance of bond-breaking and bond-making reactions in the protein, and it is conceivable that relative binding enthalpies may reflect the degree of alteration. In the case at hand, the degree of stimulation of AChE toward MSF correlates better with enthalpies than free energies of ligand binding (provided nonbonded repulsions between the bound ligands are absent in the ternary complex). Since we have already shown[6] that a correlation of the form $\delta\Delta H = T_c\delta\Delta S$, where T_c = 288°K, holds for the binding of some 35 TMA salts on AChE, an endothermic release of cleft-bound water molecules accounts best for the structurally induced fluctuations in the binding enthalpies.[6] Hence, the rough correlation between acceleration and enthalpies of binding may be explained by the loss of water from the cleft, as this would increase the chemical potential of the esteratic nucleophiles and relax their conformation. This latter effect would merely constitute a case of free-energy transmission from one region of the cleft to another in the form of mechanical free energy.[5] The effects of enzyme modifiers may perhaps be accounted for in similar physical terms, although much work remains to be done before generalizations can be attempted.

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(26) J. D. Roberts, 19th National Organic Chemistry Symposium of the American Chemical Society, Tempe, Ariz., June 1965, p 77.

(27) W. Kauzmann, *Advan. Protein Chem.*, **14**, 1 (1969).

(28) A. Wishnia, *J. Phys. Chem.*, **67**, 2079 (1963).

Communications to the Editor

On the Existence of Polar Conformations of Cycloheptane, Cyclooctane, and Cyclodecane

Sir:

Cyclooctane is a *polar molecule*. The application of the molecular beam electric deflection method,[1,2] *i.e.*, deflection (refocussing) of beams of these molecules in an inhomogenous electric field (quadrupole focusser), to cycloheptane, cyclooctane, and cyclodecane has revealed the existence of polar conformations[3] of these molecules.

Cyclopentane[4] appears to be nonpolar using this method. Apparently the barrier to pseudorotation is

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(1) (a) L. Wharton, R. A. Berg, and W. Klemperer, *J. Chem. Phys.*, **39**, 2023 (1963); (b) W. E. Falconer, A. Büchler, J. L. Stauffer, and W. Klemperer, *ibid.*, **48**, 312 (1968).

(2) E. W. Kaiser, J. S. Muenter, and W. Klemperer, *ibid.*, **48**, 3339 (1968).

(3) (a) The X-ray analyses of Dunitz on cyclododecane and on derivatives of cyclodecane, cyclononane, and cyclooctane have been summarized in J. D. Dunitz and V. Prelog, *Angew. Chem.*, **72**, 896 (1960). (b) For a recent, excellent, and comprehensive review see J. D. Dunitz, "Perspectives in Structural Chemistry," Vol. II, J. D. Dunitz and J. A. Ibers, Ed., Wiley, New York, N. Y., 1968, p 1. (c) Theoretical discussion of this area may be found in J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7306, 7043, 7047 (1967).

(4) This molecule was studied with a nozzle source rather than a conventional effusion source. We have observed in electric resonance experiments that the population of internal states in molecules leaving an

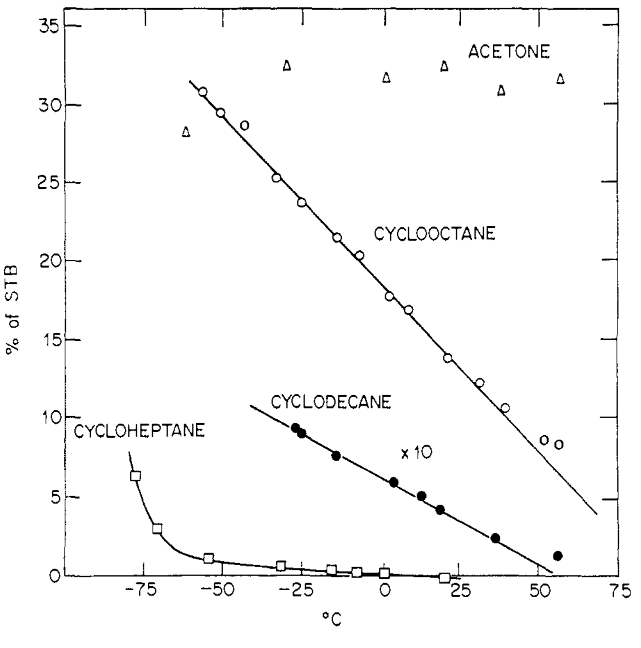

Figure 1. Refocussing intensity of acetone, cycloheptane, cyclooctane, and cyclodecane as a function of temperature. The data were taken with 25 kV on the B-field focusser and the intensity expressed as a percentage of the straight-through beam (STB).

sufficiently low that on the average the dipole moment is zero. Cyclopentane-d_1 was also not deflected by the electric fields employed, although CH_3D with a 0.005 D moment[5] is readily refocussed. The former molecule appears to be asymmetric enough to be an unfavorable case.

As expected, cyclohexane[4] and dioxane, the chair forms of which have centers of symmetry, were found to be nonpolar. Dioxane showed no refocussing at temperatures up to 900°K. Since the boat conformations for dioxane should have large dipole moments, a detectable refocussing should occur even if the beam contains only a few per cent of these conformations. Thus, either these boat forms have very high energies with respect to the ground state, or rigid boat and chair conformations may be a poor description for the excited vibrational states of these molecules. 1,4-Cyclohexadiene[4] showed no refocussing and is apparently in a planar form[6] or nearly so.

The temperature dependence of cycloheptane[7] refocussing (Figure 1) shows the effects of pseudorotation. This molecule has C_S symmetry (chair or boat) and should be polar regardless of its conformation. Refocussing was negligible at 293°K, but increased strongly near 200°K, as the population of molecules in the polar vibrational states increased.

Cyclooctane[7] is the most outstanding case in the present study and is strongly focussed by the application of the electric fields. The refocussing is appreciable at all temperatures studied (Figure 1; acetone data are included for comparison). The finding of 31% refocussing at 216°K is clearly substantial, and constitutes strong evidence for a polar ground state in cyclooctane. Of the various symmetric conformations which have been discussed for cyclooctane, one need only consider the boat-chair (C_S), the twist boat-chair (C_2), or the extended crown (chair-chair, C_{2v}). Thus, our results are in complete agreement with the nmr studies of Anet and St. Jacques,[8a] the later conclusions of Hendrickson,[3c] and the work of Dunitz on substituted cyclooctanes,[3a] all of whom concluded that the boat-chair is the predominant ground-state conformation of cyclooctane.[8b] Also, in the eight-membered series, it was readily demonstrated that 1,5-cyclooctadiene[4,9] must be in the tub form since it is strongly polar. As expected, cyclooctatetraene[4] was also found to be nonpolar.

Cyclodecane[7] is weakly focussed by the electric fields. The increase in refocussing with decrease in temperature (Figure 1) indicates a polar ground state, but the magnitude of the effect is small and might be accounted for by the temperature dependence of the beam velocity distribution and the rotational partition function.

Cyclododecane was found to be nonpolar, in agreement with the conclusions of Dunitz and Shearer,[10] based on an X-ray study of the crystal.

The results of these experiments have been summarized in Table I.

Table I. Summary of Deflection Experiments

Molecule	Temp range, °K	Polarity	Refocussing[a] % of STB	A/B voltages, kV
Cyclopentane	293[b]	Nonpolar	0	25/25
Cyclohexane	293[b]	Nonpolar	0	25/25
1,4-Dioxane	235–900	Nonpolar	0	16/25
1,4-Cyclohexadiene	293[b]	Nonpolar	0	25/25
Cycloheptane	195–293	Polar	9.1[c]	16/25
Cyclooctane	216–330	Polar	31[d]	0/25
1,5-Cyclooctadiene	293[b]	Polar	8.6	25/25
Cyclooctatetraene	293[b]	Nonpolar	0	25/20
Cyclodecane	246–329	Polar	0.9[e]	0/25
Cyclododecane	243–293	Nonpolar	0	16/25

[a] Refocussing intensity expressed as a percentage of the straight-through beam for the A and B quadrupole focussing field voltages indicated under A/B voltages. [b] A nozzle source was used for these molecules, an effusion source for the rest. [c] At 195°K. [d] At 216°K. [e] At 246°K.

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expansion nozzle can be characterized by a temperature considerably lower than the temperature of the source itself. Molecules leaving an effusion source have a distribution of states characterized by the source temperature. Also see N. Abauf, J. B. Anderson, R. P. Andres, and J. B. Fenn, *AGARD Conf. Proc.*, No. **12**, 355 (1967).

(5) I. Ozier, W. Ho, and G. Birnbaum, *J. Chem. Phys.*, **51**, 4873 (1969).

(6) *Cf.* the recent X-ray study of 1,4-cyclohexadienyl-1-glycine by R. J. Jandacek and S. H. Simonsen, *J. Amer. Chem. Soc.*, **91**, 6663 (1969).

(7) Samples of 99.9% cycloheptane and cyclooctane and 99% cyclodecane purity, obtained from Chemical Samples Co., Columbus, Ohio, were used in this experiment. No impurities could be detected using vpc, nmr, or mass spectrometry. In addition, the refocussing curves were studied at several different mass peaks. These curves are normalized to the straight-through beam and small amounts of polar impurities are detected as differences in the intensity of the deflection curves, since ionization efficiencies differ from molecule to molecule. No impurities could be detected in our samples using this criterion in addition to those cited above.

(8) (a) F. A. L. Anet and M. St. Jacques, *J. Amer. Chem. Soc.*, **88**, 2585, 2586 (1966). (b) The same conclusion has been reached by J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts (*ibid.*, **91**, 1386 (1969)) in their nmr studies of 1,1-difluorocyclooctane and 1,1,4,4-tetrafluorocyclooctane.

(9) M. St. Jacques, M. A. Brown, and F. A. L. Anet (*Tetrahedron Lett.*, 5947 (1966)) have reported that the nmr spectrum of 1,5-cyclooctadiene is not temperature dependent and thus does not yield structural information. J. D. Roberts (*J. Amer. Chem. Soc.*, **72**, 3300 (1950)) has concluded that 1,6-dichloro-1,5-cyclooctadiene is largely in the tub form on the basis of dipole moment measurements. See ref 3b, p 51, for discussion and reference to electron-diffraction studies.

(10) J. D. Dunitz and H. M. Shearer, *Helv. Chim. Acta*, **43**, 18 (1960).

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On the Conformation of 1,4-Cyclohexanedione

Sir:

The outstanding example of a simple six-membered ring which is considered to exist either predominantly,[1,2] or in some part,[3–7] in a boat or polar nonchair conformation is 1,4-cyclohexanedione. The basis for this belief has rested largely on the observation of a dipole moment of *ca.* 1.3 D.[2a,3,5–8] The view that the molecule exists predominantly in a flexible nonchair conformation is a reinterpretation[1] of dipole moment data which were originally interpreted[3,5,6] in terms of an equilibrium between chair and boat in favor of the chair. Recent X-ray structure analyses[2] have also yielded a twist boat structure for which the calculated dipole moment is in good agreement with the value measured in benzene solution. Theoretical studies[1,4,9] support the experimental findings. Infrared, Raman,[1a,b] and nmr spectroscopic[1c,d] studies have been brought to bear on this problem.

We have found that 1,4-cyclohexanedione is a *nonpolar molecule* in the gas phase, using the molecular beam electric deflection method,[10] *i.e.*, the deflection (defocussing) of a beam of this molecule in an inhomogenous electric field (quadrupole focusser). Mass 112 was monitored and no refocussed beam was observed at 293, 374, 396, and 478°K (Table I).

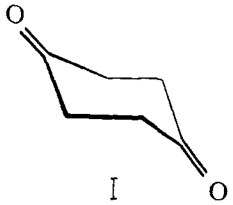
These data are incompatible with the molecule having a 1.3-D dipole moment and indicate that there is a negligible amount of polar molecules present in the temperature range studied. Although X-ray results[2] may result from intermolecular forces in the crystal[11] (reasons for this behavior are probably quite complex), our results are in direct contradiction to the dipole moment measurements in solution and in the gas phase.

Table I. 1,4-Cyclohexanedione Defocussing as a Function of Temperature

Temp, °K	Sensitivity^a	Defocussed beam^b 25/0^c	0/25^d	25/25^e
293	0.34	0.06	0.06	0.00
374	0.30	0.08	0.08	0.00
396	0.32	0.08	0.07	0.02
478	0.31	0.12	0.14	0.14

^{a} Scattered beam as per cent of straight-through beam. ^{b} Expressed as per cent of straight-through beam. ^{c} 25 kV on the A-field focusser. ^{d} 25 kV on the B field. ^{e} 25 kV on the A and B fields. Other samples run at room temperature did not show the small increase in signal at this voltage setting.

The experimental results can be interpreted in terms of a nonpolar chair I or fully extended twist boat II.



I

II

Also, complicated tunneling behavior connecting the various polar boat forms could occur. However, refocussing should be observed in the latter case if the potential energy barrier for the motion is not too low (*i.e.*, if the molecule is not completely "flexible"). As an example, ammonia, which has roughly analogous "inversion" behavior, refocusses strongly[12] from the vibrational states below the potential barrier (*i.e.*, the inversion doublets). Thus, it would seem reasonable that our results imply a chair or fully extended twist-boat conformation for the molecule. Our experiments cannot distinguish between these two possibilities. However, the relationship between the carbonyl group and the adjacent methylenes in the chair form is much more like that established for acetaldehyde,[13] which has eclipsed C=O and C—H bonds, than it is in the fully extended twist boat. The chair conformation would thus seem to be the most likely ground state for 1,4-cyclohexanedione in the gas phase.

Acknowledgment. This work was supported by the National Science Foundation and the Atomic Energy Commission.

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[2] (a) A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Lett.*, 1247 (1963); we are indebted to Professor R. B. Woodward for having pointed out this reference to us; A. Mossel and C. Romers, *Acta Crystallogr.*, **17**, 1217 (1964); the latter reference was kindly pointed out by Professor J. Z. Gougoutas, who also offered helpful discussion of it; (b) P. Groth and O. Hassel, *Proc. Chem. Soc.*, 218 (1963); *Acta Chem. Scand.*, **18**, 923 (1964).

[3] R. J. W. LeFevre and C. G. LeFevre, *J. Chem. Soc.*, 2696 (1935); 3549 (1956).

[4] P. Hazebrook and L. J. Oosterhoff, *Disc. Faraday Soc.*, No. **10**, 87 (1951).

[5] O. Hassel, *Quart. Rev., Chem. Soc.*, 7, 221 (1953); *Trans. Faraday Soc.*, 30, 874 (1934).

[6] M. T. Rogers and J. M. Cannon, *J. Phys. Chem.*, **65**, 1417 (1961).

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[8] However, the dipole moment and the references cited above should be viewed in the light of the experiments and comments of A. Aihara, K. Chitoku, and K. Higasi (*Bull. Chem. Soc. Jap.*, **35**, 2057 (1962)) who report a dipole moment of 0.43 D for the title compound. See ref 1d for further confirmatory discussion of this illuminating paper.

[9] N. L. Allinger, *J. Amer. Chem. Soc.*, **81**, 5730 (1959).

[10] P. Dowd, T. Dyke, R. Neumann, and W. Klemperer, *ibid.*, **92**, 6325 (1970). See references cited therein for a discussion of the method.

[11] Of particular interest in this connection are the findings of P. Groth and O. Hassel (*Acta Chem. Scand.*, **19**, 1733 (1965); *Tetrahedron Lett.*, 65 (1964)) with respect to the X-ray structures of the diiodoacetylene and mercuric chloride complexes of 1,4-cyclohexanedione. The observation that the angle between the carbonyl groups in the latter case opens up to 175° might indicate some sensitivity of this molecule to its environment in the solid state.

[12] (a) J. P. Gordon, H. J. Zeiger, and C. H. Townes, *Phys. Rev.*, **99**, 1264 (1955); (b) W. E. Falconer, A. Büchler, J. L. Stauffer, and W. Klemperer, *J. Chem. Phys.*, **48**, 317 (1968).

[13] R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *ibid.*, **26**, 1695 (1957).

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