As an example of the application of these thoughts, let us consider the complex formed between the nicotinamide moiety of NAD^+ and a solvent available tryptophanyl residue in 3-phosphoglyceraldehyde dehydrogenase. We can assume that virtually maximum orbital overlap occurs, since the complex exhibits an intense charge-transfer absorption for which a high degree of overlap is required. If furthermore we assume that one face of the tryptophanyl residue is blocked by the adjacent polypeptide chain of the protein (a common feature for exposed tryptophanyl residues in proteins, according to available crystallographic evidence), then a single in-plane rotational isomer should be favored for the coplanar nicotinamide–indole part of the NAD^+–enzyme complex. Of course, the almost-equivalent complex in which the nicotinamide moiety is rotated around its dipole axis by about 180° may be close enough in *total* interaction energy so as to cause a significant fraction of complexes with this geometry to occur, in addition to those with the "best" total interaction energy. It occurs to us that nature may have been aware of this as well, and so (according to the experimental evidence[28]) designed the coenzyme in such a fashion so as to block one face of the nicotinamide ring with an adenine ring. In this view, one of the biological functions of the adenine ring in NAD^+ (or in NADH) may be simply to ensure that the enzyme–coenzyme complex is formed with the proper geometry for subsequent efficient enzymatic catalysis.

(28) D. W. Jiles and D. W. Urry, *J. Biol. Chem.*, **243**, 4181 (1968); N. J. Oppenheimer, L. J. Arnold, and N. O. Kaplan, *Proc. Nat. Acad. Sci. U. S.*, **68**, 3200 (1971); J. R. Barrio, J. A. Secrist III, and N. J. Leonard, *ibid.*, **69**, 2039 (1972).

In conclusion, complexes between asymmetric planar ring structures with nonzero dipole moments are inherently capable of exhibiting the same kind of stereochemical selectivity (provided that at least one of the ring faces of one molecule of the pair is blocked) that appears to operate in the more usual three-dimensional interactions between enzymes and substrates. This is most easily visualized by considering a planar surface on which three or more point changes are asymmetrically located. A second surface having opposite charges in mirror positions will exhibit minimum energy in contact with the first surface only when the charge pairs are in exact registry, all other things (degree of overlap) being equal. Furthermore, interactions between molecules with large permanent dipole moments represent a selective advantage for enzymatic efficiency over those with no permanent moment: as a molecule with a large permanent moment approaches its binding site on the enzyme, the long-range mutual interaction of the dipoles serves to orient the molecules with respect to each other until such time as the short range van der Waals and specific atom-pair Coulombic forces can act to finalize the geometry and stabilize the interaction.

Supplementary Material Available. A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1585.

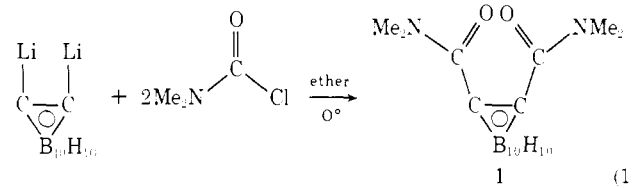
Communications to the Editor

Stereodynamics of Substituted Carboranes. I. 1,2-Bis(*N*,*N*-dimethylcarbamoyl)-1,2-dicarba-*closo*-dodecaborane(12) and 1,7-Bis(*N*,*N*-dimethylcarbamoyl)-1,7-dicarba-*closo*-dodecaborane(12). Barriers to Rotation and the Aromaticity of the Carborane Cage

Sir:

Many recent reports have been concerned with elucidating the nature of nondestructive dynamical processes which occur in a wide variety of boron hydrides and boron hydride metal complexes.[1] There have been no papers regarding the effect of the apparently aromatic carborane cage on the conformational dynamics of attached substituents. This report concerns the observation of a dramatic acceleration in the rate of rotation about a carbonyl carbon–nitrogen bond as compared to a simple amide induced by efficient π-bonding involving the carborane cage.

The reaction of the lithium salt of the 1,2-dicarba-*closo*-dodecaborane(12) [*o*-carborane] dianion with *N*,*N*-dimethylcarbamoyl chloride in ether at 0° produced 1,2-bis(*N*,*N*-dimethylcarbamoyl)-1,2-dicarba-*closo*-dodecaborane(12) (**1**): mp 119–120°; ir, 1650 (C=O), 1480 and 1370 cm^{-1} (CH_3). *Anal.* Calcd: C, 33.54; H, 7.74. Found: C, 33.82; H, 7.77 (eq 1).



1 (1)

Examination of the ^1H dnmr spectrum (60 MHz) of **1** (0.1 *M* in $CHCl_3$) at 56.6° (Figure 1) revealed a sharp singlet methyl resonance (δ 3.20) consistent with all methyl protons in **1** being rendered equivalent due to a rate process which is rapid on the dnmr time scale. Upon lowering the temperature, the NMe_2 dnmr spectrum broadens substantially giving evidence for the slowing of two distinct rate processes (Figure 1). For example, at −11.9°, the two sharp singlets correspond to a rate process which is slow on the dnmr time scale but these sharp peaks are superimposed on another exchange-broadened spectrum corresponding to a more rapid equilibration. At lower temperatures, the spectrum sharpens into a series of four singlet reso-

(1) H. Beall and C. H. Bushweller, *Chem. Rev.*, 73, 465 (1973).

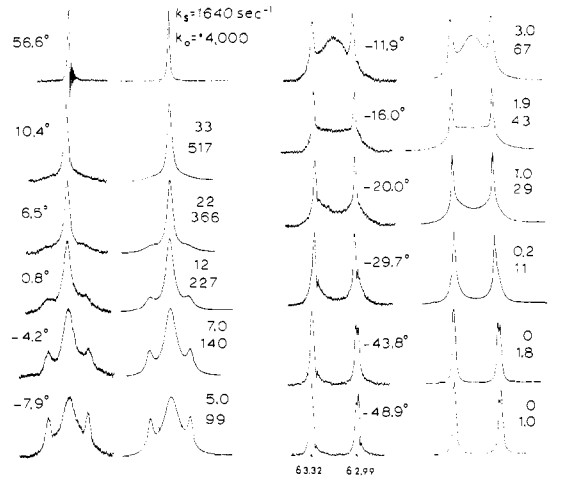
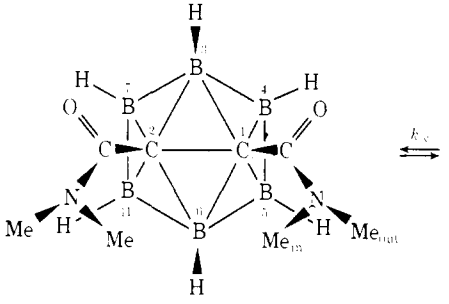


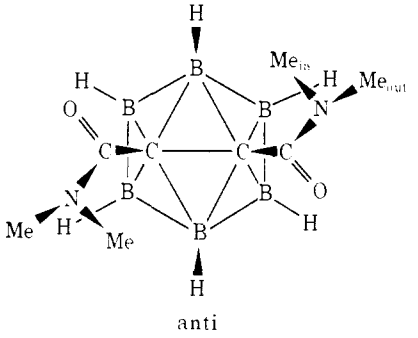
Figure 1. The experimental ^{1}H dnmr spectra (60 MHz) of **1** (0.1 *M* in $CHCl_3$) as a function of temperature and theoretical spectra calculated as a function the rate of NMe_2 rotation in the syn (k_s) and anti (k_a) isomers.

nances at δ 3.31, 3.30, 2.99, and 2.96 with respective relative intensities of 0.35:0.15:0.15:0.35 established from a complete line shape analysis under slow exchange conditions.

The most reasonable rationale for such spectral behavior involves a mixture of the syn and anti isomers of **1** in which there are different barriers to NMe_2 rotation (eq 2). Equation 2 represents only one pair of two



syn



anti

(2)

equivalent pairs of syn and anti isomers of **1**. It is also clear that rotation about the carborane carbon–carbamoyl carbon bond (k_{cc}, eq 2) must also be slow in order to observe four methyl peaks at slow exchange. Fast carbon–carbon rotation (k_{cc}, eq 2) with slow NMe_2 rotation would produce *two* singlet resonances for the "in" and "out" methyl groups (eq 2) being time averaged between syn and anti isomers.

The larger set of two singlets (δ 3.31, 2.96) is tentatively assigned to the anti isomer in which nonbonded repulsions between the two large NMe_2 groups are effectively eliminated as compared to the syn. It is obvious from Figure 1 at $-11.9°$ that the syn isomer is rotating very slowly as evidenced by two sharp singlets in contrast to the anti which gives an exchange-broadened signal. However, as data presented below will show, C–C rotation (k_{cc}, eq 2) may be slow even at 56.6° (Figure 1). Thus, the syn:anti ratio observed (Figure 1) may be kinetically controlled (eq 1) and not represent an equilibrated system.

A series of theoretical dnmr spectra were generated[2] using a model incorporating different rates of NMe_2 rotation in syn and anti isomers with *no C–C rotation* (k_{cc} = 0, eq 2). As illustrated in Figure 1, excellent fits of experimental to theoretical spectra were obtained. Introduction of a small amount of syn $\leftrightarrows$ anti equilibration in the temperature range from -20 to 30° produced theoretical spectra which deviated significantly from experimental. The unfortunate near coincidence of the time-averaged NMe_2 resonances due to the two isomers precludes extraction of any meaningful information regarding C–C rotation from the dnmr spectra above 30°. However, the necessity of employing a constant syn:anti ratio (30:70) in generating the theoretical spectra from -20 to 30° when one might expect a variation for a system in equilibrium also speaks against fast C–C rotation at least to ~50°. From the complete line shape analysis (Figure 1), activation parameters were derived for NMe_2 rotation in the syn isomer ($\Delta H^{\ddagger}$ = 15.2 ± 0.6 kcal/mol, $\Delta S^{\ddagger}$ = 2 ± 2 gibbs, $\Delta G^{\ddagger}$ = 14.6 ± 0.1 kcal/mol at 0.8°) and for the anti ($\Delta H^{\ddagger}$ = 12.9 ± 0.6 kcal/mol, $\Delta S^{\ddagger}$ = -1 ± 2 gibbs, $\Delta G^{\ddagger}$ = 13.1 ± 0.1 kcal/mol at $-17°$). The higher barrier to NMe_2 rotation for the syn isomer seems reasonable in light of increased nonbonded repulsions involving the other adjacent large NMe_2 group in the transition state as compared to the carbonyl moiety in the anti form.

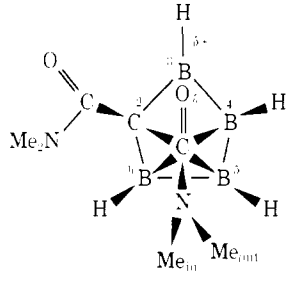
Subsequent examination of the ^{1}H dnmr spectra of the *m*-carborane derivative 1,7-bis(*N*,*N*-dimethylcarbamoyl)-1,7-dicarba-*closo*-dodecaborane(12) (**2**) (0.1 *M* in $CHCl_3$) revealed a singlet NMe_2 resonance at room temperature which separated at lower temperatures into just two singlets of equal area (δ 2.96, 3.24) consistent with slowing NMe_2 rotation ($\Delta H^{\ddagger}$ = 13.8 ± 0.6 kcal/mol, $\Delta S^{\ddagger}$ = 4 ± 2 gibbs, $\Delta G^{\ddagger}$ = 12.8 ± 0.1 kcal/mol at $-17°$). Although many different rotational isomers are possible in **2**, no evidence for different NMe_2 rotational barriers is observed consistent with eliminating the complicating steric interactions in **1**. Indeed, the barrier to NMe_2 rotation in **2** is very similar to that for the anti isomer of **1** in which steric crowding between NMe_2 groups is relieved.

It is important to note that the barriers to NMe_2 rotation in **1** and **2** are substantially lower than those in normal amides, *e.g.*, *N*,*N*-dimethylacetamide ($\Delta H^{\ddagger}$ = 19.0 kcal/mol, $\Delta S^{\ddagger}$ = 2.7 gibbs),[3] attesting to the ability of the *o*- and *m*-carborane cages to compete effectively with the carbamoyl nitrogen for π-bonding to the carbonyl carbon. Such π-bonding will reduce the carbonyl carbon–nitrogen bond order as compared to an amide and reduce the NMe_2 rotational barrier.[4]

(2) D. A. Kleier and G. Binsch, *J. Magn. Resonance*, **3**, 146 (1970).
(3) R. C. Newman, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968).
(4) C. H. Bushweller, P. E. Stevenson, J. Golini, and J. W. O'Neil, *J. Phys. Chem.*, **74**, 1155 (1970).

The propensity of the carborane cages to π-bond and delocalize electron density from the *N,N*-dimethylcarbamoyl group could be considered a measure of the aromaticity of the carborane cage. Since the phenyl ring is now firmly established as a highly aromatic system, a comparison of the barriers to NMe_2 rotation in **1** and **2** to that in *N,N*-dimethylbenzamide ($\Delta H^{\ddagger} \sim$ 15 kcal/mol)[5] reveals the carborane cages to be highly aromatic systems or efficient electron "sinks." Indeed, the low potential barriers to NMe_2 rotation in **2** or the anti form of **1** seem to suggest that the carborane cage is "superaromatic." Since all of the cage boron–carbon and carbon–carbon bonds may π-bond to the carbonyl carbon in **1** or **2**, there may be no directional requirements for optimizing π-overlap, and electron delocalization is apparently very efficient. This is, of course, in contrast to *N,N*-dimethylbenzamide in which the p orbital of the carbonyl carbon is restricted to essentially one orientation for maximized π-bonding to the phenyl system.

The origin of the apparent high barrier to C–C rotation (k_{cc}, eq 2) in **1** is intriguing in light of the probable nondirectional π-bonding properties of the *o*-carborane cage which obviously would not provide a hindering potential to C–C rotation. However, examination of a projection looking down the carbonyl carbon–carborane carbon bond of the essentially planar carbamoyl group on C1 reveals the sterically most favorable conformation to be that in which the plane of the NMe_2 group bisects the angle defined by the two B–H bonds at B5 and B6 (**3**). This conformation



3

places one NMe group closer to the cage (Me_{in}, **3**) than the other introducing the possibility of significant repulsions between Me_{in} and the hydrogen atoms on B5 and B6. Another consequence of adopting conformation **3** is the placing of the *partially negatively charged* carbonyl oxygen at a distance of closest approach to the *partially positively charged* B(3)–H group[6] introducing a stabilization due to electrostatic attraction. The apparently lower stability of the syn form of **1** may be due in part to the fact that two carbonyl oxygens in a syn form must compete for the positive charge on B3 (or B6) compared to one in an anti form. Although an incisive depiction of the origin of the high barrier to C–C rotation cannot be given, it is apparent that steric effects involving proximate carbamoyl groups and cage hydrogens as well as electrostatic considerations are important.

(5) F. G. Riddell and D. A. R. Williams, *J. Chem. Soc., Perkin Trans. 2*, 587 (1973).

(6) R. Hoffman and W. N. Lipscomb, *J. Chem. Phys.*, **36**, 3489 (1962); J. A. Potenza and W. N. Lipscomb, *Inorg. Chem.*, **5**, 1471 (1966); M. D. Newton, F. P. Boer, and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **88**, 2353 (1966).

We are investigating the dnmr spectra and X-ray crystal structures of a number of other *o*- and *m*-carborane derivatives in order to elucidate the roles of the carborane cage in affecting substituent conformational dynamics and preferences.

Acknowledgment. We are grateful to the National Science Foundation (Grant No. GP-18197) and the National Cancer Institute (Grant No. 5R01 CA 12025-02) for support, to Dr. P. E. Stevenson for helpful discussions, and to Olin Mathieson Chemical Corporation for a supply of *o*- and *m*-carborane.

(7) Alfred P. Sloan Research Fellow, 1971–1974; Camille and Henry Dreyfus Teacher–Scholar, 1972–present.

C. Hackett Bushweller,*[7] Chih Y. Wang, William J. Dewkett Warren G. Anderson, Stuart A. Daniels, Herbert Beall

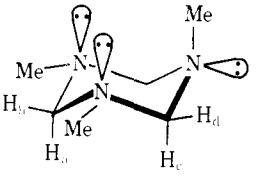
Department of Chemistry, Worcester Polytechnic Institute Worcester, Massachusetts 01609

Received August 30, 1973

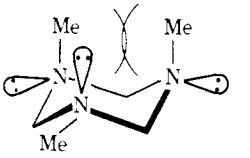
Stereodynamics of Multinitrogen Heterocycles. I. Direct Observation of Nitrogen Inversion and Axial *N*-Methyl Groups in *N,N',N''*-Trimethyl-1,3,5-triazane

Sir:

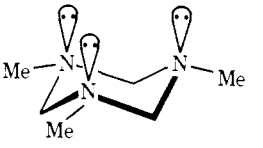
Recent conformational investigations of six-membered heterocyclic compounds have revealed significant deviations in both substituent[1a–c] and ring[1d] conformational biasing as compared to cyclohexane analogs.[2] In a variety of *N,N'*-dimethyl-1,3-diazanes, trends in time-averaged (ring reversal and/or nitrogen inversion) nmr data indicate a significant population of the chair conformer having an axial *N*-methyl group.[1a] However, the indirect nature of these measurements precluded a quantitative measure of axial *N*-methyl populations. Dipole moment studies of *N,N',N''*-triethyl-1,3,5-triazane and *N,N',N''*-trimethyl-1,3,5-triazane (**1**) indicated the unusual result that in the presumed chair form of the six-ring the monoaxial (**2**) and diaxial (**3**) *N*-methyl conformers are present in *equal* amounts with very little of the triequatorial form (**4**) present.[1c] The existence of a nontrivial concen-



2



3



4

tration of axial *N*-methyl substituents in ring systems having nitrogen atoms 1,3 to each other is apparently a

(1) (a) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968); E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *Tetrahedron Lett.*, 3409 (1971); (b) J. E. Anderson and J. D. Roberts, *J. Amer. Chem. Soc.*, **90**, 4186 (1968); (c) R. A. Y. Jones, A. R. Katritsky, and M. Snarey, *J. Chem. Soc. B*, 135 (1970); (d) C. H. Bushweller, G. U. Rao, and F. H. Bissett, *J. Amer. Chem. Soc.*, **93**, 3058 (1971), and references therein.

(2) F. R. Jensen and C. H. Bushweller, *Advan. Alicyclic Chem.*, **3**, 140 (1971), and references therein.