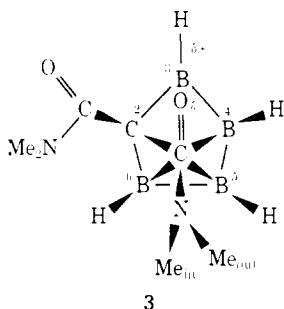


The propensity of the carborane cages to π -bond and delocalize electron density from the *N,N*-dimethylcarbamoyl group could be considered a measure of the aromaticity of the carborane cage. Since the phenyl ring is now firmly established as a highly aromatic system, a comparison of the barriers to 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_{rot} , 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



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 group⁶ 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.

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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.

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

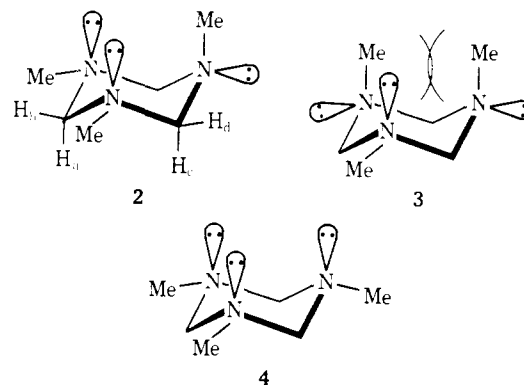
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Stereodynamics of Multinitrogen Heterocycles. I. Direct Observation of Nitrogen Inversion and Axial *N*-Methyl Groups in *N,N',N''*-Trimethyl-1,3,5-triazane

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-



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.

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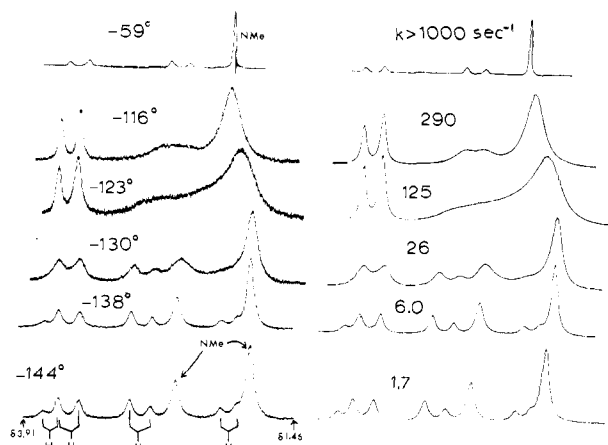


Figure 1. The experimental ^1H dnmr spectra (60 MHz) of N,N',N'' -trimethyl-1,3,5-triazine (**1**, 5% v/v in CH_2CHCl_3) and theoretical spectra calculated as a function of the rate of nitrogen inversion. The various peak assignments at -144° are made with reference to conformer **2**.

general phenomenon and reflects a unique combination of a variety of nonbonded attractions and repulsions.^{1a,3}

This report concerns an ^1H dnmr study of **1** giving direct evidence for a strong preference for conformation **2** and what we believe to be the first unambiguous measurement of the barrier to nitrogen inversion in a six-ring conformation in which nitrogen inversion is free of all rate-retarding factors except the energy required to rehybridize nitrogen to a planar transition state and angle strain associated with the six-ring formation in the transition state.

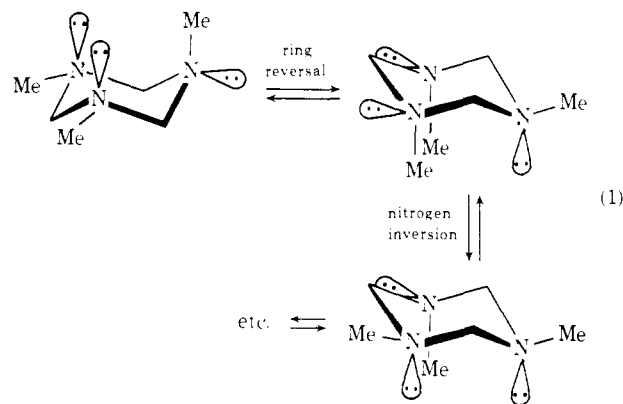
At room temperature, the ^1H dnmr spectrum of **1** in CCl_4 consists of two singlet resonances for the methylene (6 H, δ 3.05) and methyl groups (9 H, δ 2.18) consistent with rapid ring reversal and nitrogen inversion.⁴ However, examination of the ^1H dnmr spectrum (60 MHz) of **1** (5% v/v in CH_2CHCl_3) at -59° (Figure 1) reveals a single AB spectrum (δ 3.55, 2.68; $J_{\text{AB}} = -10.3$ Hz; NCH_2) and a singlet resonance (δ 2.19, NCH_3) consistent with *slow ring reversal* on the dnmr time scale ($\Delta H^\ddagger = 15.2 \pm 0.2$ kcal/mol, $\Delta S^\ddagger = 7.5$ gibbs, $\Delta G^\ddagger = 13.2 \pm 0.2$ at -5°)⁴ and *fast nitrogen inversion*. However, below -100° (Figure 1), complex changes in the spectrum occur consistent with slowing *nitrogen inversion*. Under conditions of slow exchange (-144° , Figure 1) the complete spectrum of **1** consists of two superimposed AB spectra (δ 3.65, 2.13; $J_{\text{AB}} = -7.9$ Hz; 2 H and δ 3.49, 2.90; $J_{\text{AB}} = -10.7$ Hz; 4 H) and two methyl resonances at δ 2.58 (3 H) and 1.94 (6 H). The observed spectrum of **1** at -144° is best rationalized in terms of a strong if not exclusive preference for conformer **2**. The significantly upfield component of the smaller AB spectrum at δ 2.13 is assigned to H_a of **2** based on the established anisotropic effect of a nitrogen lone pair trans to a proton.⁵ Indeed, H_a experiences the combined effect of *two* trans lone pairs. The component of the larger AB spectrum at δ 2.90 is assigned to the two H_c protons of **2** consistent with

the attenuated effect of *one* trans lone pair. In line with this analysis, the smaller NCH_3 resonance at δ 2.58 is assigned to the axial NCH_3 of **2** and that at δ 1.94 to the two equatorial NCH_3 groups. Any significant concentration of **3** or **4** would be expected to alter the relative intensities of the various resonances from the observed values.

The above results are in obvious contrast to the dipole moment data which indicate equal populations for **2** and **3**.^{1c} Indeed, it is apparent that the serious syn-axial methyl-methyl repulsion in **3** predominates over other stabilizing interactions such as relief of apparent syn-axial lone pair-lone pair repulsions.

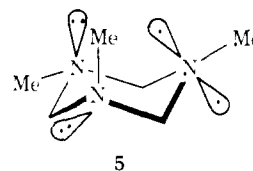
A total dnmr line shape analysis, using as a kinetic model interconversion between **2** and its two equivalent conformers (Figure 1), gave the following activation parameters:⁶ $\Delta H^\ddagger = 7.6 \pm 0.4$ kcal/mol, $\Delta S^\ddagger = 3 \pm 2$ gibbs, $\Delta G^\ddagger = 7.2 \pm 0.1$ kcal/mol at -122.5° . These activation parameters for nitrogen inversion in the six-ring formation are in good agreement with a previous prediction based on interpolation between the barriers in *N*-methylpyrrolidine (8 kcal/mol) and *N*-methylhomopiperidine (7 kcal/mol).⁷

Having established **2** and its two equivalent forms as the most stable conformations for **1**, it is possible to envisage a plausible itinerary for ring reversal in **1**. Ring reversal starting from a monoaxial form could proceed to give a diaxial form as an *unstable intermediate* (eq 1) and subsequent facile inversion at one of



the nitrogens bearing an axial methyl group would give another stable monoaxial form.

A reasonable itinerary for simple nitrogen inversion in the event of no ring reversal in **1** (*i.e.*, below -100°) involves inversion of *one nitrogen at a time* via a planar nitrogen transition state (*e.g.*, **5**) to unstable diaxial



(6) The dnmr line shape program used is DNMR3 by D. A. Kleier, G. Binsch, A. Steigel, and J. Sauer, *J. Amer. Chem. Soc.*, **92**, 3787 (1970); Program 165, Quantum Chemistry Program Exchange, Indiana University, 1969. The program has been modified locally to provide the capability of automatically superimposing two separate and distinct spin systems both subject to dynamical effects.

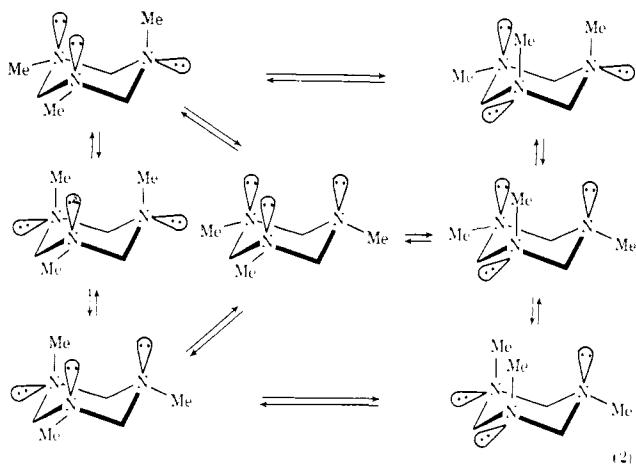
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or triequatorial intermediates which then invert at *one* nitrogen to give stable monoaxial forms (eq 2). Simul-



taneous inversion at two or three nitrogens is not statistically likely. Indeed, to invert *two* nitrogens simultaneously would require an increase in potential energy due to rehybridization at least twice the barrier to nitrogen inversion for a simple unconstrained acyclic trialkylamine (e.g., dibenzylmethylamine, $\Delta H^\ddagger = 7.2 \pm 0.4$ kcal/mol)⁸ or about 14 kcal/mol *in addition* to the angle strain associated with the six-ring formation in the transition state. Such a high barrier is clearly not consistent with the nitrogen inversion data presented here.

Although ring reversal had been observed previously,⁹ the same general type of dnmr spectral changes as seen in **1** were observed for the CH_2 resonance of *N,N',N''*-tri-*tert*-butyl-1,3,5-triazane (**6**, 5% v/v in CH_2CHCl) at substantially lower temperatures (-140 to -160°) than for **1** consistent with slowing nitrogen inversion and a significant population of axial *N-tert*-butyl.¹⁰ The *N-tert*-butyl resonance of **6** also changed in a complex fashion consistent with slowing both nitrogen inversion and *tert*-butyl rotation. The broad dnmr lines observed for **6** at low temperatures and the apparent inability to reach slow exchange conditions precluded an accurate measure of axial *N-tert*-butyl population. Other effective solvent systems are being sought.

Acknowledgment. We are grateful to the National Science Foundation (Grant No. GP-18197) for support.

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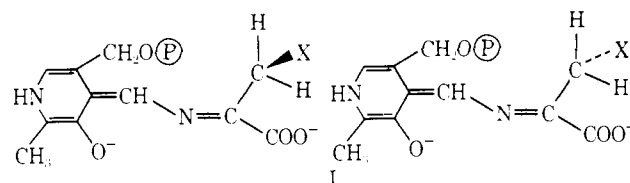
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Stereochemistry of the Tryptophan Synthetase Reaction

Sir:

We wish to report on the determination of the steric course of the tryptophan synthetase-catalyzed sub-

stitution reaction at C-3 of serine. Tryptophan synthetase (E.C. 4.2.1.20)¹ belongs to a group of pyridoxal phosphate-containing enzymes, which catalyze nucleophilic β -substitution reactions and/or α,β -elimination reactions of certain amino acids. These reactions are thought² to proceed *via* a ketimine intermediate (**I**) which then undergoes elimination of the electronegative β -substituent to give an enzyme-bound α -aminoacrylate-pyridoxal phosphate Schiff base. Addition of a new nucleophilic substituent at the β -carbon followed by reversal of the process constitutes the enzymatic substitution reaction, whereas hydrolysis of the Schiff base ultimately leads to pyruvate and ammonia (α,β -elimination reaction). In the removal and addition of the β -substituent, orientation of both these ligands perpendicular to the plane of the π system is required in order to optimize interaction of the electron pair of the σ -bond to be broken or formed with the electrons of the extended π system. Thus, reaction should only be possible in the two conformations shown.



The incoming and the outgoing substituent can orient either on opposite faces of the double bond plane, resulting in reaction with inversion of configuration at C-3 of the amino acid, or on the same face, leading to retention of configuration. In the latter case the reaction must either proceed by a ping-pong mechanism⁸ or it must involve a significant conformational change of the enzyme as part of the catalytic process. As a variation of this mechanism, Braunstein⁴ has suggested that the replacement of the hydroxyl group of serine by indole in the tryptophan synthetase reaction involves an $\text{S}_{\text{N}}2$ process, which of necessity would result in inversion of configuration.

To study this question (2*S*,3*R*)- and (2*S*,3*S*)-3-phosphoglyceric-3-*t* acid (specific activity $>100 \mu\text{Ci}/\mu\text{mol}$), available from earlier work,⁵ were converted into phosphoserines using an enzyme preparation from *E. coli* and essentially the conditions given by Pizer.⁶ The phosphoserines were hydrolyzed with alkaline phosphatase directly in the reaction mixture and the serine samples were isolated by adsorption on Dowex 50 H^+ and elution with 1.5 *M* NH_4OH and purified by paper chromatography in *n*-butyl alcohol:acetic acid:water (35:10:25) (yields 30–50%). They were then mixed with L-serine- $U\text{-}^{14}\text{C}$ to give T/ ^{14}C ratios of 3.70 and 3.31 (3*R* and 3*S* isomer, respectively) and incubated with purified native tryptophan synthetase from *N. crassa*.⁷ Indole was used as the second substrate,

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