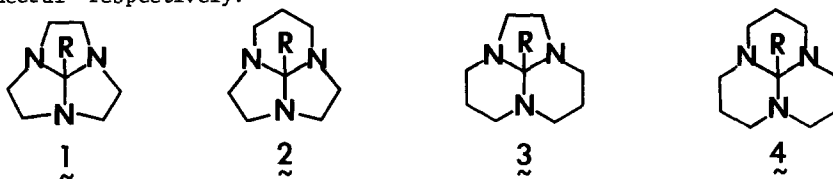


TRICYCLIC ORTHOACETAMIDES AND ORTHOPROPIONAMIDES: CONFORMATIONAL  
 ANALYSIS AND STEREOCHEMICAL EFFECTS UPON  $^{13}\text{C}$  NMR SPECTRA

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**Abstract:** A novel series of tricyclic orthoacetamides and orthopropionamides has been prepared. A dramatic dependence of  $^{13}\text{C}$  shifts upon stereochemistry is reported.

Communications by our group<sup>1</sup> and others<sup>2,3</sup> concerning novel orthoamides 1a - 4a have recently appeared in the literature. We now wish to report preparation of the methyl (1b - 4b) and ethyl (1c - 4c) homologs of this series.<sup>4</sup> These new compounds, which represent the first authentic examples of 1,1,1-triaminoethanes (orthoacetamides)<sup>5,6</sup> and 1,1,1-triaminopropanes (orthopropionamides), were prepared by condensations of macrocyclic triamines with N,N-dimethylacetamide dimethylacetal<sup>7</sup> and N,N-dimethylpropionamide dimethylacetal<sup>7</sup> respectively.

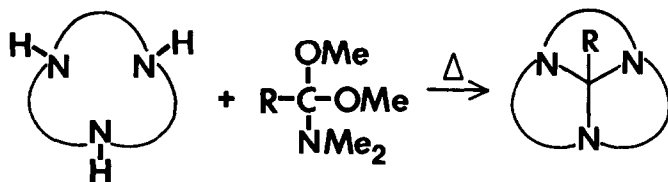


a: R = H;

b: R = CH<sub>3</sub>;

c: R = C<sub>2</sub>H<sub>5</sub>

Products were purified by Kugelrohr distillation, gas chromatography (15% carbowax 20M, 5% KOH on Chrom W), column chromatography (basic alumina, CH<sub>2</sub>Cl<sub>2</sub>/ethanol) or sublimation. Assigned structures were confirmed by high resolution mass spectra and/or CHN analyses and are consistent with all spectral data.



| Product  | Yield (%) |    |
|----------|-----------|----|
|          | b         | c  |
| <u>1</u> | 82        | 53 |
| <u>2</u> | 85        | 43 |
| <u>3</u> | 81        | 82 |
| <u>4</u> | 89        | 65 |

$^{13}\text{C}$  NMR data for the new compounds are presented in Tables 1 and 2.

Table 1: Orthoacetamides:  $^{13}\text{C}$  NMR ( $\delta_{\text{c}}$ ,  $\text{CDCl}_3$ ).

| Compound               | $\begin{array}{c} \text{N} \\ \diagup \\ \text{N}-\text{C}-\text{N} \\ \diagdown \\ \text{CH}_3 \end{array}$ | $\text{CH}_2-\text{N}$ | $\text{CH}_2-\text{CH}_2-\text{CH}_2$ | $\text{C}-\text{CH}_3$ |
|------------------------|--|------------------------|---------------------------------------|------------------------|
| <u>1b</u>              | 111.4  | 51.8                   | -----                                 | 27.7                   |
| <u>2b</u>              | 94.7   | 54.9, 51.9             | 13.1                                  | 23.8                   |
|                        |  | 44.6                   |                                       |                        |
| <u>3b</u>              | 86.9   | 49.4, 45.6             | 20.1                                  | 10.0                   |
|                        |  | 43.7                   |                                       |                        |
| <u>4b</u> <sup>a</sup> | 86.0   | 49.0                   | 24.6                                  | -4.0                   |
| <u>4b</u> <sup>b</sup> | 85.9   | 48.7(br)               | 24.7(br)                              | -6.6(br)               |

a. T = 302°K;

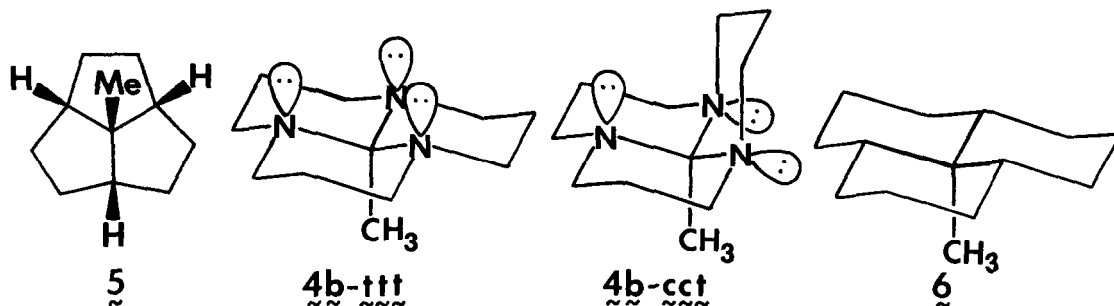
b. T = 206°K

Table 2: Orthopropionamides:  $^{13}\text{C}$  NMR ( $\delta_{\text{c}}$ ,  $\text{CDCl}_3$ ).

| Compound               | $\begin{array}{c} \text{N} \\ \diagup \\ \text{N}-\text{C}-\text{N} \\ \diagdown \\ \text{CH}_2 \end{array}$ | $\text{CH}_2-\text{N}$ | $\text{CH}_2-\text{CH}_2-\text{CH}_2$ | $\text{CH}_2-\text{CH}_3$ | $\text{CH}_2\text{CH}_3$ |
|------------------------|--|------------------------|---------------------------------------|---------------------------|--------------------------|
| <u>1c</u>              | 113.8  | 51.9                   | -----                                 | 33.6                      | 9.6                      |
| <u>2c</u>              | 97.0   | 55.8, 52.1             | 12.5                                  | 28.2                      | 9.8                      |
|                        |  | 44.7                   |                                       |                           |                          |
| <u>3c</u>              | 88.8   | 48.9, 45.6             | 19.8                                  | 11.4                      | 7.4                      |
|                        |  | 43.3                   |                                       |                           |                          |
| <u>4c</u> <sup>a</sup> | 87.1   | 49.1                   | 22.3                                  | 13.0                      | 7.9                      |
| <u>4c</u> <sup>b</sup> | 86.5   | 51.0, 48.4             | 26.3, 19.6                            | 12.9                      | 8.2                      |
|                        |  | 46.5                   |                                       |                           |                          |

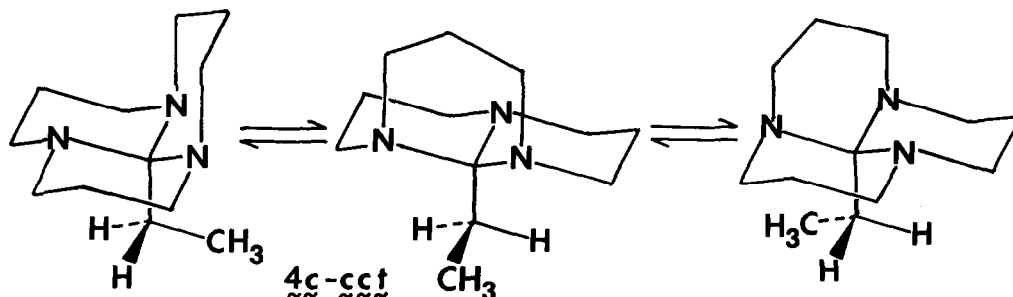
a. T = 302°K (acetone- $\text{d}_6$ );b. T = 193°K (acetone- $\text{d}_6$ )

Attention is called to the large range of methyl carbon chemical shifts in the ortho-acetamide series ( $\Delta\delta_{\text{c}} = 31.7$  ppm, amb. T). In analogy with 1a<sup>1</sup> and on the basis of empirical force field calculations (MM2<sup>8</sup>), 1b is assigned a slightly twisted ( $\text{C}_3$ ) all-cis configuration such that all three nitrogen lone-pairs are approximately syn to the central C- $\text{CH}_3$  bond.  $\delta_{\text{c}}$ (methyl) of model hydrocarbon 5 has been reported to be 28.4 ppm<sup>9</sup>, in close agreement with the value for 1b. The remarkably high field (-4.0 ppm) methyl resonance of 4b indicates the predominance of sterically compressed ( $\text{C}_{3v}$ ) all-trans configuration 4b-ttt, in which the methyl carbon is gauche to six methylene carbons.  $\delta_{\text{c}}$ (methyl) of model hydrocarbon 6 is calculated to be + 6.8 ppm<sup>10</sup> however, so lone-pair orientation effects or increased steric compression (due to the shorter C-N bonds) must be invoked to explain the additional upfield shift of the 4b methyl resonance. Several reports have documented that carbons antiperiplanar to nitrogen lone-pairs in amines<sup>11-13</sup>, aziridines<sup>14</sup>, oxaziridines<sup>15</sup>, and oximes<sup>16</sup> resonate upfield of carbons which are gauche or syn to nitrogen lone-pairs. The origin of the effect is presumably a net-stabilizing (hyperconjugative) overlap between the lone-pair orbital and the anti  $\sigma_{\text{C-C}}^*$  orbital. Thus, the methyl group of 4b-ttt, which is antiperiplanar to three lone-pairs, is expected to experience a large effect analogous to the reported effect upon the methine  $^1\text{H}$  resonance of 4a<sup>1,2</sup>.



The dynamic  $^{13}\text{C}$  NMR behavior of  $4b$  is also consistent with the predominance of  $4b\text{-}t\bar{t}\bar{t}$  over ( $C_s$ ) cis, cis, trans configuration  $4b\text{-}c\bar{c}\bar{t}$ . At temperatures below ambient, as exchange was slowed, the methyl signal (as well as the other signals) broadened and then began to resharpen at lower temperatures, the shift changing from  $-4.0$  ppm to  $-6.6$  ppm during the process. This latter value represents the  $\delta_c(\text{methyl})$  of  $4b\text{-}t\bar{t}\bar{t}$ . No peaks attributable to  $4b\text{-}c\bar{c}\bar{t}$  were observed at the lowest attainable temperature (in  $\text{CDCl}_3$ ). However, the slow exchange limit had not been achieved so peaks due to the minor configuration may still have been broadened into the baseline. Chemical shift interpolation based upon an estimated<sup>10,12</sup>  $\delta_c(\text{methyl})$  of  $12.4$  ppm for  $4b\text{-}c\bar{c}\bar{t}$  yields 14%  $c\bar{c}\bar{t}$  at  $302^\circ\text{K}$ . Since  $\Delta S_{\text{on}}(4b\text{-}c\bar{c}\bar{t}\text{-}4b\text{-}t\bar{t}\bar{t})$ , the trivial entropy contribution due to symmetry number, is  $2.18$  cal/mole·deg, it is expected that  $4b\text{-}c\bar{c}\bar{t}$  should amount to only ca. 4% of the equilibrium mixture at  $206^\circ\text{K}$ .

Orthopropionamide  $4c$  is unambiguously assigned the ( $C_s$ ) cis, cis, trans configuration on the basis of low temperature  $^{13}\text{C}$  NMR spectra (see Table 2). The molecule undergoes a degenerate dynamic equilibrium (below) which yields  $^{13}\text{C}$  spectra indicative of average  $C_{3v}$  symmetry at higher temperatures. Complete lineshape analysis<sup>17</sup> of the coalescence of the  $\text{CH}_2\text{-N}$  resonances gives  $\Delta G^\ddagger = 11.76 \pm 0.2$  kcal/mole ( $233^\circ\text{K}$ ; acetone- $d_6$ ) for this interesting process, which necessarily involves nitrogen inversions and concomitant torsions.



Detailed conformational analyses and the unusual properties and reactivities of these compounds will be presented in future publications.

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