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TRICYCLIC ORTHOAMIDES: EFFECTS OF LONE-PAIR ORIENTATION UPON NMR SPECTRA

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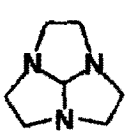
Abstract: A series of novel tricyclic orthoamides has been synthesized. The stereochemical dependence of methine ^{1}H chemical shifts and $^{1}J_{CH}$ are reported.

The stereochemistry and conformational analysis of polycyclic polyamines with bridgehead nitrogens continue to be areas of active research[1-3]. Our interest in the field led us to prepare a series of tricyclic orthoformamides, 1-4, whose ^{1}H and ^{13}C NMR spectra exhibit dramatic stereochemical dependence. Recent preliminary reports by Atkins[4,5] on members of this series prompt our communication.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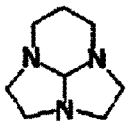
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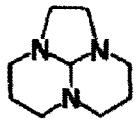
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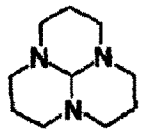
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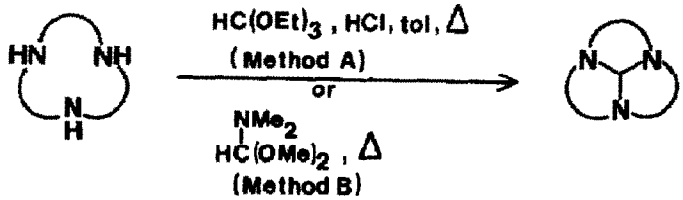
Syntheses of the orthoamides were accomplished either via acid-catalyzed condensation of the corresponding macrocyclic triamines[6] with triethylorthoformate in toluene (Method A)[7] or by uncatalyzed condensation with neat dimethylformamide dimethylacetal (Method B)[4]. Yields were considerably better with the latter, more reactive reagent[8] but no attempts at optimization have been made to date. 1-4 could be purified by Kugelrohr distillation and gas chromatography (15% Carbowax 20 M, 5% KOH on Chrom W). Mass spectra of the orthoamides all exhibit strong molecular ions and the proposed structures are consistent with all other spectral data as discussed below.



Product	Yield (%) Method A	Method B
1	9	25
2	-	85*
3	38	68
4	-	36

*200 mg scale; all others 50 mg scale

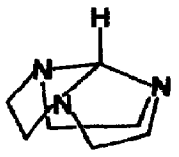
NMR data for 1–4 are listed in Table 1. The most striking feature of the ^{1}H data is the large (2.71 ppm) variation in δmethine, which can be attributed to changes in the dihedral angles between the methine hydrogen and nitrogen lone pairs through the series. The dependence of ^{1}H chemical shift upon stereochemical orientation of adjacent nitrogen is well documented for six-membered[9], five-membered[10], and three-membered rings[11]. Generally protons anti-periplanar to a lone pair resonate upfield of those gauche or syn to a lone pair[12]. The effect is generally held to be attributable to a combination of $n-\sigma^*_{CH}$ interaction (lone pair effect) and C-C and C-H magnetic anisotropies (alkyl effect), although the relative importance of these factors is still a matter of some controversy[9,11,13].

Table 1

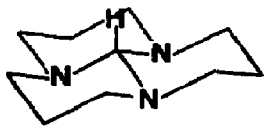
		^{13}C NMR (δ_C, $CDCl_3$)			
Product	60MHz ^{1}H NMR (δ, $CDCl_3$)	N–CH–N	$-CH_2-N$	$-CH_2-CH_2-CH_2-$	$^1J_{CH}$(methine)(Hz)
1	2.5-3.35(AA'BB',12H) 5.03 (s,1H,methine)	104.1	52.0	---------	184 ± 1
2	1.05 (d of quintets, J=13;3Hz,1H) ca. 1.5-2.3(m,1H) ca. 2.2-3.7(m,12H) 4.32 (s, 1H, methine)	93.3	45.9, 49.0 56.2	16.5	169 ± 1
3	1.1-3.37 (m)‡	96.6	47.7, 48.9 51.8	23.6	140 ± 3
4	1.22-1.49 (m,3H)* 1.58-2.22 (m,9H) 2.25 (s,1H,methine) 2.61-2.90 (m,6H)	100.0	53.9	24.2	141 ± 3

‡Neither 60 MHz nor 90 MHz spectra permitted assignment of the methine
*90 MHz, acetone-d_6; δ(methine) in $CDCl_3$ = 2.32

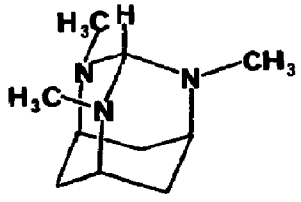
We assign configurations 1a (all cis) and 4a (all trans) to 1 and 4 respectively. The methine hydrogen is approximately syn to all three lone pairs in 1a but anti-periplanar to all three in 4a. Δδ (syn-anti) therefore amounts to 0.9 ppm per nitrogen. It is interesting that the reported δmethine (3.67 ppm) for 5, in which all three lone pairs are held gauche to the methine hydrogen, is almost exactly intermediate between the values for 1 and 4[14].



1a

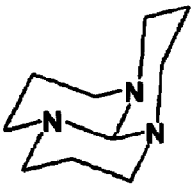


4a

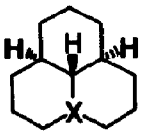


5

Stereochemical assignment of 1 as 1a is supported by the absence of Bohlmann bands[14] in the IR. 2, 3, and 4 all exhibit strong absorptions in the 2700-2800 cm^{-1} region. Assignment of 4 as 4a (as opposed to 4b) is supported by comparison of the ^{13}C chemical shifts with those of model compounds 6[15] and 7[16] and by the absence of conformational broadening in the ^{13}C spectrum down to -100°C.



4b



6 : X = CH

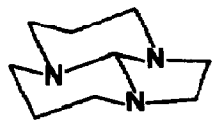
7 : X = N

The very substantial difference in $^{1}J_{CH}$(methine) (~43 Hz) between 1 and 4 provides the most dramatic example of the effect of adjacent lone pair orientation on $^{1}J_{CH}$ to date and further substantiates our configurational assignments[17-19]. The (syn-anti) difference is in the direction theoretically predicted[20] and equal in magnitude (+14 Hz per nitrogen) to that observed in oximes[17]. Work is in progress to further document $^{1}J_{CH}$ stereochemical dependence in orthoamides and aminals.

In light of our interpretations for 1 and 4, the data for 2 and 3 are most consistent with 2a and 3a respectively. While 2b must be considered a viable alternative to 2a, ^{13}C chemical shifts and lack of dynamic broadening of ^{13}C resonances at -100°C point to the sterically compressed 2a. This aspect will be more fully discussed in the full paper.

2a

2b



3a

ACKNOWLEDGMENT

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