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An Acyclic Trialkylamine Virtually Planar at Nitrogen. Some Chemical Consequences of Nitrogen Planarity

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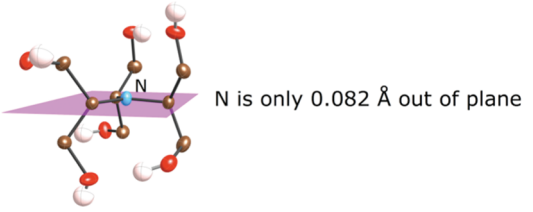
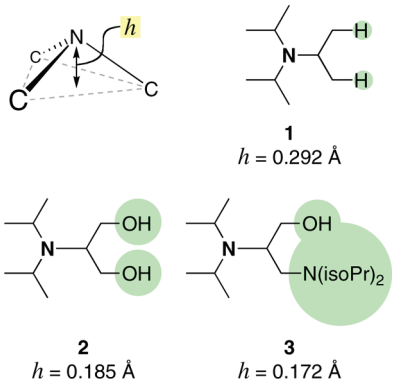


The synthesis of the exceedingly congested amine tris(1,3-dihydroxy-2-propyl)amine, **9**, was achieved in 47− 51% overall yield. The nitrogen atom of **9** is virtually planar; it is 0.082 Å out of the plane defined by the three attached carbons. The corresponding out-of-plane measurement is 0.282 Å for triisopropylamine and ca. 0.4 Å for uncongested trialkylamines. The N−C bonds of **9** are quite short, despite the steric congestion. The conjugate acid of **9** (viz., **9**H$^+$) is very strong: pK_a = 3.08 (cf. Et_3NH^+ pK_a = 10.7). Comparison with suitable model compounds suggests **9** is less basic than predicted by ca. 1.5 pK_a units. The structure of **9**H$^+$Cl$^-$ was determined by X-ray crystallography. Here too, the nitrogen is severely flattened relative to ordinary ammonium cations. In **9**H$^+$Cl$^-$, the proton on the nitrogen of **9**H$^+$ forms three intramolecular hydrogen bonds to hydroxyl groups, i.e., a so-called trifurcated hydrogen bond. The NH···O lengths in **9**H$^+$ are slightly shorter than comparable trifurcated hydrogen bonds. Cyclic voltammetry (CV) on **9** finds $E_{1/2}^{ox}$ is 0.88 V, which is consistent with the inductive effect of the 1,3-dihydroxy-2-propyl groups attached to nitrogen. It is also observed that the electrochemical oxidation of **9** is reversible on the CV time scale. The ^{15}N NMR chemical shift of the essentially planar nitrogen atom of **9** is discussed.

Introduction

Amines with planar nitrogens are, per se, neither rare nor intriguing. However, *trialkyl*amines, that is, those amines with nitrogen bonded to three tetrahedral carbon atoms, are rarely found to be planar at nitrogen; when they are, they arouse curiosity. Triisopropylamine, **1**, was thought for some time to be a simple trialkylamine that was planar at nitrogen.[1−3] However, when its X-ray crystal structure was obtained, **1** was found to be much flatter than an ordinary trialkylamine, but not planar.[4] (We will use the word "planar" henceforth as a shorthand for the phrase "planar at nitrogen"). The sum of C−N−C bond angles ($\Sigma\phi_{CNC}$) for a perfectly planar amine would be 360°. For **1**, $\Sigma\phi_{CNC}$ was 348.6° (T = 84 K).[4] Illustrated below is another measure of nitrogen planarity, which we shall call "h": it is the distance from nitrogen to the plane defined by the three carbon atoms to which it is bonded. For **1**, h is 0.292 Å (T = 84 K).[4] By comparison, an ordinary trialkylamine generally has h > 0.4 Å. For example, for $N(C_2H_5)_3$, h = 0.44 Å.[5]



It is not unreasonable to posit that **1** tends toward planarity in response to the steric demands of the bulky isopropyl groups. It also stands to reason that **2** should be

(1) Bock, H.; Goebel, I.; Havlas, Z.; Liedle, S.; Oberhammer, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 187–190.

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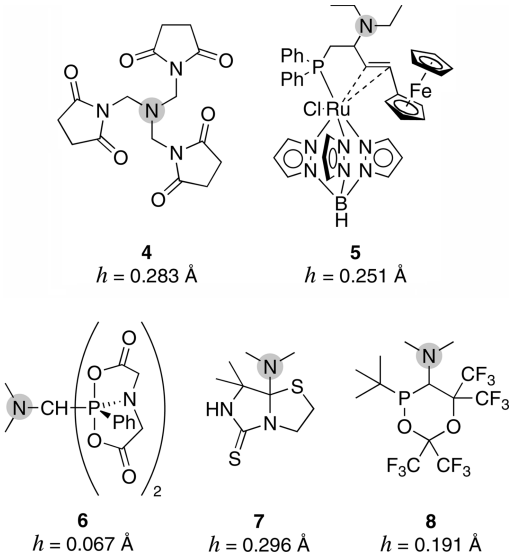
more planar than **1** (as it indeed is)[6] because two hydrogens of **1** are replaced by bulkier OH groups to give **2**. Replacing one OH group of **2** by a much bulkier diisopropylamino group[7] leads to **3**, which in turn ought to be much more planar than **2**. However, on going from **2** to **3**, the change in *h*, −0.013 Å, is insignificant.[6] Furthermore, there are examples of substantially planarized trialkylamines that do not appear to have enough substituents of adequate bulk to cause the observed planarity. Some examples of this, viz., **4**,[11] **5**,[12] **6**,[13] **7**,[14] and **8**,[15] are shown below. Therefore, one is led to a consideration of effects other than purely steric ones to account for structural trends in highly planar trialkylamines.



Our previous work with highly planar trialkylamines like **2**, **3**, and others led us to propose an electronic effect that qmay operate in concert with steric effects in determining the geometry at nitrogen in such cases.[6] Briefly, consider a *planar* amine, R_2N-CHA_2, where A stands for some single atom (e.g., Cl) or atom in a group (e.g., C in CH_3). An "orbital mixing diagram" for this molecule is shown in Figure 1. The interaction of the occupied nitrogen p-orbital with the unoccupied side chain 2a″ orbital is a stabilizing interaction that favors the planar form of the amine. As A is made more electronegative, the side chain orbitals move to lower energies while the nitrogen p-orbital does not, resulting in a smaller ΔE. This makes the interaction stronger and stabilizes the planar form still more.[16] For example, when A = Cl, the molecule is absolutely planar (*h* = 0.00 Å).[17]

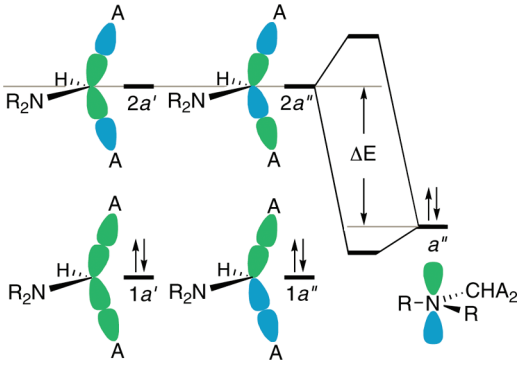


FIGURE 1. Orbital mixing diagram for planar R_2N-CHA_2. The π-type interaction shown stabilizes the planar geometry more effectively as ΔE decreases.

We report herein the synthesis of tris(1,3-dihydroxy-2-propyl)amine, **9**. The steric demands of three secondary alkyl groups bound to nitrogen[17] and the electronic effect (viz., Figure 1, A = CH_2OH) of three 1,3-dihydroxy-2-propyl groups should conspire to dramatically flatten the nitrogen atom of **9**.

Results and Discussion

Synthesis of 9. The synthesis of amine hexaalcohol **9** is shown in Scheme 1. According to a published procedure,[19] commercially available dihydroxyacetone dimer, **10**, was reductively aminated with NH_4Cl to give amine tetraalcohol **11**. In our hands, the yield of **11** was somewhat variable; in particular, the product of monoamination, 2-aminopropane-1,3-diol, **12**, was a stubborn contaminant.

The protection of **11** as the bis-acetonide **13** was reported by the same authors.[19] However, their yield of 74% of crude **13** ("sufficiently pure for further elaboration")[19] was higher than we obtained by following their procedure. Yields on our many attempts were scattered in the range of 30−70%. Further, the crude **13** obtained by the literature method gave poor results in the next reaction in our synthetic scheme, the insertion of the carbenoid derived from diazo diester **15** into the N−H bond of **13**, as will be discussed shortly. Purification of **13** according to the literature protocol engendered a large loss of material. We modified the procedure for

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(3) Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1996**, *61*, 1290–1296.
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(7) The conformational energy ("**A**-value") of the OH group is 0.60 kcal/mol (cyclohexane solvent),[8] 0.72 kcal/mol (acetone-d_6 solvent),[9] or 0.95 kcal/mol ($(CH_3)_2CHOH$ solvent),[8] whereas that of the NMe_2 group (a model for the $N(iPr)_2$ group) is 1.31 kcal/mol (toluene-d_8 solvent)[10] or 1.53 kcal/mol ($CFCl_3$−$CDCl_3$ solvent).[10]
(8) Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487–5495.
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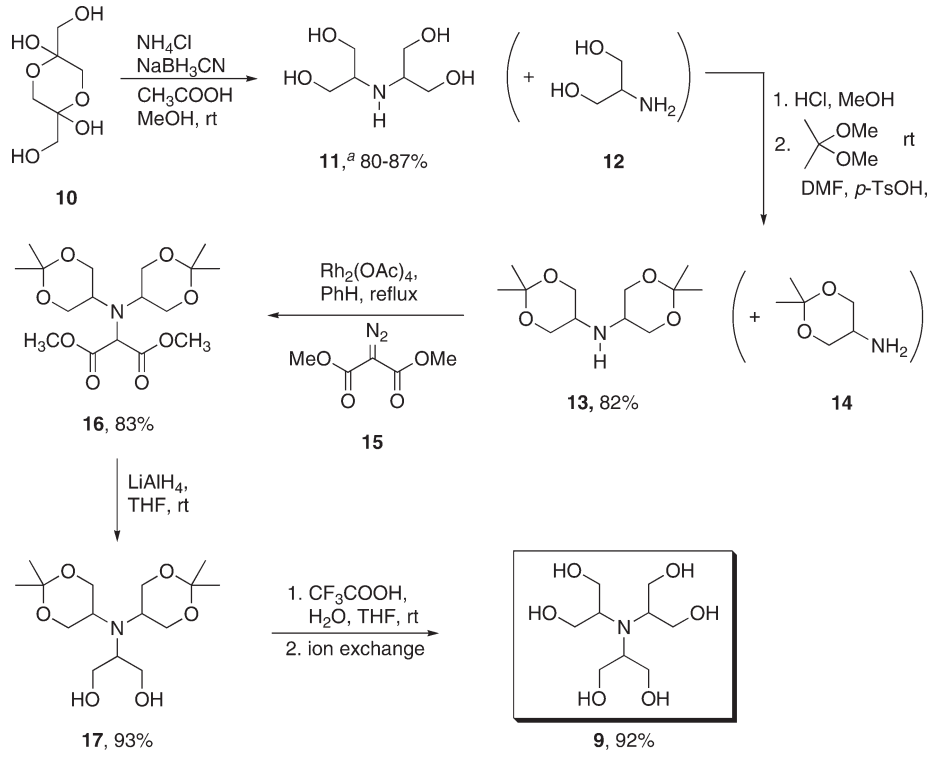
SCHEME 1. Synthesis of 9



[a]Reference 19.

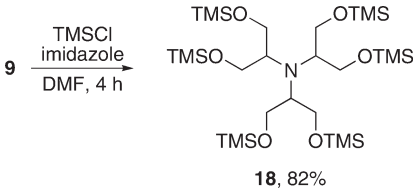
preparation of **13** by first preparing and isolating the hydrochloride salt of **11** and then using **11**·HCl in the reaction with 2,2-dimethoxypropane (DMP). We found that crystallization of the product from hexane was a satisfactory purification method; we obtained an 82% yield of **13**, pure enough to use in the carbenoid N−H insertion step.

In that regard, the $Rh_2(OAc)_4$ catalyst in the conversion of **13** to **16** is known to form strong complexes with Lewis bases (including some amines).[20] Such complexation would be expected to inhibit the reaction of the catalyst with dimethyl diazomalonate, **15** ("DDM"). In fact, Porter and co-workers found that the catalytic activity of $Rh_2(OAc)_4$ was strongly inhibited by primary amines.[21] Since empirically the outcome of the $Rh_2(OAc)_4$-catalyzed carbene N−H insertion reaction does depend on the purity of **13**, it seems reasonable to aver that purification of **13** removes 5-amino-2,2-dimethyl-1,3-dioxane, **14**, the primary amine formed by reaction of impurity **12** with DMP, and a compound capable of forming a strong complex with $Rh_2(OAc)_4$. An earlier report from our laboratory[22] reported a 71% yield of **16**, using 4 mol % of the catalyst. We report now, with proper attention to purification of **13**, an 83% yield of **16** using 2 mol % catalyst. Using a 20% excess of DDM brought the yield only to 84%. Using a 50% excess did not further improve the yield.

Reduction of **16** by means of $LiAlH_4$ (6:1 molar ratio of $LiAlH_4$ to **16**) produced **17** in 93% yield. Unreacted starting material could be recovered easily; the yield based on recovered starting material was 98%.

Removal of the acetonide functionalities of **17** was accomplished with trifluoroacetic acid in aqueous THF, as previous work in our laboratory showed that the use of aqueous HCl required long reaction times.[22] Conversion of $9H^+CF_3CO_2^-$ to the free base was accomplished using an ion-exchange resin. The overall yield of water-soluble **9** from dihydroxyacetone dimer was 47−51%, depending on the yield of the first step.

Compound **18**, the hexatrimethylsilyl ether derivative of **9** could be prepared easily in 82% yield.



Structure of 9. Figure 2 shows the structure of **9** derived from X-ray crystallography. There is an intricate hydrogen-bonding network. Every one of the six oxygen atoms of **9** is both a hydrogen-bond donor and a hydrogen-bond acceptor. Two hydrogen bonds are internal: O1−H1···O2 and O3−H3···O4. In Figure 2, hydrogen-bond donor

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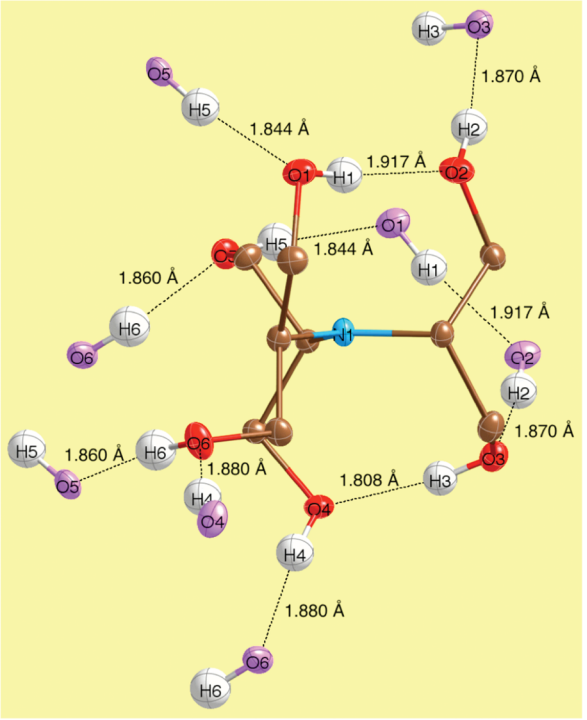
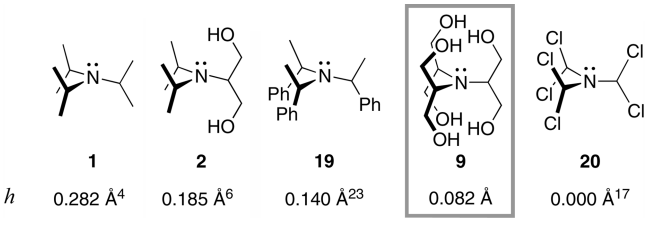


FIGURE 2. Thermal ellipsoid plot of **9** at the 50% probability level. Carbon atoms are shown in brown; other elements are labeled. Oxygen atoms on neighboring molecules are lavender. Hydrogen atoms bound to carbon are not shown. Hydrogen bonds are indicated by dotted lines (···).

and acceptor atoms external to the molecule are shown in lavender.

Figure 2 also makes it clear that the central nitrogen (shown in blue) is virtually planar. For **9**, the sum of C−N−C angles is 359.06° and $h = 0.082$ Å. For comparison, consider h values in a series of trialkylamines in which each nitrogen is bonded to three secondary carbons, shown below. Here again, it is clear that the nitrogen atom of **9** is exceedingly flat.



Although it is natural to ask *why* **9** is so flat, a reasonably satisfying answer is difficult to provide. To any answer that might be offered, several objections could be raised: (1) the geometry at nitrogen might be affected by the H-bonding network, (2) crystal packing forces might perturb the gas-phase geometry in unpredictable ways.[24] Even so, we believe that the major forces at work can be classified under two familiar headings: steric and electronic. The steric demands

(24) Alabugin, I. V.; Manoharan, M.; Buck, M.; Clark, R. J. *J. Mol. Struct. THEOCHEM* **2007**, *813*, 21–27.

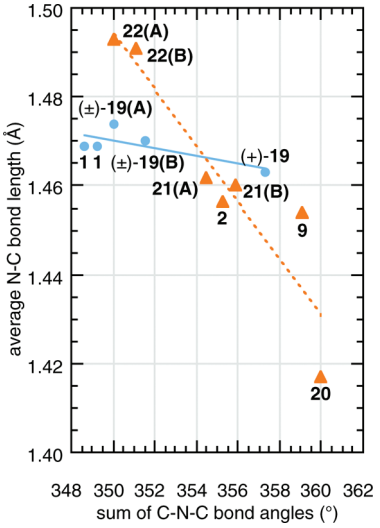
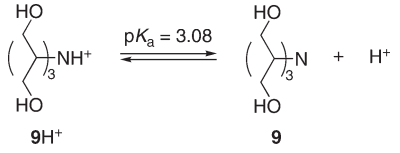


FIGURE 3. Relation of N−C bond length to nitrogen planarity for amines capable of the proposed electronic effect (orange triangles) and amines incapable of it (blue circles). Compound **21** is 2-(*N*,*N*-dicyclohexylamino)propane-1,3-diol, and **22** is 2-(2,2,6,6-tetramethyl-1-piperidinyl)propane-1,3-diol.[6]

of the 1,3-dihydroxy-2-propyl groups are large, obviously. The electronic effect mentioned in the introduction is also a contributing factor. Support for this is provided by the finding that increased planarity at nitrogen is accompanied by contraction of the N−C bond length (Figure 3). The average N−C bond length of **9**, 1.454 Å, puts it in the lowest quartile of 1402 trialkylamine N−C bond lengths compiled by Allen et al.[25] The relation between flatter nitrogen and shorter N−C bonds is stronger in those cases in which the electronic effect can operate (i.e., those with heteroatoms at α or β positions; orange triangles in Figure 3) than in cases lacking this feature (blue circles in Figure 3). The π interaction between the nitrogen 2p orbital and the adjacent σ^* orbital would be expected to result in a shorter N−C bond length.

Basicity of 9. The pK_a of protonated **9**, i.e., **9**H$^+$, was found to be 3.08 ± 0.03 at 25 °C (eq 1).



Compared to an ordinary trialkylamine such as triethylamine whose conjugate acid has a pK_a of 10.70,[26] **9** would appear to be an exceptionally weak base. However, the presence in an amine of an electronegative OH group β to nitrogen should weaken basicity, and **9** has six such OH groups. Figure 4 plots pK_a versus the number of -C-C-OH groups attached to the nitrogen of various protonated tertiary amines.

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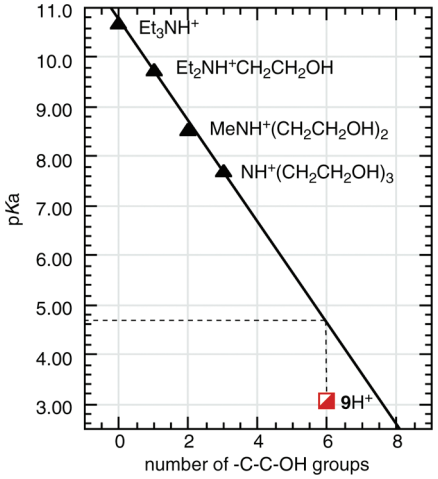


FIGURE 4. pK_a of protonated tertiary amines as a function of the number of OH groups β to nitrogen. Except for **9**H$^+$, data were taken from ref 27. The least-squares line is a fit to the filled triangles.

One may extrapolate the data for protonated amines having 0, 1, 2, and 3 -C-C-OH groups (filled triangles in Figure 4) to a protonated tertiary amine with six such groups, viz., **9**H$^+$, which should have a pK_a of 4.62. The observed pK_a of 3.08 means compound **9** is *less* basic than predicted on electronic grounds by roughly 1.5 pK_a units. Should this 1.5 pK_a unit decrease be called a "planarization effect"? The pK_a's of $Et_3NH^+ClO_4^-$ and $(iPr)_3NH^+ClO_4^-$ are 7.9 and 7.0, respectively, measured in 2-methoxyethanol at 20 °C.[28] If one allows that the electronic effects of an ethyl group and an isopropyl group are not very different, these data suggest the existence of a planarization effect on basicity. However, at present it would be difficult to support the proposal convincingly since electronic factors affect both planarity and basicity. In any event, we believe it is reasonable to suggest that the diminished basicity of **9** might be due to difficulty in deforming the essentially planar nitrogen of **9** to accommodate the additional ligand, a proton, in **9**H$^+$. Fortuitously (i.e., by mistake), in the course of other work with **9**, we prepared **9**H$^+$Cl$^-$ as a crystalline material suitable for X-ray crystallography.

Structure of 9H$^+$. A thermal ellipsoid plot of **9**H$^+$ at the 50% probability level is shown in Figure 5. As shown in Table 1, the nitrogen of **9**H$^+$ is severely flattened relative to two examples of "ordinary" ammonium ions. The 115.6° average C−N−C angle is closer to the trigonal planar value (120°) than it is to the tetrahedral value (109.5°).

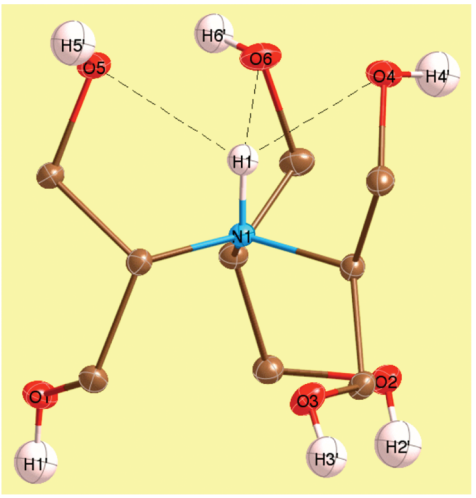


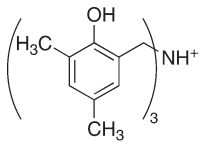
FIGURE 5. Thermal ellipsoid plot of **9**H$^+$Cl$^-$ at the 50% level. Carbons, unlabeled, are shown in brown; other atoms are labeled. Hydrogen atoms bound to carbon are not shown. Internal H-bonds are shown by dashed lines. Cl$^-$ is not shown here but has close contacts with OH hydrogen atoms on four neighboring cations, namely, Cl···H2′, 2.341 Å; Cl···H3′, 2.436 Å; Cl···H4′, 2.359 Å; Cl···H5′, 2.222 Å.

TABLE 1. Geometries of Protonated Acyclic Trialkylamines

ammonium ion	av N−C length (Å)	av H−N−C angle (deg)	av C−N−C angle (deg)	no. of examples[a]
uncongested (i.e., ordinary)				
$(CH_3)_3NH^+$	1.48	107.5	111.4	49
$(HOCH_2CH_2)_3NH^+$	1.50	107.0	111.8	21
congested				
$((CH_3)_2CH)_3NH^+$[b]	1.533	105.1	113.5	1
9H$^+$[c]	1.528	102.3	115.6	1

[a]From the Cambridge Crystallographic Database. [b]Bock, H.; Göbel, I.; Bensch, W.; Solouki, B. *Chem. Ber.* **1994**, *127*, 347−351. [c]This work.

An interesting feature of **9**H$^+$ is the presence of a trifurcated (or "four-center") hydrogen bond involving the N$^+$-H hydrogen (H1) and three neighboring oxygens (O4, O5, and O6). The relevant lengths are H1···O4, 2.255 Å; H1···O5, 2.218 Å; and H1···O6, 2.181 Å. The N-protonated conjugate acid of triethanolamine also exhibits an NH···$(OH)_3$ trifurcated H-bond. In that case the NH···O length is 2.33 Å, which is an average of X-ray data from 15 or so literature reports of this cation.[29] Trifurcated H-bonds of the NH···$(OH)_3$ type are also reported for $(HOOCCH_2CH_2)_2NH^+(CH_2CH_2OH)$, **23**, and **24**, with average NH···O lengths 2.29, 2.30, and 2.27 Å, respectively.[30] It thus appears that the average NH···O length in **9**H$^+$, 2.22 Å, is slightly shorter than these closely comparable examples.



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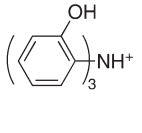

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A wider search of the crystallographic database for NH···$(O)_3$, NH···$(O)_2(N)$, NH···$(O)(N)_2$, and NH···$(N)_3$

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four-center hydrogen bonds revealed 37 more examples, including N-protonated cryptands and several forms of nitrilotriacetic acid.[31−33] Although no examples of NH···(O)(N)$_2$ trifurcated H-bonds were found, for the other three classes of trifurcated hydrogen bonds, average NH···X (X = O or N) bond distances were 2.29 Å (NH···(O)$_3$), 2.29 Å (NH···(O)$_2$(N)), and 2.31 Å ((NH···(N)$_3$). Here again, **9**H$^+$ exhibits shorter trifurcated H-bonds than found, on average, in the 37 related cases.

Electrochemical Oxidation of 9. The one-electron oxidation potential, $E_{1/2}{}^{ox}$, of **9** is 0.88 V, as measured by cyclic voltammetry (CV). Our earlier CV investigation of severely flattened trialkylamines[6] found that values of $E_{1/2}{}^{ox}$ in this class of amines correlated poorly with degree of nitrogen planarity but much more strongly with the net inductive effect of the three alkyl groups attached to nitrogen, as suggested by Mann.[34] In keeping with this idea, we note that a plot (not shown) of $E_{1/2}{}^{ox}$ for triisopropylamine, **1** (0.73 V),[18] 2-(dicyclohexylamino)-1,3-propanediol, **20** (0.77 V),[6] and **9** (0.88 V) versus the number of 1,3-dihydroxy-2-propyl substituents borne by the central nitrogen is linear, with r^2 = 0.995. Little, if any, quantitative significance should be attached to this three-point correlation! Qualitatively, the trend is in the correct direction, namely, toward more positive oxidation potentials with more electron-withdrawing substituents.

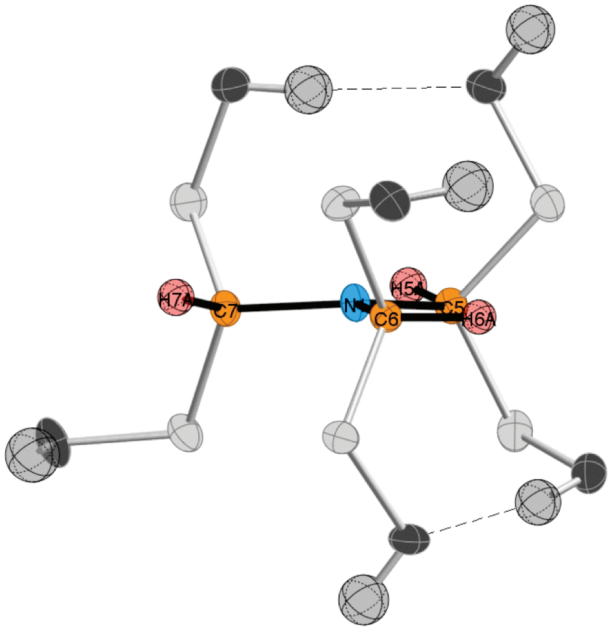

FIGURE 6. Thermal ellipsoid plot of **9** at the 50% level, drawn to emphasize the near-orthogonality of the nitrogen p-orbital and the adjacent C−H bonds. Atoms of interest are in color.

The oxidation of **9** is reversible, even at a sweep rate of 20 mV/s, scanning between 0 and 1.5 V. Most trialkylamines examined by cyclic voltammetry exhibit an oxidation wave but lack a reduction wave.[34] The explanation commonly invoked for this is that one-electron oxidation of nitrogen to an amine radical cation, which is responsible for the oxidation peak, is followed by rapid and irreversible loss of an α proton.[35] That this decomposition route, viz., the loss of an α-proton, is apparently slow in the present case is a consequence of geometry: in **9**, the C−H bonds α to nitrogen lie essentially in the nodal plane of the nitrogen p-orbital, as is shown in Figure 6. The dihedral angles C5−N1−C6−H6A, C6−N1−C7−H7A, and C7−N1−C5−H5A are 6.6°, 16.0°, and 17.0° respectively. One expects the geometry of the radical cation **9**$^{+\bullet}$ to be virtually unchanged. The near-orthogonality of all α C−H bonds to the nitrogen p-orbital precludes stabilization of the incipient α radical center via overlap with the adjacent p-orbital. Similar CV behavior by triisopropylamine has been reported, and a similar explanation offered.[1,18]

^{15}N NMR of 9. In D_2O solvent, **9** exhibits one peak in its ^{15}N NMR spectrum at −366.3 ppm (referenced to external CH_3NO_2). Triethanolamine in the same solvent appears at −352.3 ppm. Parameters that permit one to predict the ^{15}N chemical shift of a simple mono-, di-, or trialkylamine were developed by Duthaler and Roberts.[36] Using these, Wong, Collazo, and Guziec[2] compared predicted and observed nitrogen chemical shifts of four sterically congested tertiary

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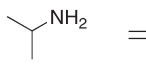
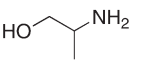
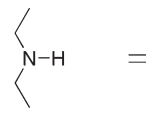
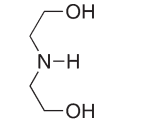
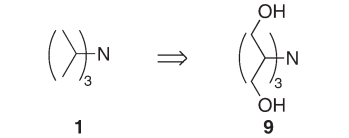
amines, namely, diisopropylmethylamine, diisopropylethylamine, di-*tert*-butylmethylamine, and triisopropylamine (**1**). The agreement between predicted and observed shifts (CH_3OH solvent) was good for the first three amines (within 2 ppm), but **1** deviated significantly (ca. 11 ppm upfield of the prediction). Wong et al. argued that this was consistent with the first three amines being pyramidal and **1** being planar.

In the case of **9**, it is a little more difficult to decide if a chemical shift of −366.3 ppm is "expected" or anomalous. ^{15}N NMR data for β-hydroxyamines are somewhat sparse, and solvent effects on ^{15}N chemical shifts can be substantial. Nevertheless, using the published ^{15}N chemical shifts of β-hydroxyamines and of structurally similar non-β-OH containing amines, one may crudely estimate the chemical shift change resulting from a single N-C-CH_3 → N-C-CH_2OH change, a parameter we will arbitrarily call "**A**". The method is illustrated in Table 2.

TABLE 2. Two Examples of the Calculation of A

			A
	⟹		-8.4 ppm
–337.6 ppm		–346.0 ppm	
	⟹		-8.7 ppm
–334.0 ppm		–351.4 ppm	

These and seven more comparisons are collected in the Supporting Information.[36,37] The average value of **A** is −7.4 ± 1.5 ppm. As shown below, triisopropylamine can be transformed to **9** by six N-C-CH_3 → N-C-CH_2OH changes, leading to a predicted ^{15}N chemical shift for **9** of −328.1 + 6(**A**) = −372.5 ppm. The observed ^{15}N chemical shift for **9**, −366.3 ppm, differs from the prediction by 6.2 ppm. We consider this to be within the limits of uncertainty arising from the small number of comparisons used to calculate the average **A** value and the necessity of comparing chemical shifts of compounds measured as neat samples with shifts of other compounds measured in methanol or cyclohexane solution.



1 δ^N = –328.1 ppm[2]

9 δ^N = –372.5 ppm predicted

The fact that the ^{15}N chemical shift of **9** did not exhibit the same sort of anomaly as was found by Wong, et al. for **1** makes sense, because that anomaly arose from the comparison of a "planar" amine to several pyramidal amines, but in the present case, two "planar" amines (one slightly more planar than the other) were compared.

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Experimental Section

Bis(1,3-dihydroxy-2-propyl)amine, 11. This compound was prepared by the method of Fleet et al.[19]

Bis(4,4-dimethyl-3,5-dioxanyl)amine, 13. Secondary amine **11** (4.00 g, 24.2 mmol) was dissolved in methanol (60 mL), and 37.5% HCl solution (10 mL) was added and stirred for 2 h at rt. The solvent was removed on a rotary evaporator. The residue was dissolved in DMF (40 mL). Under nitrogen, *p*-toluenesulfonic acid (0.700 g, 3.60 mmol) and 2,2-dimethoxypropane (10.0 mL, 81.6 mmol) were added to the solution. The resulting clear solution was allowed to stir overnight (at least 12 h), at which time Et_3N (0.600 mL, 4.00 mmol) was added and allowed to stir for an additional 10 min. The mixture was concentrated in vacuo and treated with Et_3N (3.40 mL, 24.2 mmol) and EtOAc (150 mL). The precipitate was removed by filtration, and the filtrate was concentrated. The residue was crystallized from hexane to give 82% yield, mp 58.5−59.5 °C. The spectroscopic data were consistent with those previously reported.[19] ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (6 H, s), 1.42 (6 H, s), 2.75 (2 H, tt, J = 4.1, 6.8), 3.62 (4 H, dd, J = 6.8, 11.7), 3.93 (4 H, dd, J = 4.1, 11.7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 24.7, 50.0, 64.7, 98.4.

Dimethyl 2-(*N*,*N*-Bis(4,4-dimethyl-3,5-dioxanyl)amino)-malonate, 16. Under N_2, to a solution of acetonide amine **13** (0.980 g, 4.00 mmol) in benzene (20 mL) was added 0.760 g of **15**[38] (4.80 mmol) and rhodium(II)acetate dimer (32.0 mg, 0.0700 mmol) at rt. The mixture was heated to reflux and continued for 2.0−2.5 h, at which time TLC showed the absence of diazo compound and acetonide amine. The solvent was removed in vacuo. The residue was purified by silica gel chromatography (EtOAc/hexane 1:3 v/v), which yielded white tertiary amine **16** (1.25 g, 83.3%), mp 63−64.5 °C (lit. 63−64.5 °C).[22b] Anal. Calcd for $C_{17}H_{29}NO_8$: C, 54.39; H, 7.79; N, 3.73. Found: C, 54.64; H, 7.78; N, 3.60. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36, 1.40 (12H, 2s), 3.34 (2 H, m), 3.72 (4H, dd, J = 6.9, 12.0), 3.77 (6H, s), 3.96 (4H, dd), 4.99 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.3, 51.4, 52.6, 63.5, 64.3, 98.2, 170.3. EI-HRMS calcd for $C_{17}H_{29}NO_8$ 375.1893, found 375.1888.

2-(*N*,*N*-Bis(4,4-dimethyl-3,5-dioxanyl)amino)-1,3-propanediol, 17. Tertiary amine **16** (0.380 g, 1.00 mmol) was dissolved in THF (4 mL) and added dropwise to a suspension of $LiAlH_4$ (0.230 g, 6.00 mmol) in THF (10 mL). The reaction was stirred overnight at room temperature. Water (0.230 mL), 15% sodium hydroxide (0.230 mL), and water (3 × 0.230 mL) were added sequentially. The mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography (ethyl acetate) to give a colorless sticky liquid **17** (0.300 g, 93.0%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.38, 1.45 (12 H, s), 3.15 (2 H, m), 3.27 (1 H, quint), 3.47 (2 H, dd, J = 7.4, 10.7), 3.59 (2 H, dd, J = 10.9, 6.05), 3.71 (4 H, dd, J = 12.0, 5.5), 3.82 (4 H, dd, J = 12.0, 9.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 27.0, 49.1, 58.8, 62.3, 63.7, 97.7. EI-HRMS calcd for $C_{15}H_{29}NO_6$ 319.1995, found 319.1983.

Tris(1,3-dihydroxy-2-propyl)amine, 9. At 0 °C, trifluoroacetic acid (1.00 mL) was added to a solution of **17** (1.49 g, 4.67 mmol) in THF and H_2O (25 mL, THF/H_2O = 4:1 (v/v)). The resulting solution was allowed to warm to rt and was left overnight. Solvent was removed in vacuo. The residue was purified on an ion exchange column (Amberlite, IR-120, H^+). The column was eluted with water first, followed by a solution of aqueous ammonia (1 M). The solvent was removed to give white solid tertiary amine **9** (1.10 g, 92.0%), mp > 190 °C (dec). Anal. Calcd for $C_9H_{21}NO_6$: C, 45.18; H, 8,85; N, 5.85. Found: C, 45.02; H, 8.82; N, 5.74. ^1H NMR (400 MHz, D_2O): δ 3.16 (3 H, m), 3.53 (12 H, m). ^{13}C NMR (100 MHz, D_2O, methanol, 49.5): δ 57.1, 61.3. ^1H NMR (400 MHz, DMSO-d_6): δ 2.91 (3H, m), 3.31(12H);

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4.91 (6H, q); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.1, 60.8. ^{15}N NMR (40.6 MHz, D_2O) δ_N: 14.23. pK_a = 3.08 (T = 25 °C, 0.01 M, titrant: 0.1 N HCl standard solution). $E_{1/2}^{ox}$ = 0.88 V (rt, 0.5 M Na_2SO_4, in water, Au electrode). A crystal 0.32 mm × 0.20 mm × 0.39 mm was selected for X-ray crystallography with 0.71073 Å (Mo Kα) radiation. Unit cell dimensions a = 10.915(2) Å, b = 8.9100(18) Å, c = 23.635(5) Å, $\alpha = \beta = \gamma = 90°$; Z = 8. Ambient temperature, absorption coefficient = 0.114 mm^{-1}; 21931 reflections were collected, 2858 independent (R_{int} = 0.0239), $-14 \le h \le 14$, $-11 \le k \le 11$, $-31 \le l \le 30$; full-matrix least-squares on F^2, data-to-parameter ratio = 16.8, Goodness-of-fit 1.026, R1 = 0.0361, wR2 = 0.1009 ($I > 2\sigma(I)$), R1 = 0.0378, wR2 = 0.1032 (all data); extinction coefficient = 0.0235(19).

Cyclic Voltammetry. The apparatus and procedures used have been described previously.[6] Conditions for **9**: 3 mM 0.5 M aq Na_2SO_4, 0 °C, Au electrode, 100 mV/s sweep rate, reference electrode Ag/AgCl satd KCl. At a sweep rate of 20 mV/s, a reduction wave was in evidence.

Tris(1,3-dihydroxy-2-propyl)amine Hydrochloride, 9H$^+$Cl$^-$. (a) Unintended formation on reaction of 9 with $SiCl_4$. A solution of tertiary amine **9** (100 mg, 0.420 mmol) in DMF (3 mL) was cooled to −5 °C. Silicon tetrachloride (96.5 μL, 0.840 mmol) was added dropwise. The reaction mixture was warmed gradually to room temperature, and an initially formed precipitate dissolved. The reaction was stirred for 4 h at rt (after 1.5 h, the solution became cloudy and some precipitate formed again). The reaction mixture was filtered to give 120 mg of a white solid. This was dissolved in H_2O (15 mL) and filtered. The filtrate was concentrated under reduced pressure to give a white solid (91.7 mg). This was recrystallized from methanol to give a crystalline solid. ^{1}H NMR (400 MHz, D_2O): δ 4.03 (1 H, m; 2H, m), 3.94 (2H, m); ^{13}C NMR (100 MHz, D_2O): δ 63.8, 57.9. The X-ray crystal structure showed it was tertiary amine HCl salt 9H$^+$Cl$^-$. A crystal 0.278 mm × 0.165 mm × 0.280 mm was selected for X-ray crystallography with 0.71073 Å (Mo Kα) radiation: monoclinic a = 6.8972(4) Å, b = 8.2335(5) Å, c = 11.2422(7) Å, α = 92.2850(10)°, β = 102.8470(10)°, γ = 91.2820(10)°; Z = 2; 3019 reflections were collected, 2805 independent, $-9 \le h \le 9$, $-10 \le k \le 10$, $-14 \le l \le 14$; full-matrix least-squares refinement on F^2, data-to-parameter ratio = 12.4, goodness-of-fit = 1.068, R1 = 0.0313, wR2 = 0.0842 (all data), R1 = 0.0297, wR2 = 0.0831 ($I > 2\sigma(I)$). **(b) Reaction of 9 with HCl.** A 212.5 mg (0.881 mmol) portion of **9** was dissolved in 0.25 mL of 12.1 M HCl (3.0 mmol). Solvent was removed on a rotary evaporator, and the residue dried further on the vacuum line overnight, affording 222.0 mg of 9H$^+$Cl$^-$ (91% yield). This material was pure by NMR; a portion was recrystallized from methanol, yielding a colorless crystalline solid, mp 152−152.5 °C. Anal. Calcd for $C_9H_{22}NO_6Cl$: C, 39.20; H, 8.04; N, 5.08. Found: C, 39.21; H 8.20; N, 5.11.

Protected Tertiary Amine, 18. At 0 °C, trimethylsilyl chloride (0.480 mL, 3.78 mmol) was added to a stirred solution of tertiary amine **9** (100 mg, 0.420 mmol) and imidazole (260 mg, 3.78 mmol) in DMF (10 mL). The mixture was stirred at 0 °C for 1 h and for 4 h at rt. Water (20 mL) was added to the reaction solution at 0 °C. The reaction mixture was extracted with ether (3 × 20 mL), and the organic layer was washed with brine (2 × 15 mL), dried with sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent to give 230 mg (82%) of compound **18** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (12 H, d), 3.06 (3 H, m), 0.15 (54 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.9, 58.1, −0.3. Anal. Calcd for $C_{27}H_{69}NO_6Si_6$: C, 48.23; H, 10.34; N, 2.08. Found: C, 48.51; H 10.56; N, 2.21.

Supporting Information Available: NMR spectra for new compounds, table of comparisons used to calculate **A**, CIF files and ORTEP plots of **9** and 9H$^+$Cl$^-$. This material is available free of charge via the Internet at http://pubs.acs.org.