JOC Article

Trialkylamines More Planar at Nitrogen Than Triisopropylamine in the Solid State

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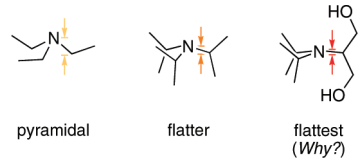
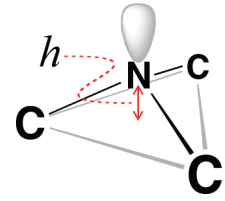


A short synthesis of exceedingly congested amines, with insertion of a rhodium carbenoid into an N−H bond as the key step, is described. Trialkylamines such as 2-(diisopropylamino)propane-1,3-diol (**8**) and 2-(2,2,6,6-tetramethyl-1-piperidinyl)propane-1,3-diol (**10**) may be prepared easily. Examination of amines of this type by X-ray crystallography reveals nearly planar nitrogens. Indeed, they are all more planar than the nitrogen of triisopropylamine, which had long been thought to be perfectly planar, but which is in fact very slightly pyramidal. The distance (*h*) of the nitrogen of triisopropylamine to the plane defined by the three carbons to which it is bonded is 0.28−0.29 Å. In **8**, by comparison, *h* is 0.185 Å. A qualitative orbital interaction explanation is proposed to rationalize the tendency of nitrogen to planarize when attached to the 1,3-dihydroxy-2-propyl group. Cyclic voltammetric measurements of nitrogen one-electron oxidation of the nearly planar trialkylamines revealed no correlation between $E_{1/2}^{ox}$ and degree of planarity.

Introduction

Triisopropylamine, **1**, has held a certain fascination for organic chemists. It is a small, simple trialkylamine, with no heteroatoms other than the central nitrogen, that seems to be very nearly planar about nitrogen. As such, it seemed to define the achievable limit for steric distress in a simple trialkylamine; the even more congested *tert*-butyldiisopropylamine, di-*tert*-butylisopropylamine, and tri-*tert*-butylamine[1] have not yet been reported. Intimations of **1**'s planarity were provided by electron diffraction studies.[2] These gave a value for the C−N−C angle of 119.2(3)°, thus a sum of angles at nitrogen ($\Sigma\phi_{CNC}$) of 357.6°, quite close to the 360° diagnostic of a planar nitrogen. NMR studies confirmed the ED result.[3,4] In 1998, however, Boese et al. managed to crystallize **1** at low temperature and obtain its crystal structure.[5] At 84 K, the C−N−C bond angle was found to be 116.2(1)° ($\Sigma\phi_{CNC}$ = 348.6°). Thus, the nitrogen of triisopropylamine was found to be not quite as flat as previously thought, yet still considerably more planar than ordinary amines. In triethylamine[6,7] and trimethylamine,[5] both ordinary trialkylamines, the perpendicular distance from N to the plane defined by the three attached carbons (*h*) is 0.467 and 0.450 Å, respectively, compared with 0.27−0.29 Å (depending on temperature) in **1**:[5]



Most organic chemists would term the nearly planar triisopropylamine sterically hindered or sterically congested. In

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[†] Auburn University.
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(1) Back, T. G.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 924–927.
(2) Bock, H.; Goebel, I.; Havlas, Z.; Liedle, S.; Oberhammer, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 187–190.
(3) Wong, T. C.; Collazo, L. R.; Guziec, F. S., Jr. *Tetrahedron* **1995**, *51*, 649–656.
(4) Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1996**, *61*, 1290–1296.
(5) Boese, R.; Bläser, D.; Antipin, M. Y.; Chaplinski, V.; de Meijere, A. *Chem. Commun. (Cambridge)* **1998**, 781–782.
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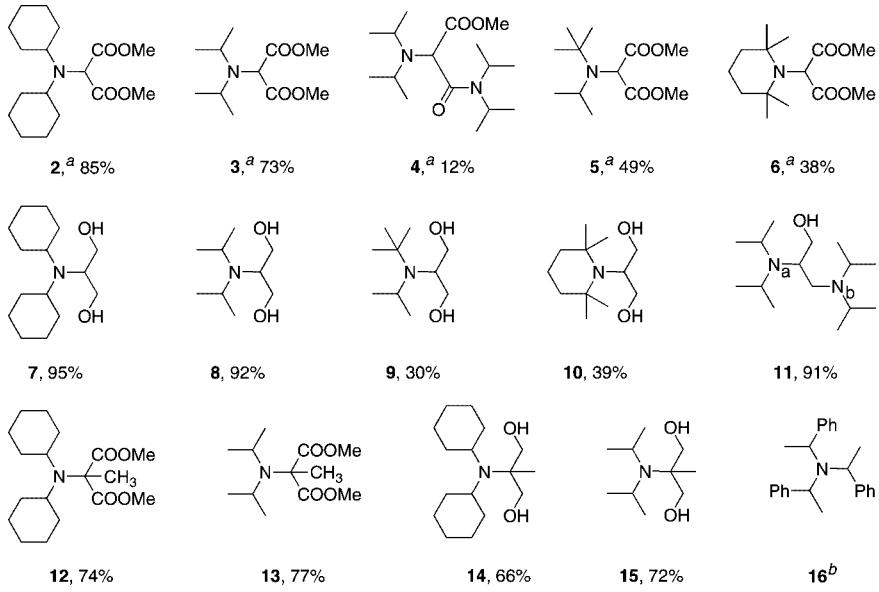
CHART 1



[a] Reference 10. [b] Reference 11.

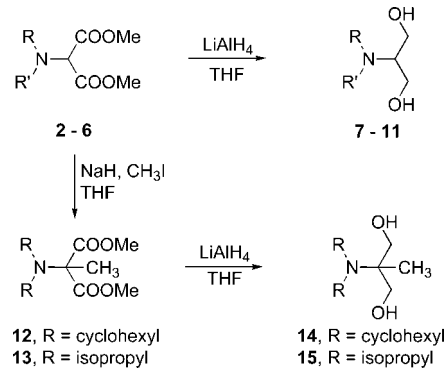
examining precisely what these terms mean, Nau and coworkers[8] measured the rate of exciplex formation of several trialkylamines with azoalkanes, a reaction whose rate they argued should be quite sensitive to steric effects. They found that **1** was indeed sterically hindered, but other trialkylamines, including some that organic chemists would readily deem sterically hindered (e.g., diisopropylethylamine), were not. Nau et al. noted that the only trialkylamines in their study that exhibited low rates of exciplex formation, and which were therefore labeled sterically hindered, were amines with three secondary alkyl groups (isopropyl and higher)[8] bonded to nitrogen. But how are the concepts steric hindrance/congestion and nitrogen planarity related, if at all? Tricyclopropylamine has nitrogen bonded to three secondary alkyl groups, but its geometry at nitrogen is patently pyramidal: $\Sigma\phi_{CNC} = 330.3°$, $h = 0.47$ Å.[9]

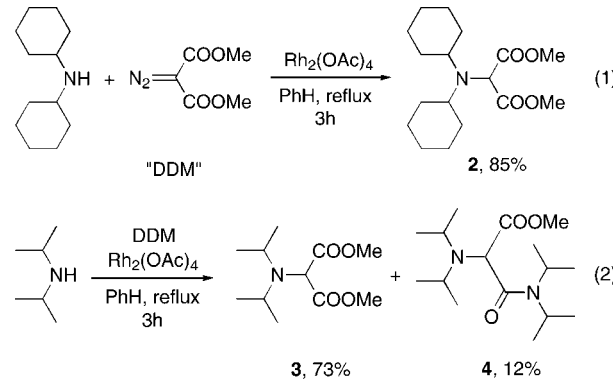
We previously reported that $Rh_2(OAc)_4$-catalyzed insertion of carbenes into the N−H bond of sterically hindered secondary amines was an easy route to ostensibly sterically hindered tertiary amines (taking the phrase "sterically hindered" from the lingua franca of organic chemists).[10] We now report that derivatives of the tertiary amines available by that route are among the most planar simple trialkylamines known.

Results and Discussion

The reaction of dimethyl diazomalonate (DDM) with hindered secondary amines[10] is illustrated in eq 1. Compounds **2**−**6** were synthesized in this way (Chart 1). In the case of diisopropylamine only (eq 2), a 12% yield of amide **4** was obtained along with the expected diester **3** in a 73% yield. (Although the reaction of DDM with di-*tert*-butylamine was tried, all attempts to isolate any dimethyl 2-(*N*,*N*-di-*tert*-butylamino)propanedioate that might have been formed failed.)

SCHEME 1





As shown in Scheme 1, reduction of the ester groups (and in the case of **4**, the amide group too) produced the alcohols **7**−**11** in generally high yield. (Yields reported in Chart 1.) Attempted deprotonation of the malonate side chain of **2**, **3**, **5**, and **6** and methylation of the resulting carbanion failed using Na_2CO_3 or NaOMe as a base. However, use of NaH in THF afforded methylated diesters **12** and **13** in 74% and 77% yields,

(7) Born, M.; Mootz, D.; Schaefgen, S. *Z. Naturforsch., B: Chem. Sci.* **1995**, *50*, 101–105.
(8) Pischel, U.; Zhang, X.; Hellrung, B.; Haselbach, E.; Muller, P.-A.; Nau, W. M. *J. Am. Chem. Soc.* **2000**, *122*, 2027–2034.
(9) de Meijere, A.; Chaplinski, V.; Winsel, H.; Kusnetsov, M. A.; Rademacher, P.; Boese, R.; Haumann, T.; Traetteberg, M.; Schleyer, P. V. R.; Zysietz, T.; Jiao, H.; Merstetter, P.; Gerson, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2430–2468.
(10) Yang, M.; Wang, X.; Li, H.; Livant, P. *J. Org. Chem.* **2001**, *66*, 6729–6733.
(11) Wyatt, P.; Butts, C. P.; Patel, V.; Voysey, B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4222–4223.

TABLE 1. Structural Parameters of Various Trialkylamines from X-ray Crystallography

entry	compound[a]	*h* (Å)[b]	sum of C−N−C angles (deg)	C−N bond lengths (Å)
1[c]	NMe_3	0.454	331.9	1.448, 1.448, 1.448
2[c]	NEt_3	0.467	*d*	*d*
3[e]	NEt_3	0.444	335.1	1.490, 1.517, 1.514
4[f]	NEt_3	0.425	336.0	1.471, 1.475, 1.471
5[c,g]	**1**	0.292	348.6	*1.469(1)*[h]
6[c,i]	**1**	0.282	349.2	*1.469(1)*[h]
7	**7(A)**	0.200	354.44(14)	1.466(2), 1.463(2), 1.458(2)
8	**7(B)**	0.172	355.89(14)	1.469(2), 1.458(2), 1.453(2)
9	**8**	0.185	355.25(9)	1.4603(15), 1.4584(15), 1.4504(14)
10	**10(A)**	0.275	350.08(12)	1.5011(19), 1.4991(19), 1.4780(19)
11	**10(B)**	0.260	351.08(13)	1.497(2), 1.495(2), 1.480(2)
12	**11** N_a	0.172	355.87(18)	1.462(3), 1.452(3), 1.443(3)
13	**11** N_b	0.366	342.12(18)	1.478(3), 1.473(3), 1.469(3)
14	**14**	0.270	350.31(9)	1.4943(16), 1.4898(15), 1.4824(16)
15[j]	(+)-**16**	0.140	357.3	1.4622(16), 1.4622(16), 1.4652(15)
16[j]	(±)-**16(A)**	0.250	351.5	1.4700(14), 1.4700(13), 1.4701(13)
17[j]	(±)-**16(B)**	0.272	350.0	1.4739(13), 1.4739(13), 1.4739(13)

[a] The labels (A) and (B) refer to two independent molecules in the unit cell. [b] *h* is the perpendicular distance from N to the plane defined by the three ipso carbons. [c] Reference 5. [d] Disorder. [e] Reference 6. [f] Reference 7. [g] $T = 84$ K. [h] Italics indicate an average value. [i] $T = 118$ K. [j] Reference 11.

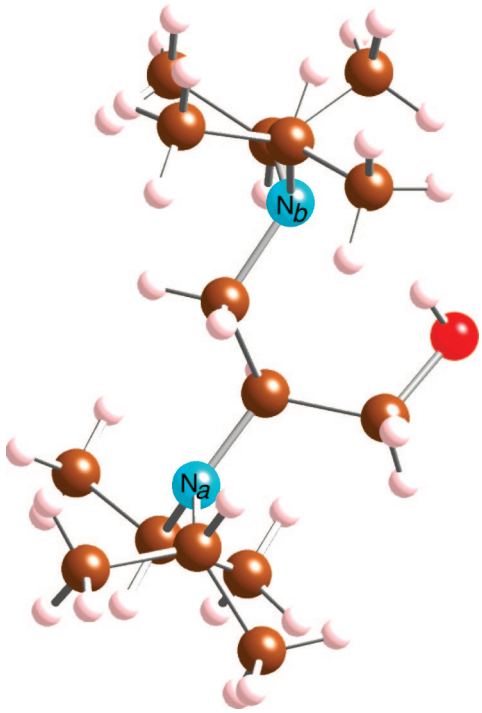
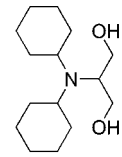


FIGURE 1. X-Ray crystal structure of **11**. Atoms are presented as spheres of an arbitrary diameter (key: red = oxygen, blue = nitrogen, brown = carbon, light pink = hydrogen).

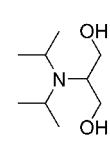
respectively. With **5** and **6**, NaH/CH_3I/THF afforded only recovered starting material. Sluggish $LiAlH_4$ reduction of **12** and **13**, in turn, led to the diols **14** and **15**.

The diesters were, with the exception of **2**, oils that we could not crystallize at low temperature. The diols **7**, **8**, **10**, and **14**, as well as aminoalcohol **11**, were crystalline solids amenable to X-ray crystallography. The results of X-ray crystallographic studies on these compounds are summarized in Table 1. Also included in Table 1 for comparison are structural parameters of the unstrained amines trimethylamine and triethylamine, as well as those of triisopropylamine (**1**) and the previously reported **16**.[11] Figure 1 shows the X-ray structure of compound **11**, in which N_a is flattened ($h = 0.172$ Å) and N_b is more normal ($h = 0.366$ Å).

From Table 1, one sees that while triisopropylamine is indeed much less pyramidal than simple unstrained amines, all other nitrogen centers listed, save entry 13, are even more planar than the nitrogen of triisopropylamine. In trying to make sense of the data in Table 1, one wonders first what limits of precision should be attached to these parameters, beyond the parenthetical estimated standard deviations (esd's). One notices that in the cases of **7**, **10**, and **16**, there are two nonidentical molecules in the asymmetric unit, i.e., two versions of the same molecule, denoted (A) and (B). The cause of any differences in geometrical parameters between (A) and (B) versions cannot be structural, obviously. Rather, it is reasonable to ascribe those differences to crystal packing effects. By ignoring differences in geometrical parameters between different molecules that are smaller than differences in geometrical parameters between (A) and (B) versions of the same molecule, we hope to avoid the pitfall of overanalysis. Considering **7(A)** and **7(B)**, the two *h* values differ by 0.028 Å. In **10(A)** and **10(B)**, the range is 0.015 Å. In (±)-**16(A)** and (±)-**16(B)**,[11] the difference in *h* is 0.022 Å. Therefore, differences in *h* less than 0.03 Å should be ignored. This leads one to conclude, for example, that the nitrogen atoms of **7** and **8** are equally planar. Such a conclusion is clearly reasonable, given the similarity of the two structures.

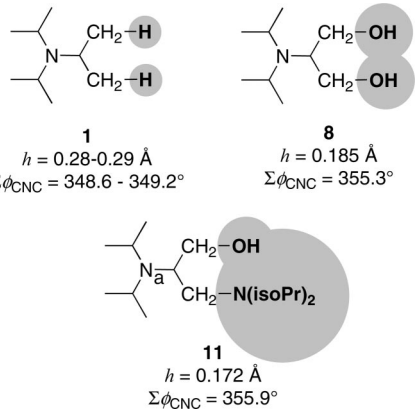


7
h = 0.200, 0.172 Å
$\Sigma\phi_{CNC}$ = 354.4, 355.9°

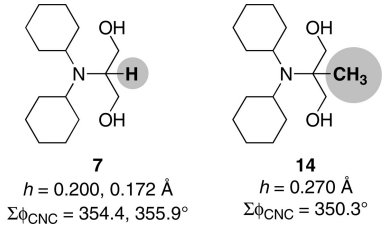


8
h = 0.185 Å
$\Sigma\phi_{CNC}$ = 355.2°

Examination of Table 1 at this level of detail raises some interesting questions. For example, when one compares **1**, **8**, and **11** (below), the increased flattening of **8** relative to **1** (*h* drops by about 0.100 Å) is understandable because bulkier OH groups replace two hydrogens in **1**. However, in **11**, an OH group in **8** is replaced by a much bulkier diisopropylamino group,[12] but **11** is essentially just as flat as **8**, the difference in *h* being a trifling 0.013 Å.



The comparison of **7** and **14** is also counterintuitive. Despite the replacement of an α-hydrogen by an α-methyl, the nitrogen of **14** is more pyramidal than that of **7** ($\Delta h \cong 0.084$ Å). These examples are counterintuitive, given the intuition that increased steric hindrance should result in a more planar nitrogen geometry.



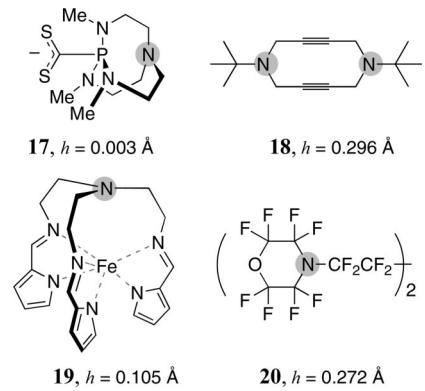
To sort through such apparent anomalies, it is imperative to at least try to define terms. At the risk of stating the obvious, steric hindrance in a trialkylamine refers to the difficulty of physical access to the amine nitrogen. That is, in comparing several trialkylamines, the amine with the least accessible nitrogen is the one that is most sterically hindered. Unfortunately, assessing steric hindrance is not a straightforward matter. A seemingly reasonable approach is to measure the rate, or position of equilibrium, of a reaction in which the steric hindrance of the amine is thought to be the major factor controlling the rate or position of equilibrium. This was the approach of Nau et al., as mentioned before.[8] This was also the approach of Zhao and Collum,[16] who classified 37 trialkylamines into four categories of steric hindrance based on the effect each had on the deaggregation of $(LiHMDS)_n$. By this criterion, triisobutylamine, strangely, was found to be more sterically hindered than triisopropylamine (**1**).

It is hard to think of a reaction that has a strong dependence on trialkylamine steric hindrance while having no dependence at all on trialkylamine basicity or nucleophilicity. This is a potential source of trouble. We assert the common sense idea that steric hindrance at a trialkylamine nitrogen results principally from steric congestion, i.e., steric bulk near the nitrogen. (However, it has been suggested that nitrogen accessibility could be diminished by increased steric bulk remote from the nitrogen center.[17]) Thus, in our view, steric hindrance in a trialkylamine is a consequence of sheer numbers of atoms neighboring nitrogen: the more atoms near nitrogen, the bigger they are, and the nearer to nitrogen they are (i.e., the more sterically congested the nitrogen center is), the more sterically hindered (i.e., inaccessible) the nitrogen of the trialkylamine ought to be. We suggest that assessing steric hindrance at a trialkylamine nitrogen should be an exercise in solid geometry, somewhat akin to measuring cone angles of trialkylphosphines.

Planarity at nitrogen, in contrast to the concept of steric hindrance in a trialkylamine, is straightforward. The degree of planarity is quantitated by $\Sigma\phi_{CNC}$ or h, as defined before.

In order to begin to understand what factors cause nitrogen to flatten in a trialkylamine in general, and in those in Table 1 in particular, we took an empirical approach and searched the Cambridge Crystallographic database for trialkylamines (i.e., N bonded to three sp^3 carbons) for which h was equal to or less than 0.3 Å (a number chosen to approximate h in triisopropylamine). Excluded were structures for which $R > 0.10$.

The trialkylamines that were found could be grouped into several categories: (i) trialkylamines in which nitrogen is the bridgehead atom in a bicyclic or tricyclic structure, (ii) medium ring or macrocyclic trialkylamines, (iii) trialkylamines with multidentate contacts with a metal center, (iv) highly fluorinated trialkylamines, and (v) others. Some examples are shown below, and the complete set of structures is included in the Supporting Information.



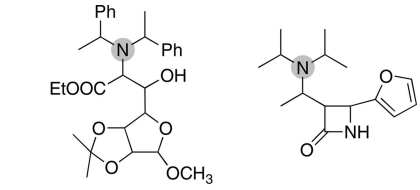
Incorporation of nitrogen into a cyclic, bicyclic, or multicyclic structure is a confounding factor. Not only will steric forces depend in a complicated way on the size, substituents, and other peculiarities of each particular ring, but also the cases we seek to understand, namely, those in Table 1, are, save **10**, those in which the trialkylamine nitrogen is not part of a ring. Therefore, we restricted ourselves to only those cases in which nitrogen is not part of a ring.

Of these, many were cases in which the flattened nitrogen was flanked by three secondary carbons, per Nau et al.'s suggestion.[8] Some of the 20 examples of this type are shown below. (The complete set is included in the Supporting Information.)

All examples are derivatives, in one way or another, of triisopropylamine. Therefore, one could argue that whatever factor (or set of factors) causes triisopropylamine to flatten so considerably is also at work in these cases and might be

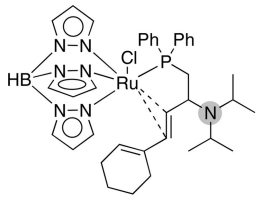
(12) The conformational energy ("*A*-value") of the OH group is 0.60 kcal/mol (cyclohexane solvent),[13] 0.72 kcal/mol (acetone-d_6 solvent),[14] or 0.95 kcal/mol ($(CH_3)_2CHOH$ solvent),[13] while that of the NMe_2 group (a model for the $N(isoPr)_2$ group) is 1.31 kcal/mol (toluene-d_8 solvent)[15] or 1.53 kcal/mol ($CFCl_3$–$CDCl_3$ solvent).[15]

(13) Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487–5495.
(14) Aycard, J. P. *Spectrosc. Lett.* **1989**, *22*, 397–404.
(15) Booth, H.; Jozefowicz, M. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 895–901.
(16) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411–14424.
(17) Naiki, M.; Shirakawa, S.; Kon-i, K.; Kondo, Y.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 5467–5471.

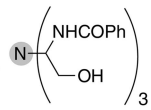


21, h = 0.139 Å

22, h = 0.240 Å

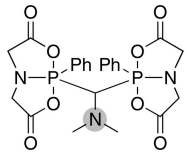


23, h = 0.152 Å

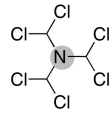


24, h = 0.236 Å

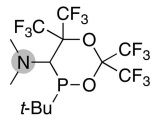
sufficient to explain their flattened nitrogens. Yet, many other cases were found that did not fit Nau et al.'s prescription,[8] i.e., were not derivatives of triisopropylamine. Some of these cases are shown below.



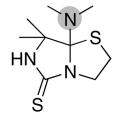
25, h = 0.067 Å



26, h = 0.000 Å



27, h = 0.191 Å



28, h = 0.296 Å

Obviously, flanking nitrogen with three secondary carbons (i.e., increasing steric congestion about N) is not strictly necessary to cause the nitrogen to significantly flatten; in **25**, **27**, and **28**, two of the three groups bound to N are methyls. The case of tris(dichloromethyl)amine, **26**, is both dramatic and alluring: dramatic, because nitrogen is absolutely flat; alluring, because the case is simple enough to encourage attempts to rationalize the planarity.

A common feature of **25**−**28** is the presence of one or more heteroatoms β to nitrogen. This suggests that in addition to the steric congestion that Nau et al. focused on,[8] flattening at the nitrogen may also be caused by an effect related to the heteroatoms.

We describe below a very simple, qualitative analysis of what we propose to be the nonsteric component of the planarity of heteroatom-substituted trialkylamines like **26**. To present the idea, we compare **26** to triisopropylamine, **1**. This analysis will serve as a helpful framework for understanding some of the odd structural trends in Table 1. It is a straightforward extension of a discussion given by Albright et al.[18] of R_3N systems in which one or more R groups have either a π-acceptor orbital or a π-donor orbital adjacent to N.

The extension is simple to consider: in place of the adjacent π-acceptor orbital in Albright et al.'s discussion is a side chain

(18) Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley & Sons: New York, 1985; pp 140−148.

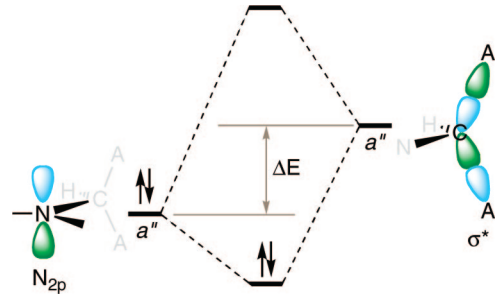


FIGURE 2. Orbital interaction diagram for a N_{2p} orbital and a CA_2 fragment σ^* orbital. When A = C, the diagram pertains to **1**; when A = Cl, it pertains to **26**.

σ^* orbital of π symmetry.[19] This is shown in Figure 2, where A stands for either C (to model a side chain of **1**) or Cl (to model a side chain of **26**). (Only the larger lobe of each sp^3-like orbital is sketched.)

The orbital interaction diagram in Figure 2 refers to the planar form of the amine. The energy-lowering filled−unfilled interaction indicated tends to stabilize the planar form relative to the pyramidal form. As A becomes more electronegative (i.e., C → Cl as in **1** → **26**), the energy of the side chain antibonding orbital becomes more negative and ΔE becomes smaller. This in turn strengthens the $N_{2p}-\sigma^*$ interaction. Since the interaction favors the planar form, one predicts **26** (A = Cl) to be more planar than **1** (A = C), consistent with observation.

In the cases reported here (**7**, **8**, **10**, **11**, and **14**), in contrast to **26**, atom "A" is not itself a highly electronegative element; it is bonded to one, namely oxygen or nitrogen. So, the $N_{2p}-\sigma^*$ effect will be weaker in these amines. Also, these amines bear only one side chain capable of the $N_{2p}-\sigma^*$ effect, rather than the three present in **26**. This will further attenuate the overall effect. Nevertheless, the $N_{2p}-\sigma^*$ interaction should contribute not only to flattening of nitrogen but also to a shorter N−C bond length. The N−C bond length of **26**, 1.418(2) Å, is much shorter than the mean N−C bond length of 1.469 ± 0.014 Å in a sample of 1042 relevant amines.[20] When distances from N to the carbon of the heteroatom-containing side chain are plotted for **7**, **8**, **10**, **11**, and **14** versus $\Sigma\phi_{CNC}$ values, the slope of the least-squares line is about 7 times larger than the slope of the analogous N−C vs $\Sigma\phi_{CNC}$ plot for compounds containing no side chain heteroatoms. (Plots are shown in the Supporting Information.)

How may one use the notion of the $N_{2p}-\sigma^*$ interaction to make sense of the anomalies in Table 1 that were pointed out earlier? The first of these was the comparison of **1**, **8**, and **11**. Compound **8** is more planar than **1** partly for steric reasons, but also because the two electronegative oxygen atoms lower the energy of the side chain σ^* orbital, strengthening the $N_{2p}-\sigma^*$ interaction. Replacing one −OH by $-N(iPr)_2$ on going from **8** to **11** adds steric bulk, favoring planarity, but also replaces an oxygen with a less electronegative nitrogen, weakening the $N_{2p}-\sigma^*$ interaction and disfavoring planarity. The two effects approximately cancel each other, and **11** is essentially as flat as **8**.

The second anomaly was the replacement of an α-hydrogen of **7** with a bulkier methyl group, resulting in a nitrogen (in **14**)

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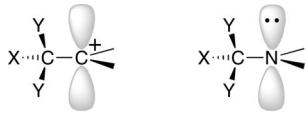
(20) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.

TABLE 2. Oxidation Potentials of Various Trialkylamines

entry	compound	$E_{1/2}^{ox}$ (V)[a] vs Ag/AgCl	vs SCE
1	**1**	0.73	0.68[b]
2	**2**	1.23	1.18[c]
3	**7**	0.77	0.72[c]
4	**8**	0.84	0.79
5	**9**	0.76	0.72
6	**10**	0.82	0.77
7	**11** N_a	0.55	0.50
8	**11** N_b	1.114	1.067[c]
9	**14**	0.65	0.60
10	**15**	0.65	0.60

[a] Irreversible peak potentials unless otherwise noted, determined by extrapolation to infinite scan rate. [b] Reference 8. [c] Reversible oxidation.

less planar than the one in **7**. Here the change takes place at a site lying in the nodal plane of the N_{2p} orbital, taking the nitrogen to be planar, for the sake of discussion. In **29**, changing X (which lies in the nodal plane of the adjacent empty p-orbital) from H to CH_3 produced a calculated net stabilization of the substituted ethyl cation.[21] The effect was greater for Y = F than for Y = CH_3. In **30**, the same change from X = H to X = CH_3 (a model for **7** becoming **14**) would produce destabilization of the planar form of the amine since the adjacent p-orbital in **30** is full.



29 **30**

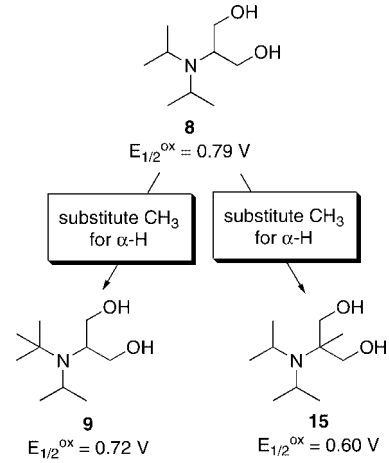
Electrochemical Studies

Cyclic voltammetric studies were undertaken to test whether amine oxidation potentials might correlate with amine planarity. Such a correlation would allow one to roughly determine the planarity of an amine that did not crystallize. Our results are shown in Table 2.

Plotting $E_{1/2}^{ox}$ versus $\Sigma\phi_{CNC}$ yielded a graph (not shown) with a lot of scatter and very weak correlation. Mann[22] found a dependence of oxidation potential of secondary and tertiary amines on the Hammett−Taft parameter σ^*; however, he cautioned that good correlation is to be expected only for reversible oxidations. Indeed, although **8** would be predicted to have a lower $E_{1/2}^{ox}$ than **1** because two $-CH_3$ groups of **1** ($\sigma^* = 0$) are replaced in **8** by $-CH_2OH$ groups (modeled by $-CH_2OCH_3$, $\sigma^* = -0.52$), $E_{1/2}^{ox}$ for **8** is 0.10 V higher than that of **1**.

The comparison shown below may be explained by invoking notions of electron donation and withdrawal, rather than a steric argument.

Both **9** and **15** have an additional $-CH_3$ group α to the amine N. It is reasonable to expect that the addition of an electron donating group would lower the oxidation potential, which is exactly what is observed for **9** and **15** relative to **8**. Also, one might expect a $-CH_3$ group added to the α C most electron deficient should produce a larger effect than a relatively electron-



rich C. For example, the addition of methyl groups to ferrocene decreases the oxidation potential, but the first methyl group results in the greatest shift with subsequent methyls producing smaller and smaller shifts.[23]

Compound **2** having ester groups β to the amine N showed a substantial shift (~0.45 V) to more positive potentials, as would be expected from Hammett−Taft parameters. Compound **11** with two proximal nitrogens shows values for $E_{1/2}^{ox}$ consistent with other multicenter redox compounds. In the case of two redox units that electronically overlap, one center is oxidized at potentials more negative of a single redox unit, and the second center is oxidized at a more positive potential.[24] In compound **11** with two closely spaced N centers, each center alone (based on the oxidation potentials of structurally similar **1** and **8**) would have an oxidation potential between +0.73 and +0.84 V. Since we observe oxidations at +0.55 and +1.11 V, there appears to be significant electronic interaction between the two centers. Since we see a very weak correlation between $\Sigma\phi_{CNC}$ and $E_{1/2}^{ox}$, electron density (substituent) effects are significantly more important in explaining the redox potential.

Experimental Section

The X-ray diffractometer was a Bruker SMART APEX with CCD detector. All data were collected at T = 193 K using a radiation of λ = 0.710 73 Å. All structures were solved by direct methods and full matrix least-squares refinement on F^2.

Cyclic voltammetry (50 mV/s to 20 V/s) was performed with a modified AFRDE4 potentiostat with signals driven by a PAR173 programmer. The programmer was triggered by a National Instruments LabPC+ board in a 233 MHz PC. This DAQ board also provided data collection and digitization of the resulting signals. A three-electrode cell was used with an acetonitrile solution degassed with Ar. The reference electrode was a saturated KCl, Ag/AgCl electrode, and the counter electrode was a spiral Pt wire.

Microelectrodes were either 125 or 25 μm diameter Pt wire, ~1 cm long. These were Ag painted perpendicular to a Cu disk that was further attached to a glass tube. Clear epoxy was used to encapsulate the wire and insulate the Cu contact. Excess epoxy was removed by polishing with 400 grit then 1000 grit abrasive paper. The electrodes were then polished with 5 μm and then 0.3 μm alumina powder on a felt pad. The electrodes were washed with water, acetone and chloroform, and then used for experiments.

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(22) Mann, C. K. *Anal. Chem.* **1964**, *36* (13), 2424–2626.
(23) (a) Hall, D. W.; Russell, C. D. *J. Am. Chem. Soc.* **1967**, *89*, 2316–2322. (b) Silva, M. E. N. P. R. A.; Pombeiro, A. J. L.; daSilva, J. J. R. F.; Herrmann, R.; Deus, N.; Bozak, R. E. *J. Organomet. Chem.* **1994**, *480*, 81–90.
(24) Hunig, S.; Bernath, H. *Top. Curr. Chem.* **1980**, *92*, 1–44.

These electrodes were repolished with 0.3 μm alumina powder between experiments.

General Procedure for the Diester Reductions. Under a nitrogen atmosphere, the diester (1 equiv, 0.7−1.8 mmol) in 3 mL of dry THF was added dropwise to a stirred suspension of lithium aluminum hydride (6 equiv, *n* grams) in 7 mL of dry THF. The reaction was heated to 60 °C for 12 h or 2 days, as indicated below. The reaction mixture was cooled, and to it were added sequentially *n* mL of water, *n* mL of 5% aqueous NaOH, and 3*n* mL of water. The mixture was filtered, and the filtrate was evaporated. The residue was purified by recrystallization or column chromatography as specified in each case. This procedure was also followed in the reduction of ester-amide **4**.

2-(Dicyclohexylamino)propane-1,3-diol, 7. Diester **2** (230 mg, 0.74 mmol), $LiAlH_4$ (170 mg, 4.47 mmol), 12 h, recrystallization from EtOAc/hexane 2:1 (v/v). Colorless solid, mp 135−135.5 °C, 180 mg, 95% yield. Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.44; N, 5.48. Found: C, 70.30; H, 11.50; N, 5.51. ^{1}H NMR (250 MHz, $CDCl_3$): 3.58 (m, 4H), 3.08 (quintet, J = 7.3 Hz, 1H), 2.60 (m, 2H), 2.43 (br, 2H), 1.79−0.99 (m, 20H). ^{13}C NMR (63 MHz, $CDCl_3$): 61.9, 58.0, 54.1, 34.4, 26.5, 25.6. A needle-shaped crystal (1.00 × 0.086 × 0.050 mm) was chosen for X-ray crystallography. Crystal data: monoclinic, $P2_1/c$, Z = 8, a = 12.9231(11) Å, b = 6.6306(6) Å, c = 35.487(3) Å, β = 96.199(2)°. A total of 29 956 reflections (7517 independent reflections) were collected to a maximum 2θ of 56.60°, data-to-parameter ratio 23.1. Structure solution and refinement on F^2 resulted in final R indices of $R1$ = 0.0608, w$R2$ = 0.1276 ($F^2 > 2\sigma(F^2)$), $R1$ = 0.1200, w$R2$ = 0.1494 (all data) and a goodness of fit on F^2 of 0.921.

2-(Diisopropylamino)propane-1,3-diol, 8. Diester **3** (430 mg, 1.87 mmol), $LiAlH_4$ (360 mg, 9.47 mmol), 12 h, recrystallization from EtOAc/hexane 1:5 (v/v). Colorless solid, mp 67−68 °C, 300 mg, 92% yield. Anal. Calcd for $C_9H_{21}NO_2$: C, 61.68; H, 12.08; N, 7.99. Found: C, 61.94; H, 12.18; N, 7.98. ^{1}H NMR (250 MHz, $CDCl_3$): 3.60 (m, 4H), 3.16 (septet, J = 6.5 Hz, 2H), 3.06 (quintet, J = 7.3 Hz, 1H), 2.68 (br, 2H), 1.07 (d, J = 6.5 Hz, 12H). ^{13}C NMR (63 MHz, $CDCl_3$): 61.9, 57.0, 44.8, 23.4. A prism-shaped crystal of **8** (0.50 × 0.30 × 0.30 mm) was chosen for X-ray crystallography. Crystal data: triclinic, $P\bar{1}$, Z = 2, a = 7.4601(7) Å, b = 7.5153(7) Å, c = 11.1194(10) Å, α = 86.462(2)°, β = 72.485(2)°, γ = 64.2070(10)°. A total of 4426 reflections (2239 unique) were collected to a maximum 2θ of 53.46°, data-to-parameter ratio 20.5. Structure solution and refinement on F^2 resulted in final R indices of $R1$ = 0.0481, w$R2$ = 0.1241 ($F^2 > 2\sigma(F^2)$), $R1$ = 0.0529, w$R2$ = 0.1284 (all data) and a goodness of fit on F^2 of 1.034.

2-(*N*-*tert*-butyl-*N*-isopropylamino)propane-1,3-diol, 9. Diester **5** (350 mg, 1.43 mmol) $LiAlH_4$ (440 mg, 9.47 mmol), 2 days, column chromatography (CH_2Cl_2/CH_3OH 6:1 (v/v)). Pale yellow oil, 80 mg, 30% yield. ^{1}H NMR (250 MHz, $CDCl_3$): 3.81−3.64 (AB quartet, 4H), 3.40 (septet, J = 6.8 Hz, 1H), 3.24 (quintet, J = 7.6, Hz, 1H), 1.22 (s, 9H), 1.17 (d, J = 6.8 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$): 66.2, 58.8, 57.0, 47.7, 30.9, 24.0. HRMS calcd for $C_{10}H_{24}NO_2$ (M + H) 190.1807; found, 190.1809.

2-(2,2,6,6-Tetramethyl-1-piperidinyl)propane-1,3-diol, 10. Diester **6** (320 mg, 1.18 mmol) $LiAlH_4$ (260 mg, 6.84 mmol), 2 days, column chromatography (CH_2Cl_2/CH_3OH 6:1 (v/v)). Colorless solid, mp 105−7 °C, 100 mg, 39% yield. Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.78; H, 11.82; N, 6.32. ^{1}H NMR (250 MHz, $CDCl_3$): 3.80−3.67 (m, 4H), 3.57 (m, 1H), 3.57 (br, 2H), 1.61−1.51 (m, 6H), 1.22 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 63.5, 58.6, 56.3 (br), 44.8 (br), 30.0, 17.9. ^{13}C NMR (100 MHz, DMSO-d_6): 63.3, 59.5, 55.5, 53.9, 44.8, 41.8, 29.8, 17.5. A prism-shaped crystal of **10** (0.550 × 0.160 × 0.128 mm) was selected for X-ray crystallography. Crystal data: triclinic, $P\bar{1}$, Z = 4, a = 7.2537(15) Å, b = 12.906(3) Å, c = 14.907(3) Å, α = 65.765(4)°, β = 85.429(4)°, γ = 83.200(4)°. A total of 10 352 reflections (4555 independent) were collected to a maximum 2θ of 50.36°, data-to-parameter ratio 16.7. Structure solution and refinement on F^2 resulted in final R indices of $R1$ = 0.0515, w$R2$ = 0.1388 ($F^2 > 2\sigma(F^2)$), $R1$ = 0.0665, w$R2$ = 0.1477 (all data) and a goodness of fit on F^2 of 1.057.

2,3-Bis(diisopropylamino)-1-propanol, 11. Ester-amide **4** (320 mg, 1.07 mmol) $LiAlH_4$ (200 mg, 5.26 mmol), 2 days, column chromatography (CH_2Cl_2/CH_3OH 6:1 (v/v)). Colorless solid, mp 35−35.5 °C, 250 mg, 91% yield. Anal. Calcd for $C_{15}H_{34}N_2O$: C, 69.71; H, 13.26; N, 10.84. Found: C, 69.63; H, 13.34; N, 10.79. ^{1}H NMR (250 MHz, $CDCl_3$): 3.84 (q, J = 9.3 Hz, 1H), 3.53 (m, 1H), 3.10 (m, 5H), 2.62 (m, 2H), 1.09 (d, J = 6.6 Hz, 6H), 1.03 (d, J = 6.8 Hz, 12H), 0.98 (d, J = 6.6 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$): 66.8, 51.5, 49.2, 48.0, 45.1, 23.6, 23.3, 22.5, 18.3. A needle-shaped crystal of **11** (0.50 × 0.02 × 0.02 mm) was selected for X-ray crystallography. Crystal data: monoclinic $P2_1/n$, Z = 4, a = 10.9485(6) Å, b = 11.1399(6) Å, c = 14.3517(8) Å, β = 103.7000(10)°. A total of 14 117 reflections (3232 independent) were collected to a maximum 2θ of 51.36°, data-to-parameter ratio 16.5. Structure solution and refinement on F^2 resulted in final R indices of $R1$ = 0.0729, w$R2$ = 0.1996 ($F^2 > 2\sigma(F^2)$), $R1$ = 0.0945 w$R2$ = 0.2191 (all data) and a goodness of fit on F^2 of 1.055.

2-(Dicyclohexylamino)-2-methylpropane-1,3-diol, 14. Diester **12** (420 mg, 1.29 mmol), $LiAlH_4$ (230 mg, 6.05 mmol), 60 °C for 2 days, column chromatography (CH_2Cl_2/CH_3OH 6:1 (v/v)). Colorless solid, mp 115−116 °C, 230 mg, 66.2% yield. Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.59; H, 11.85; N, 5.22. ^{1}H NMR (250 MHz, $CDCl_3$): 3.54 (q, J = 10.9 Hz, 4H), 2.86 (br, 2H), 2.74 (m, 2H), 1.79−0.97 (m, 20H), 1.17 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): 66.6, 64.2, 57.2, 36.1, 27.6, 26.2, 20.4. A needle-shaped crystal of **14** (1.35 × 0.110 × 0.094 mm) was selected for X-ray crystallography. Crystal data: monoclinic, $P2_1/c$, Z = 4, a = 6.4556(7) Å, b = 13.4106(15) Å, c = 17.6286(19) Å, β = 95.762(2)°. A total of 12 299 reflections (2775 independent) were collected to a maximum 2θ of 50.68°, data-to-parameter ratio 16.0. Structure solution and refinement on F^2 resulted in final R indices of $R1$ = 0.0458, w$R2$ = 0.1260 ($F^2 > 2\sigma(F^2)$), $R1$ = 0.0511 w$R2$ = 0.1298 (all data) and a goodness of fit on F^2 of 1.052.

2-(Diisopropylamino)-2-methylpropane-1,3-diol, 15. Diester **13** (210 mg, 0.86 mmol) $LiAlH_4$ (170 mg, 4.86 mmol), 12 h, column chromatography (CH_2Cl_2/CH_3OH 8:1 (v/v)). Pale yellow oil, 120 mg, 72% yield. ^{1}H NMR (250 MHz, $CDCl_3$): 3.53 (q, J = 10.6 Hz, 4H), 3.30 (septet, J = 6.9 Hz, 2H), 3.12 (br, 2H), 1.20 (d, J = 6.9 Hz, 6H), 1.19 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): 65.7, 64.7, 46.3, 24.6, 19.4. HRMS Calcd for $C_{10}H_{24}NO_2$ (M + H) 190.18058; found, 190.18070.

General Procedure for Methylations. A greater than 3-fold excess (relative to the diester) of NaH as a 50% dispersion in mineral oil was added to dry THF and filtered under nitrogen, and the solid transferred quickly to the tared reaction vessel and weighed. Dry THF (10 mL) was added, followed by the diester, and the mixture was stirred for 0.5 h. Iodomethane (0.85−0.93 equiv relative to NaH) was added dropwise. The mixture was stirred at rt until ^{1}H NMR analysis indicated no starting material remained. TLC was not useful for monitoring the progress of the reaction since the R_f of the product and the R_f of the starting material were usually nearly identical. The reaction was quenched by addition of water and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed on the rotary evaporator. The residue was subjected to silica gel column chromatography.

Dimethyl 2-(Dicyclohexylamino)-2-methylpropane-1,3-dioate, 12. Diester **2** (310 mg, 1.00 mmol), NaH (110 mg, 4.58 mmol), CH_3I (550 mg, 3.87 mmol). Elution solvent EtOAc/hexane 1:20 (v/v). Afforded 240 mg (74% yield) of **12**, as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 3.73 (s, 6H), 2.67 (m, 2H), 1.83−0.99 (m, 20H), 1.70 (s, 3H). ^{13}C NMR (63 MHz,

$CDCl_3$): 174.2, 73.2, 60.0, 52.3, 34.5, 27.5, 26.3, 24.7. HRMS Calcd for $C_{18}H_{31}NO_4$ 325.22531; found, 325.22564.

Dimethyl 2-(Diisopropylamino)-2-methylpropane-1,3-dioate, 13. Diester **3** (330 mg, 1.43 mmol), NaH (110 mg, 4.58 mmol), CH_3I (610 mg, 4.27 mmol). Elution solvent EtOAc/hexane 1:4 (v/v). Afforded 270 mg (77% yield) of **13**, as a colorless oil. Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.90; H, 9.41; N, 5.46. ^{1}H NMR (250 MHz, $CDCl_3$): 3.74 (s, 6H), 3.21 (septet, J = 6.8 Hz, 2H), 1.71 (s, 3H), 1.14 (d, J = 6.8 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$): 174.2, 73.3, 52.3, 49.4, 24.2, 23.4.

Supporting Information Available: Tables listing literature crystal structure parameters for flattened trialkylamines, ORTEP plots of **7**, **8**, **10**, **11**, and **14**, ^{1}H and ^{13}C NMR spectra of **7**−**15**, and plots of N−C bond length vs planarity. This material is available free of charge via the Internet at http://pubs.acs.org.

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