Conformational studies by dynamic NMR. 39. Clefts in simple acyclic organic molecules. Correlated stereodynamics of N-tert-alkylbenzylamines studied by dynamic NMR spectroscopy, x-ray diffraction, and molecular mechanics calculations

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(1 H, dd, J = 8.9 and 12.3 Hz, H-9a'), 5.001 (1 H, dd, J = 2.4 and 12.3 Hz, H-9b'), 3.698 (3 H, s, COOMe), 6.00 (1 H, br d, J = 10.2 Hz, NH). O- or N-Acetyl protons (15 H) appeared at 1.880, 2.015, 2.024, 2.029, and 2.156 ppm.

(6*S*)-[6-^{2}H]Methyl 2,3,4-Tri-*O*-benzyl-[methyl (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2-6)-β-D-glucopyranoside. (11a). A mixture of **10a** (38 mg) and barium metal (3 mg) was processed in the same way for the preparation of **7a** to give a glassy **11a** (23 mg, 74%). ^{1}H NMR (CD_3OD) of Glc residue: δ 4.311 (1 H, d, J = 8.1 Hz, H-1), 3.529 (3 H, s, OMe), benzyl protons (15 H) appeared at 4.512, 4.662, 4.714, 4.744, 4.774, and 4.85 ppm, and phenyl protons appeared between 7.2 and 7.35 ppm. NeuNAc: δ 1.780 (1 H, t, J = 12.2 Hz, H-3ax'), 2.773 (1 H, dd, J = 4.6 and 12.2 Hz, H-3eq'), 2.001 (3 H, s, NAc) 3.811 (3 H, s, COOMe).

(6*S*)-[6-^{2}H]Methyl 2,3,4-Tri-*O*-benzyl-[methyl (5-acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl)onate]-(2-6)-β-D-glucopyranoside (11b). A mixture of **10b** (41 mg) and barium (3 mg) in methanol was processed in the same way for the preparation of **7a** to afford a glassy **11b** (16 mg, 48%). ^{1}H NMR (CD_3OD) of a Glc residue: δ 4.334 (1 H, d, J = 8.1 Hz, H-1), 3.568 (3 H, s, OMe), benzyl protons appeared between 4.55 and 4.80 ppm, and phenyl protons appeared between 7.2 and 7.4 ppm. NeuNAc: δ 1.689 (1 H, t, J = 12.5 Hz, H-3ax'), 2.443 (1 H, dd, J = 4.8 and 12.8 Hz, H-3eq'), 2.022 (3 H, s, NAc), 3.621 (3 H, s, COOMe).

(6*S*)-[6-^{2}H]Methyl [Methyl (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2-6)-β-D-glucopyranoside (12a) and (6*S*)-[6-^{2}H]Methyl [(5-Acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onic]-(2-6)-β-D-glucopyranoside (13a). A mixture of **11a** (25 mg) and Pd black (20 mg) in methanol–acetic acid (5:1, 5 mL) was saturated with H_2 at room temperature for 8 h. After the catalyst was filtered off, the solution was concentrated to give a glassy **12a** (11.9 mg, 70%). ^{1}H NMR (400 MHz, D_2O) of a Glc residue: δ 4.352 (1 H, d, J = 8.1 Hz, H-1), 3.260 (1 H, t, virtually coupling), 3.48 (3 H, multiplet, H-3 + H-4 + H-5), 4.033 (1 H, d, J = 3.3 Hz, H-6), 3.553 (3 H, s, OMe). NeuNAc: δ 1.843 (1 H, t, J = 12.2 Hz, H-3ax'), 2.741 (1 H, dd, J = 4.4 and 12.8 Hz, H-3eq'), 3.762 (1 H, ddd, J = 4.5, 9.1, and 12.2 Hz, H-4'), 3.88 (1 H, overlapped with COOMe signals at 3.888 ppm, H-5'), 3.567 (1 H, br d, J = 8.0 Hz, H-7'), 3.659 (1 H, dd, J = 6.6 and 13.0 Hz, H-9a'), 3.85 (3 H, multiplet, H-6' + H-8' + H-9b'), 3.888 (3 H, s, COOMe), 2.040 (3 H, s, NAc).

A solution of **12a** (10 mg) in 0.2 N NaOH aqueous solution (2 mL) was stirred at room temperature for 30 min and then neutralized with Amberlite A-120. The filtered solution was lyophilized to give a glassy **13a** (5.8 mg, 60%). ^{1}H NMR data of **13a** are given in Tables I and II in the text.

(6*S*)-[6-^{2}H]Methyl [Methyl (5-acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl)onic]-(2-6)-β-D-glucopyranoside (12b) and (6*S*)-[6-^{2}H]Methyl [(5-Acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosyl)onic]-(2-6)-β-D-glucopyranoside (13b). The same procedure as that described for the preparations of **12a** and **13a** was taken for the preparations of **12b** and **13b** from **11b** (30 mg). **12b** (16 mg, 80%), glassy solid. ^{1}H NMR (400 MHz, D_2O) of a Glc residue: δ 4.378 (1 H, d, J = 8.1 Hz, H-1), 3.264 (1 H, t, J = 9.0 Hz, H-2), 3.462 (1 H, t, virtually coupling, H-3), 3.57 (2 H, m, H-4 + H-5), 3.51 (1 H, d, J = 5.2 Hz, H-6), 3.579 (3 H, s, OMe), NeuNAc residue: δ 1.797 (1 H, dd, J = 11.5 and 13.2 Hz, H-3ax'), 2.504 (1 H, dd, J = 4.9 and 13.2 Hz, H-3eq'), 4.13 (1 H, m, virtually coupling), 3.95 (2 H, m, H-5' + H-6'), 3.86 (2 H, m, H-8' + H-9a'), 3.656 (1 H, dd, J = 6.6 and 12.5 Hz, second-order coupling), 3.866 (3 H, s, COOMe), 2.059 (3 H, s, NAc). **13b** (4 mg from 10 mg of **12b**, 41%), glassy solid. ^{1}H NMR data are given in Tables I and II in the text.

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Supplementary Material Available: NMR spectra for compounds **6a–13b** (26 pages). Ordering information is given on any current masthead page.

Clefts in Simple Acyclic Organic Molecules. Correlated Stereodynamics of *N-tert*-Alkylbenzylamines Studied by Dynamic NMR Spectroscopy,[1] X-ray Diffraction, and Molecular Mechanics Calculations

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In *N-tert*-butyl-*N*-neopentylbenzylamine (1), the slowing of four processes can be observed in the NMR spectrum at low temperature. The rate constant for 120° rotation of the *N-tert*-butyl group is three times that for 180° rotation of the phenyl group at all temperatures studied, suggesting correlated rotation of these groups. Barriers for the two processes specified are 6.8 and 7.1 kcal/mol, respectively, at −120 °C. The barrier to interconversion of enantiomeric configurations by nitrogen inversion plus rotation is 9.2 kcal/mol at −77 °C. The barrier to rotation about the *tert*-butyl–CH_2 bond is 5.95 kcal/mol at −143 °C. The anti arrangement of the *t*-BuNCH_2-*t*-Bu part of the molecule greatly limits the space available for the benzyl substituent, and only one conformation about the N–benzyl bond is populated. Molecular mechanics calculations suggest that the benzyl group occupies a pocket or cleft, defined by the *tert*-butyl groups, undergoing several kcal/mol of repulsion and attraction from opposite directions. The barrier to rotation about the phenyl–CH_2 bond is unprecedentedly high for a simple molecule but is comparable to or smaller than some found in polypeptides of rigid tertiary conformation, where concerted rotation is also a feature. Similar results obtain when either *tert*-butyl group is replaced by an adamantyl group to give *N*-(1-adamantyl)-*N*-neopentylbenzylamine (**2**) and *N-tert*-butyl-*N*-(1-adamantylmethyl)benzylamine (**3**). A crystal structure determination of **2** shows a conformation very close to that predicted by molecular mechanics calculations.

A major difference between simple organic molecules and biologically significant polymers such as proteins is the organized folding of the latter, which leads to groups being close in space, although separated by many bonds

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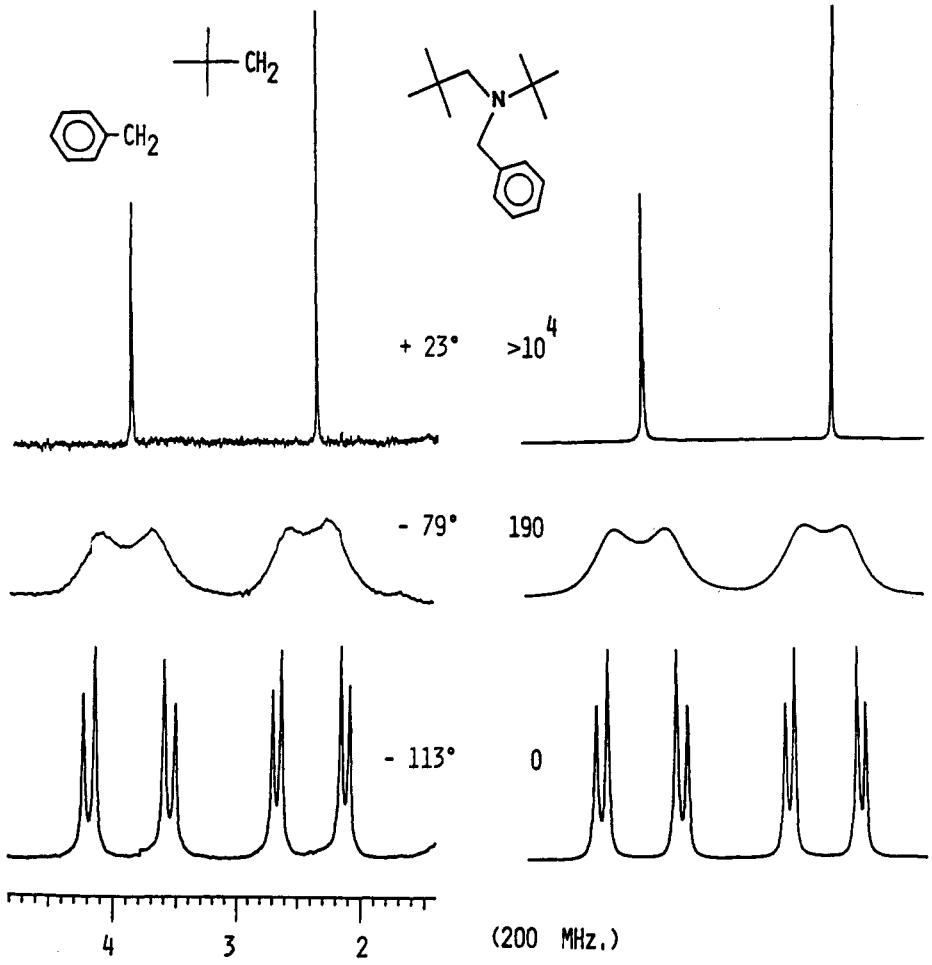

Figure 1. (Left) Methylene region of the 200-MHz proton NMR spectrum of 1 in CF_2Cl_2/CD_2Cl_2 at three temperatures. (Right) Simulated spectra with the appropriate rate constants for nitrogen inversion/rotation. The $PhCH_2$ and t-$BuCH_2$ signals are simulated with the same rate constant.

in the molecular structure. This proximity may be important for some biological function of the protein. One aspect of this, which is easy to demonstrate, is the existence of pockets or clefts in which the side chain of a remote residue is accommodated.[2,3] Pockets and clefts are distinguished from other available conformational space in that constraints are placed on the occupying group from opposite directions, often from many directions.

Of particular interest to this work is a well-known feature of some proteins, the slow rotation on the NMR time scale of the phenyl groups of phenylalanine or of tyrosine fragments,[2] which appears as separate NMR signals for the two ortho protons (or meta protons) of these groups. Occasionally on raising the temperature, a classic dynamic NMR coalescence of signals allows a determination of a barrier to rotation of the phenyl group in the range of 15–20 kcal/mol.

The slowly rotating aromatic ring is commonly in close physical proximity to another such ring,[3d] and in these circumstances, rotation of the two phenyl groups may be concerted.[3c] At least one simple tetraphenyl compound shows similar effects.[3e] Such hindered rotation is associated only with enzyme inhibitors and electron-transfer proteins whose function requires them to be rigid.[3b]

In contrast, the barrier to rotation of the phenyl group in simple unsubstituted benzyl compounds $PhCH_2X$ has never been determined by dynamic NMR spectroscopy.[4a] Even for neopentylbenzene (X = *tert*-butyl) the barrier is expected to be about 5 kcal/mol.[4,5]

An indirect determination of such barriers can be made from the magnitude of coupling constants—the J method[6]–and in the case of *N,N*-dimethylbenzylamine, which is directly relevant to the results of this paper, the phenyl rotation barrier is considered to be only 0.8 kcal/mol, the preferred conformation having the C–N bond perpendicular to the ring plane.

We now want to report the temperature dependence of the NMR spectra of the relatively simple amines **1–3**, demonstrating four conformational processes in each molecule, with particularly high barrier to rotation about the phenyl–CH_2 bond and to nitrogen inversion/rotation. Molecular mechanics calculations and a crystal structure

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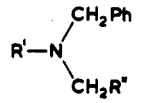

1: R′ = R″ = *tert*-butyl
2: R′ = adamantyl, R″ = *tert*-butyl
3: R′ = *tert*-butyl, R″ = adamantyl

determination for **2** suggest that the phenyl group occupies a conformational cleft in the molecule and that this, as in proteins, produces the abnormally high rotational barrier. In addition, rotations of the phenyl group and of the *tert*-alkyl group R′ appear to be correlated.

Results

Dynamic NMR Spectroscopy. As the temperature is lowered, four sets of changes are observed in the NMR spectra of each of 1 to 3. Those for **1** are now described in detail and shown in Figures 1–3.

At ambient temperature in the proton NMR, two *tert*-butyl singlets and two methylene singlets are seen at δ0.90, δ0.99, δ2.36, and δ3.83, respectively. In the aromatic region there is an A_2M_2X pattern, apparently a doublet of doublets for the ortho protons and triplets with further fine structure for the meta and para protons. The former signals at δ 7.52 is markedly downfield compared with benzylamine (7.25) and *N,N*-dimethylbenzylamine (7.30),[7] while the latter triplets are at δ 7.13 and 7.26.

On cooling, the methylene group signals broaden and split below about −77 °C (200 MHz), each giving an AB quartet, see Figure 1. Full line-shape treatment suggests that this represents slowing of a process (which we will conclude to be nitrogen inversion/rotation) with a barrier $\Delta G^{\ddagger}$ of 9.2 kcal/mol.

Over a slightly lower temperature range first the ortho proton and then the meta proton signals broaden and split below about −118 °C to give apparently two doublets of equal area with a large chemical shift and two triplets of equal area with a small relative chemical shift, respectively, see Figure 2. These with the unchanged para proton signal represent an AFKPX pattern. The process responsible for these changes, concluded to be rotation of the phenyl group as discussed later, has a barrier $\Delta G^{\ddagger}$ of 7.1 kcal/mol at −120 °C. A complete line-shape treatment of spectra at 11 temperatures between −101 and −133 °C yielded $\Delta H^{\ddagger}$ = 6.9 ± 0.25 kcal/mol and $\Delta S^{\ddagger}$ = −1.3 ± 1.7 eu.

At slightly lower temperatures, the N-*tert*-butyl signal broadens compared with other signals and splits below about −125 °C to three equal singlets, indicating that rotation of that *tert*-butyl group is slow on the NMR time scale with a barrier $\Delta G^{\ddagger}$ of 6.8 kcal/mol at −130 °C. The rate constant for 120° rotation of this group is three times that for 180° rotation of the phenyl group at all temperatures studied over a range of more than 30°, see Experimental Section.

Below about −140 °C, the *C-tert*-butyl signal shows unusual broadening and below about −151 °C it splits to a very broad 1:2 doublet which may be a 1:1:1 triplet with the latter lines unresolved and should be such a triplet due to the overall asymmetry of the molecule.[5a] Rotation about the CH_2–*tert*-butyl bond is slow on the NMR time scale with a barrier $\Delta G^{\ddagger}$ of 5.9 kcal/mol at −152 °C.

Of these four sets of spectral changes, the latter three have corresponding changes in the carbon-13 NMR spectrum, which lead to barriers comparable to those derived from proton spectra. The ortho and meta carbon signals each split to a doublet. The *N-tert*-butyl signal splits to a 1:1:1 triplet, while the *C-tert*-butyl signal splits to a 1:2

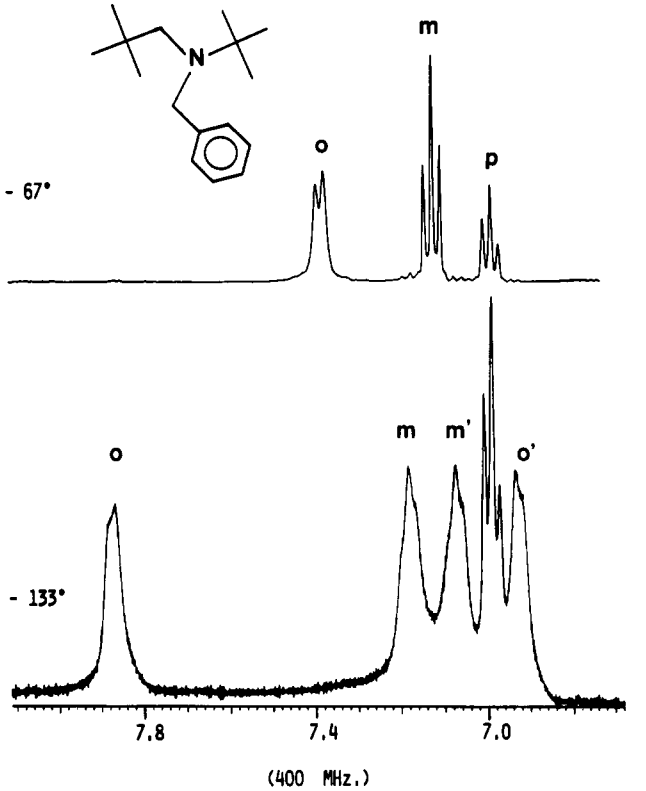

Figure 2. Aromatic region of the 400-MHz proton NMR spectrum of 1 in CF_2Cl_2/CD_2Cl_2 at −67 °C and at −133 °C when phenyl group rotation is slow on the NMR time scale.

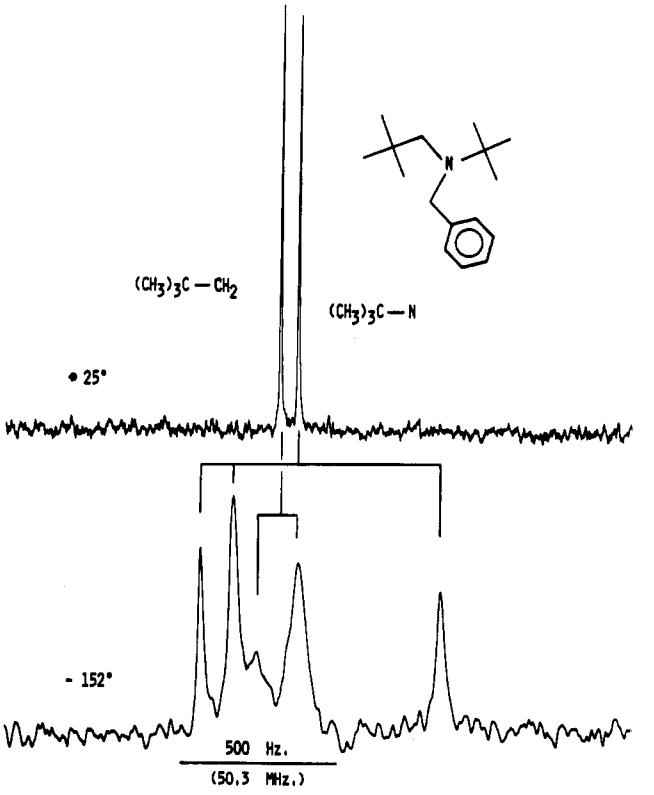

Figure 3. Methyl region of carbon-13 NMR spectra of 1 in CF_2Cl_2/CD_2Cl_2 at 50.3 Mhz operating frequency at ambient temperature and at −152 °C when *N-tert*-butyl and *C-tert*-butyl rotation are slow on the NMR time scale. The latter signal appears as a 1:2 doublet rather than a 1:1:1 triplet owing putatively to accidental overlap.

(7) Aldrich NMR Spectral Catalogue, 2nd ed., Vol. 1, pp 1066–7. Aldrich Chemical Co., 1983.

Table I. Barriers to Rotation and Nitrogen Inversion (ΔG^{+}, kcal/mol) for Compounds 1–3 (Temperatures (K) in Parentheses)

compound and solvent	nitrogen inversion		*tert*-alkyl-N rotation	phenyl-CH_2 rotation	*tert*-alkyl-CH_2 rotation
	CH_2R signal	CH_2Ph signal			
1. CF_2Cl_2/CD_2Cl_2	9.2[a] (196)	9.2[b] (196)	6.8[b] (150	7.15[b] (160)	5.9[c] (121)
Me_2O/CD_2Cl_2			7.5[d] (168)	7.8[d] (148)	5.95[d] (130)
2. CF_2Cl_2/CD_2Cl_2	9.2[b] (184)	9.2[b] (184)	*e*	8.1[b] (184)	5.85[b] (130)
Me_2O/CD_2Cl_2			7.7[d] (180)	8.15[d] (180)	
3. CF_2Cl_2/CD_2Cl_2	9.3[b] (185)	9.2[b] (185)	*e*	7.3[b] (185)	5.9[b] (129)
Me_2O/CD_2Cl_2			7.6[d] (170)		

[a] From the 200-MHz proton spectrum. [b] From the 400-MHz proton spectrum. [c] From the 50.3-MHz carbon-13 spectrum. [d] From the 75.5-MHz carbon-13 spectrum. [e] Too poorly soluble for carbon-13 spectra at low temperature. Proton spectra have overlap.

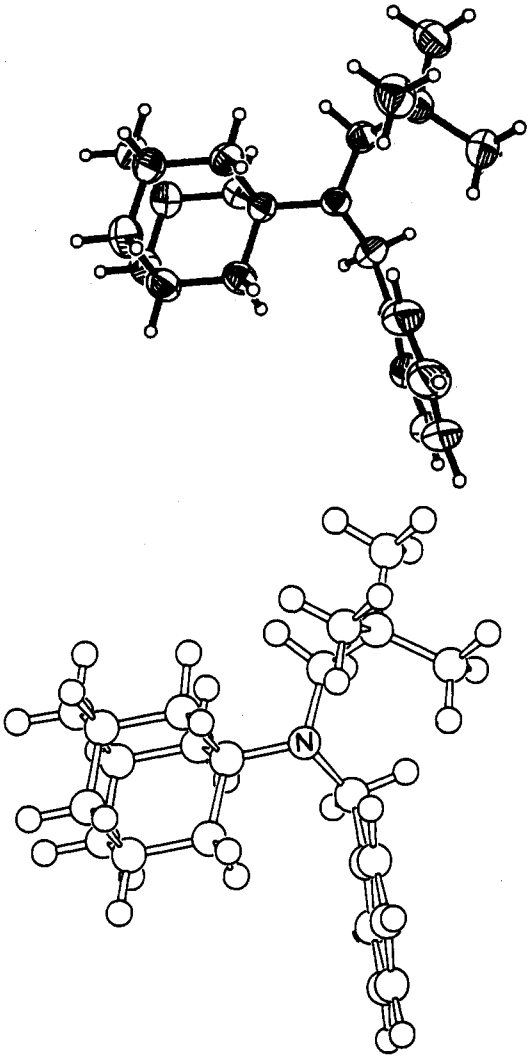

Figure 4. (Top) View of the X-ray diffraction structure of crystalline **2** and (bottom) view of the molecular mechanics calculated minimum energy conformation of **2**.

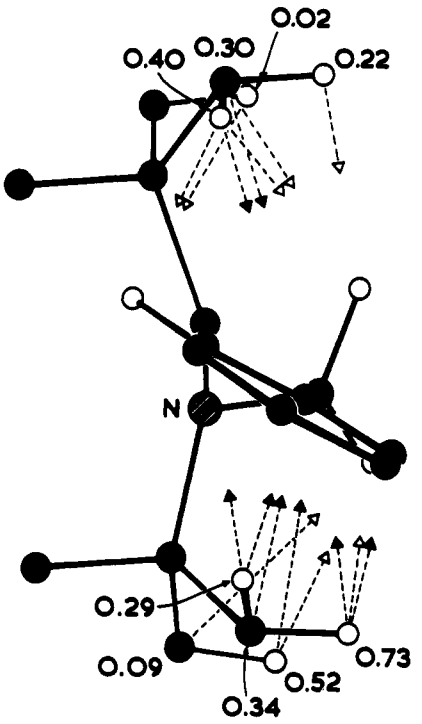

Figure 5. Repulsive interactions between the benzyl group and the two *tert*-butyl groups in **1** as suggested by molecular mechanics calculations. Open circles represent hydrogens involved; other hydrogens are suppressed. Carbon atoms are shown as filled circles. Benzyl group atoms involved are identified by arrows, open-headed or solid depending as that atom is hydrogen or carbon. Numbers indicate total repulsions (kcal/mol) from each *tert*-butyl atom involved.

doublet, presumably an unresolved, 1:1:1 triplet, see Figure 3.

Corresponding changes are seen in the NMR spectra of **2** and **3**, and the barriers measured are summarized in Table I. The α-CH_2 protons of the adamantyl group become diastereotopic as nitrogen inversion slows in a way that is now quite expected.[8]

Crystal Structure Determination and Molecular Mechanics Calculations. The solid-state structure of **2** was determined by an X-ray diffraction investigation of a single crystal of that compound. Molecular mechanics calculations of the gas-phase structures of **1–3** were carried out by using Allinger's MMP2-82 program whose provenance and suitability for aliphatic amines has recently been discussed.[9a] Figure 4 shows a space-filling representation of the crystal structure of **2** and underneath is shown shows a plot of the molecular mechanics minimum energy conformation for the same molecule. Table II summarizes relevant features of the calculated and experimentally determined structures, the generalized numbering system being indicated in structure **4**. Calculated and experimentally determined conformations described in that table and shown in Figures 4 and 5 are quite similar, and the following aspects are particularly significant.

The two tertiary alkyl groups are not perfectly anti with respect to each other, the (2–3–4–5) dihedral angle being 39.7 to 43.6° away from 180°, see **5**. By this means the *C-tert*-alkyl group is closer to the lone pair than to the benzyl group. The phenyl ring is even further removed from being anti to the *N-tert*-alkyl group, see **6**, having

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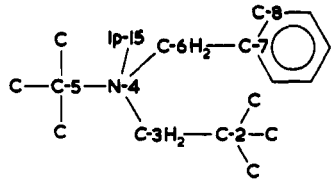

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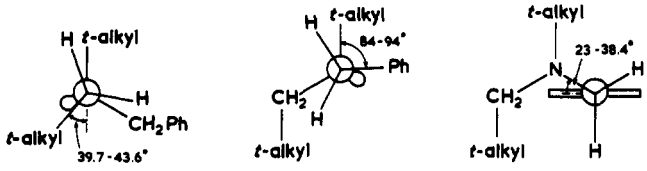
rotated beyond the lone pair until its dihedral angle (5–4–6–7) with the *N-tert*-alkyl group is only 84 to 94°.



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The C–N bond is by no means perpendicular to the benzene ring plane, the obvious expectation for a bulky group, the dihedral angle (4–6–7–8) being only 23 to 38.4° (see 7). The benzene ring is thus face-on to the nearest methyl or methylene group of the *N-tert*-alkyl group, thereby reducing the effect of the small 84–94° dihedral angle mentioned above, and it points its edge between the two nearest methyls or methylenes of the *C-tert*-alkyl group (see Figure 5). The phenyl group conformation is thus determined by long-range interactions of atoms at least four bonds apart although near-in-space.

A view of the calculated minimum energy conformation of 1 looking at the para position of the benzene ring is shown in Figure 5. Not all hydrogen atoms (open circles) are shown, only those involved in repulsive interactions between the benzyl group and the *tert*-butyl groups as suggested by calculations.

Table III sums the 356 long-range interactions between atoms of the benzyl group and the two *tert*-butyl groups, under the headings of repulsions and attractions, and suggests that in determining the cleft attractive steric interactions are at least as important as repulsive ones. Being more central, the CH_2 group and presumably the N–CH_2Ph bond conformation are more influenced by short-range repulsive interactions. The phenyl group and the phenyl–CH_2 bond conformations are affected more by attractive interactions. The rather more important role of the *N-tert*-butyl group compared with the *C–C-tert*-butyl group reflects the fact that it is one bond nearer the benzyl group.

When it is recalled that the phenyl group rotational barrier in *N,N*-dimethylbenzylamine,[6] with only short-range interactions, requires only 0.8 kcal/mol to allow the phenyl group to explore the complete 360° of conformational rotational space, it is reasonable to suggest that the long-range interactions present in the series 1 to 3, and partially enumerated above for 1, *determine* the conformation.

It is imprudent to overinterpret individual numbers emerging from molecular mechanics calculations of repulsive and attractive interactions, since the exact form of the van der Waals curve is a matter for discussion[9b] but the general picture is clear and credible. Long-range repulsive interactions between a few pairs of atoms in many-atom groups like phenyl and *tert*-butyl will inevitably be associated with a considerable sum of attractive interactions between the many remaining pairs of atoms in spite of the small size of any single attractive interaction. We think it may emerge as a general truth that when the conformation of one group is determined by atoms that are many bonds distant, attractive interactions are at least as important as repulsive ones.

The crystal structure of 2 shown in Figure 4 and the calculated repulsive interaction diagram for 1 shown in Figure 5 both clearly indicate the cleft-like environment of the phenyl group which results from these interactions. The impression is enhanced by a fuller molecular mechanics investigation of compound 1 as to the conformations about the N–neopentyl, N–benzyl, and CH_2–phenyl bonds. No other minimum other than degenerate or enantiomeric ones within 2.6 kcal/mol of the ground state was found.

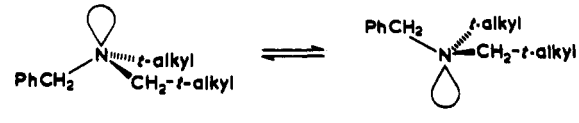
Attempts to mimic the concerted or unconcerted rotational behavior of compound 1 using molecular mechanics were unsuccessful. Rotation of the phenyl group from the ground-state conformation in either direction, while it is calculated to proceed smoothly initially, does not induce significant rotation of the *N-tert*-butyl group. Eventually before 180° rotation is achieved, the phenyl and *N-tert*-butyl groups clash and produce steric energies unrealistically higher than the observed rotational barriers. Calculated rotation of the *N-tert*-butyl group from the ground state achieves 120° of rotation with a barrier of 9.4 kcal/mol, but the phenyl group does not rotate in concert. This calculated barrier is higher than that observed experimentally, 6.8 kcal/mol, while normal experience[9c] is that calculated barriers of this kind are 40% *lower* than the experimental, so independent rotation of the *tert*-butyl group does not seem to be the process actually taking place in the molecule.

Calculated rotation of the *benzyl* group away from the ground state (+ gauche) conformation into (– gauche) rotational space does produce a metastable (ΔG_o = +2.6 kcal/mol) conformation and does induce phenyl group rotation, i.e., rotation about the N–CH_2Ph and NCH_2–Ph bonds is concerted. However rotation of either the phenyl group or the *N-tert*-butyl group from this metastable conformation does not cause rotation in concert of the other group. As a corollary, phenyl group rotation is calculated to induce rotation about the N–benzyl bond but, as 180° rotation of the phenyl group reaches completion, the benzyl group resumes its original unique stable conformation.

If the phenyl group is rotated through its 360° of rotation in 10° steps, calculating the *tert*-butyl rotational barrier at each step, higher barriers even further from the experimental one are the result, so such a simple model of the concerted rotation will not do.

Discussion

Nitrogen Inversion/Rotation. In all molecules 1–3, the first process observed on lowering the temperature is the splitting of the CH_2 proton signals with no corresponding changes in the carbon-13 NMR spectrum. That the two protons of a methylene group become diastereotopic indicates that the process 8 ⇌ 9 has become slow and the nitrogen configuration has become chiral on the NMR time scale.



8 9

It is well-known[10,11] that in trialkylamines $R_AR_BR_CN$

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Table II. Selected Parameters from MMP2-Calculated Structures for Compounds $RN(CH_2Ph)CH_2R'$ 1–3 and X-ray Diffraction Crystal Structures of 2 (Diagram 4 Indicates Numbering)

	1: R = *tert*-butyl, R′ = *tert*-butyl calcd	3: R = *tert*-butyl, R′ = adamantyl calcd	2: R = adamantyl, R′ = *tert*-butyl calcd	2: R = adamantyl, R′ = *tert*-butyl crystal structure
		Dihedral Angles (deg)		
5-4-3-2	140.1	140.3	139.3	136.4
5-4-6-7	-84.0	-85.4	-86.1	-94.0
lp-4-3-2	23.7	23.9	23.0	*a*
lp-4-6-7	32.6	31.0	30.2	*a*
4-6-7-8	-38.4	-36.4	-34.5	-23.0
C-5-4-3	176.1	176.1	175.3	179.9
C-2-3-4	-176.4	-177.4	-176.7	-176.8
		Bond Lengths[b] (Å)		
C5-N4	1.4919	1.4916	1.4937	1.497
C6-N4	1.4770	1.4772	1.4776	1.469
C3-N4	1.4783	1.4779	1.4789	1.484
		Bond Angles (deg)		
C-C5-C	105.0	105.1	105.5	106.8
	107.3	107.4	107.2	108.5
	108.5	108.1	108.3	108.9
N4-C5-C	109.6	109.6	109.6	109.6
	112.1	111.9	111.8	109.7
	113.9	113.9	114.0	113.1
C5-N-C6	113.4	113.2	113.7	113.9
C5-N-C3	113.2	113.3	113.7	114.2
C3-N-C6	110.2	110.4	110.0	110.7

[a] Not located. [b] The strainless molecular mechanics value for the C–N bond length is 1.45 Å.

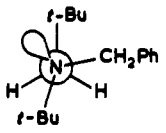
Table III. Repulsive and Attractive Long-Range Interactions (kcal/mol) between the Benzyl Group and the Two *tert*-Butyl Groups in 1 As Suggested by Molecular Mechanics Calculations

	16 repulsive interactions			340 attractive interactions		
	of the CH_2 group	of the phenyl group	total	of the CH_2 group	of the phenyl group	total
from the *N-tert*-butyl group	0.84	1.14	1.98	0.64	1.67	2.31
from the *C-tert*-butyl group	0.92	0.02	0.94	0.55	1.15	1.70
total	1.76	1.16	2.92	1.19	2.82	4.01

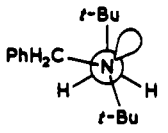
increasing bulk of the substituents R leads to faster nitrogen inversion as the following set of barriers (kcal/mol) exemplifies: $MeNEt_2$[12] 7.9; MeN(Et)*t*-Bu[13] 7.2; MeN(CH_2Ph)-*t*-Bu[13,14] 6.3.

Compound 1 extends the series by replacing the methyl group by a neopentyl group, and its much larger barrier of 9.2 kcal/mol is clearly incongruous.

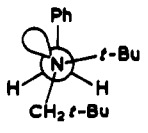
Interconversion of the ground states represented by 8 and 9 is not achieved by nitrogen inversion alone. Alternative representations 10, 11 and 12, 13 indicate that at



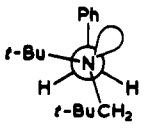
(10)



(11)



(12)



(13)

appropriate points benzyl and *C-tert*-butyl groups and phenyl and *N-tert*-butyl groups must be eclipsed, so the observed barrier also reflects these eclipsing interactions.

In the large set of trialkylamines that has been investigated,[13-22] inversion/rotation at nitrogen undoubtedly involves a range of transition states. When a planar nitrogen configuration is the high energy point, the process may be described as inversion dominant. When one compound has a lower barrier than a similar but less substituted compound, then both are likely to be involved in an inversion-dominant process. When the high energy point corresponds to two bonds being eclipsed, the inversion/rotation process may be described as rotation dominant. When one compound has a higher barrier then a less highly substituted compound, the former at least is involved in a rotation-dominant process, and we suggest that compounds 1–3 are in this category.

Phenyl Group and *N-tert*-Alkyl Group Rotation. In each compound 1–3, the second highest barrier is due to a process that affects the ortho and meta positions of the phenyl ring but not the benzyl-CH_2 group, which points to 180° rotation of the phenyl group with barriers in the range 7.5 to 8.1 kcal/mol.

(11) Montanari, F.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1969**, 1086.
(12) Bushweller, C. H.; Fleischman, S. H.; Grady, G. L.; McGoff, P.; Rithner, C. D.; Whalon, M. R.; Brennan, J. G.; Marcantonio, R. P.; Domingue, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 6224.
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(17) Fleischman, S. H.; Whalon, M. R.; Rithner, C. D.; Grady, G. L.; Bushweller, C. H. *Tetrahedron Lett.* **1982**, *23*, 4233.
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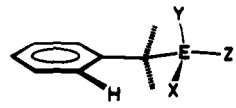
(21) Casarini, D.; Davalli, S.; Lunazzi, D.; Macciantelli, D. *J. Org. Chem.* **1989**, *54*, 4616.
(22) Berger, P. A.; Hobbs, C. A. *Tetrahedron Lett.* **1978**, 1905.
(23) Bushweller, C. H.; Anderson, W. G.; Stevenson, P. E.; O'Neil, J. W. *J. Am. Chem. Soc.* **1975**, *97*, 4228.

For a simple benzyl compound like neopentyl benzene,[4a,5] calculations suggest that the likely transition state for phenyl-CH_2 rotation, is the point where the inward-directed substituent X (see **14a**) passes through the plane,



14a: EXYZ = $C(CH_3)_3$
14b: EYZ = $N(CH_3)_2$, X = lone pair
14c ≡ **1**: E = N, X = lone pair, Y = tBu, Z = CH_2tBu

not the point where the C–E bond is coplanar with the ring. In dimethylbenzylamine, where X is a lone pair, transition-state conformation **14b** is not sterically crowded and a rotational barrier of only 0.8 kcal/mol[6] is not unreasonably small. The solid-state conformation of **2** and the calculated *ground-state conformations* of **1** to **3** are close to that of **14c**, i.e., the rotational *transition-state conformations* of simpler molecules, with the lone pair near to the plane and to the *ortho hydrogen*. The unusual conformation with benzylic protons on either side of the phenyl plane is confirmed to exist in solution by the uncommonly large[24,25] geminal coupling constant of 17.8–18.2 Hz. The phenyl group rotational barrier of about 8 kcal/mol in **1**–**3** contrasts starkly with that in dimethylbenzylamine, and it is attractive to invoke interactions beyond the β and τ positions.

The barrier to rotation of the *N-tert*-alkyl group is about 7.5 kcal/mol for each of **1** to **3**. A degree of nitrogen flattening during the process or even nitrogen inversion may lead to low rotational barriers in tertiary alkylamines, but **1** to **3** are unusual for a 200° rotation takes place on average 70 times between each nitrogen inversion, so while flattening of nitrogen undoubtedly takes place during rotation, complete nitrogen inversion is certainly not the mechanism for rotational interchange.

The size of the barriers to rotation about the *N-tert*-alkyl bonds is not unusual[26a] nor is the fact that we find similar barriers in *N-tert*-butyl and *N*-adamantyl compounds since previous examples[26b,c] have adamantyl barriers higher or lower then *tert*-butyl ones depending on circumstances.

The particularly striking feature of the 180° phenyl and 120° *N-tert*-alkyl rotations is that the frequency of the latter is always three times that of the former as measured by the dynamic NMR method for each of **1**–**3**. In other words the frequency of 360° rotation of the alkyl group appears to be the same as 180° rotation of the phenyl group.[27,28] The edge of the phenyl group, however, does not sit between two of the methyl or methylene groups of the *N-tert*-alkyl group, nor does it appear that as the phenyl group rotates it should produce *three* 120° rotations of *tert*-alkyl group. From the opposing point of view, it is not clear how three 120° rotations of the *tert*-alkyl group, producing successively identical *tert*-alkyl group conformations, would cumulatively induce one 180° phenyl group rotation. Molecular mechanics calculations have been of little direct help in understanding the co-operative process as indicated in the Results section.

An alternative explanation is that during 180° rotation of the phenyl group, accompanied by some rotation about other bonds, a point is reached where the *N-tert*-alkyl group is less constrained as compared with the ground state and rotates relatively freely. As the phenyl group completes its 180° degree rotation, the *N-tert*-alkyl group is once again constrained. The net effect in the NMR spectrum is that when phenyl group 180° rotation is slow on the NMR time scale, interconversion of all three *tert*-alkyl conformations by three or perhaps more 120° rotations is also slow.

This conformational disengagement model presents a concerted rotation which contrasts with the well-known examples of geared rotation,[29,30] where rotation of the first part is related to a specific degree of rotation of the second part. Clearly in molecules like **1**–**3** where substituents interact strongly, concerted rotation of phenyl and *N-tert* alkyl groups involves the N–benzyl, N–neopentyl, and C–*tert*-butyl bonds and even methyl group rotation. The necessary systematic molecular mechanics investigation in multidimensional conformational space is an exercise beyond our capabilities.

The entropy of activation for phenyl group rotation in **1** is −1.3 ± 1.7 eu, determined from rotational rate constants in a 32° temperature range between 140 and 172 K. It is notoriously futile to place great weight on such values determined by dynamic NMR spectroscopic methods,[31] but the small value may be some confirmation that the ground state is almost as highly organized as the transition state.

***C-tert*-Alkyl Bond Rotation.** The fourth process observed in these molecules is rotation of the *tert*-butyl or adamantyl group in the neopentyl or adamantyl-CH_2 part of the molecule with barriers in each case of 5.9 kcal/mol, reasonably in line with what has been observed[32] for simpler compounds, *tert*-butyl-CH_2X (X = Me, Br, I). That the barriers are no higher in spite of the complexity of the groups X in the present work indicates that this is another case of steric acceleration of a conformational process.

Two kinds of weak hydrogen bonding involving phenyl rings have been extensively investigated recently, that of a weakly acidic ortho proton with a lone pair on a β side-chain atom[33,34] and of an alkyl proton with a benzene π-cloud.[35] The crystal structure of **2** is consistent with such effects, but the molecular mechanics calculations

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(25) Barfield, M.; Hruby, V. J.; Meraldi, J.-P. *J. Am. Chem. Soc.* **1976**, *98*, 1308.

(26) (a) Anderson, J. E.; Pearson, H. *J. Chem. Soc., Chem. Commun.* **1972**, 908. (b) Anderson, J. E.; Pearson, H.; Rawson, D. I. *J. Am. Chem. Soc.* **1985**, *107*, 1447. (c) Anderson, J. E.; Kirsch, P. A.; Lomas, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1065.

(27) The 1:3 relationship in the rate constants is shown in Table VI, and was observed over larger or smaller temperature ranges for the three compounds depending on the suitability of spectra. Factors limiting this are interference of the nitrogen inversion dynamic effect with the rotational dynamic effects, widely differing chemical shift differences for the two rotational processes producing effects in temperature ranges that do not greatly overlap, and spectral overlap in adamantyl compounds.

(28) It may seem discrepant that we talk of concerted rotation of the *N-tert*-alkyl group and phenyl group, yet report barriers different by about 0.3 kcal/mol for the two rotations. The reported barriers are derived, using the Eyring equation, from the frequency of 120° and 180° rotation of groups as indicated by the NMR. If the concerted process involves 360° rotation, then its frequency is one-third of the frequency of 120° rotation, and the barrier calculated for the concerted process from the two signals is the same.

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(30) Iwamura, H.; Mislow, K. *Acc. Chem. Res.* **1988**, *21*, 175.

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(32) Whalen, M. R.; Bushweller, C. H.; Anderson, W. G. *J. Org. Chem.* **1984**, *49*, 1185.

(33) Oki, M. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 387, 393.

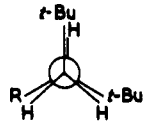
(34) Cook, N. J.; Khan, T. A.; Nasri, K. *Tetrahedron* **1986**, *42*, 249 and citations therein.

(35) Karatsu, M.; Suezawa, H.; Abe, K.; Hirota, M.; Nishio, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3529 and earlier work cited therein.

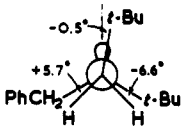
(36) Reference 9b, p 222.

arrive at a very similar structure without taking any special account of hydrogen bonding.

We have consistently found in calculations of molecules of the type t-$Bu_aCH_2X(R)$-t-Bu_b (X = N or CH, R = *tert*-alkyl) that because of the demands of substituents there is a local conformational minimum in which the *tert*-butyl nearly eclipses the nitrogen lone pair or the C–H bond of X as in **15**, which shows X = CH. In all cases the



15



16

resulting calculated conformation is nonalternating,[37] i.e., the two hydrogen atoms on the front atom fall within the R–C–*t*-Bu angle in the Newman projection as shown. In the case of **1**, the second most stable conformation, albeit 2.66 kcal/mol above the ground state, is calculated to be a nonalternating one, specifically the one shown as **16**.

Conclusion. There are thus four conformational processes within the molecules **1–3** with high barriers falling within the dynamic NMR range. Each reflects to a greater or lesser extent the unusual long-range interactions of these molecules. Two sterically demanding groups are more or less anti to each other, laying down considerable restrictions on any other substituent, but a phenyl group with its marked steric anisotropy manages to find space between them. The most significant result is the high rotational barrier for an unsubstituted phenyl group and its rotating in concert with an adjacent *tert*-alkyl group, an explanation for which we have given in terms of conformational disengagement.

Experimental Section

The tertiary amines **1–3** were prepared according to a general method,[39,40] which is described in detail for compound **1**.

***N*-*tert*-Butyl-*N*-neopentylbenzylamine (1).** *N*-*tert*-Butyl-*N*-neopentylbenzamide (**26**) (6.1 g, 25 mmol) was added to $LiAlH_4$ (1.4 g, 3.7 mmol) suspended in ether (20 mL) and *n*-butyl ether (40 mL). After 3 h at 105 °C, reduction was complete (GLC). The mixture was cooled to room temperature and 20 mL of water was added dropwise. The precipitate was filtered off and workup of the organic layer gave 5.1 g of the crude product. After distillation under reduced pressure, 4.4 g of colorless oil was obtained, $bp_{0.5}$ 92–93 °C. The product was still contaminated by secondary amine, so it was purified by preparative VPC: ^{1}H NMR 200 MHz ($CDCl_3$) δ 0.9 (s, 9 H, $CCMe_3$), 1.0 (s, 9 H, $NCMe_3$), 2.4 (s, 2 H, CH_2CMe_3), 3.8 (s, 2 H, CH_2Ph), 7.1 (t, 1 H, H-para), 7.25 (t, 2 H, H-meta), 7.5 (d, 2 H, H-ortho); ^{13}C NMR 50 MHz ($CDCl_3$) δ 27.2 (3 C, $NC^{13}CH_3$), 28.4 (3 C, $CC^{13}CH_3$), 32.6 ($C^{13}CC$), 56.1 ($N^{13}C(CH_3)_3$), 57.8 (1 C, $^{13}CH_2CMe_3$), 64.2 (1 C, $^{13}CH_2Ph$), 125.6 (1 C, Ph), 126.9 (2 C, Ph), 127.8 (2 C, Ph), 140.9 (1 C, Ph, ipso); HRMS calcd for $C_{16}H_{26}N$ 233.21435, found 233.21510. Anal. Calcd for $C_{16}H_{26}N$: C, 82.34; H, 11.66; N, 6.00. Found: C, 81.82; H, 11.45; N, 5.77.

***N*-Neopentyl-*N*-(1-adamantyl)benzylamine (2)** was obtained as a white crystalline solid, mp 127–128 °C, from *N*-benzoyl-*N*-(1-adamantyl)neopentylamine (**27**) as for **1**: ^{1}H NMR 200 MHz ($CDCl_3$) δ 0.9 (s, 9 H, $CC(Me)_3$), 1.55 (s br, 6 H, CH_2 of Ad), 1.62 (d, 6 H, CH_2 of Ad), 2.0 (s br, 3 H, CH of Ad), 2.4 (s, 2 H, CH_2CMe_3), 3.9 (s, 2 H, CH_2Ph), 7.15 (t, 1 H, H-para), 7.25 (t, 2 H, H-meta), 7.5 (d, 2 H, H-ortho); ^{13}C NMR 50 MHz ($CDCl_3$) δ 28.3 (3 C, $C^{13}CH_3$), 29.5 (3 C, ^{13}CH of Ad), 32.6 (1 C, ^{13}C-CH_3), 36.7 (3 C, $^{13}CH_2$ of Ad), 39.6 (3 C, $^{13}CH_2$ of Ad), 56.0 (1 C, $^{13}CH_2CMe_3$), 56.2 (1 C, $^{13}C_{ad}$-CH_2), 61.9 (1 C, $^{13}CH_2Ph$), 125.5 (1 C, Ph), 126.9 (2 C, Ph), 129.8 (2 C, Ph), 145.6 (1 C, Ph-ipso); HRMS calcd for $C_{22}H_{3N}$ 311.26130, found 311.26079. Anal. Calcd for $C_{22}H_{33}N$: C, 84.82; H, 10.68; N, 4.50. Found: C, 84.73; H, 10.51; N, 4.28.

***N*-*tert*-Butyl-*N*-(1-adamantylmethyl)benzylamine (3)** was obtained as a white crystalline solid, mp 56–58 °C, from *N*-benzoyl-*N*-(1-adamantylmethyl)-*tert*-butylamine (**28**) as for **1**: ^{1}H NMR 200 MHz ($CDCl_3$) δ 1.0 (s, 9 H, $NCMe_3$), 1.55 (d, 6 H, CH_2 of Ad), 1.65 (m, 6 H, CH_2 of Ad), 1.9 (s br, 3 H, CH of Ad), 2.25 (s, 2 H, NCH_2Ad), 3.6 (s, 2 H, NCH_2Ph), 7.15 (t, 1 H, H-para), 7.30 (t, 2 H, H-meta), 7.5 (d, 2 H, H-ortho); ^{13}C NMR 50 MHz ($CDCl_3$) δ 27.3 (3 C, $C^{13}CH_3$), 28.6 (3 C, ^{13}CH of Ad), 34.5 ($NCH_2{}^{13}C$ of Ad), 37.1 (3 C, $^{13}CH_2$ of Ad), 41.1 (3 C, $^{13}CH_2$ of Ad), 55.9 ($N^{13}C$ CH_3), 57.9 (C, $^{13}CH_2Ad$), 65.4 (C, $^{13}CH_2Ph$), 125.6 (1 C, Ph), 127.0 (2 C, Ph), 127.8 (2 C, Ph), 145.5 (1 C, Ph-ipso); HRMS calcd for $C_{22}H_{33}N$ 311.26130, found 311.26171. Anal. Calcd for $C_{22}H_{33}N$: C, 84.82; H, 10.68; N, 4.50. Found: C, 85.76; H, 10.88; N, 4.39.

***N*-*tert*-Butylpivalamide (29).** In a three-neck flask, 20 mL (190 mmol) of *tert*-butylamine, 26.5 mL (190 mmol) of triethylamine, and 150 mL of chloroform were mixed and after the solution was chilled at 0 °C, 19 mL (0.16 mmol) of pivaloyl chloride was carefully added (exothermic reaction). After 4 h of reflux, a white precipitate of ammonium salt had formed; the mixture was cooled to room temperature and 50 mL of water added. The organic layer was separated, washed, and dried and the solvent evaporated in vacuo to afford 26.8 g of crude product directly utilized for the next step: HRMS calcd for $C_9H_{19}ON$ 157.25788, found 157.25820. Anal. Calcd for $C_9H_{19}ON$: C, 68.74; H, 12.18; N, 8.91. Found: C, 67.91; H, 12.40; N, 8.03.

***N*-*tert*-Butylneopentylamine (30).** To a suspension of $LiAlH_4$ (4.7 g, 122 mmol) in *n*-butyl ether (80 mL) and ethyl ether (60 mL), chilled at 0 °C, under N_2 was added 12.8 g (81 mmol) of **29** all at once. The suspension was stirred for 0.5 h and then refluxed, and the solvent was distilled until the temperature reached 110 °C. After 1 h the reaction was complete. The mixture was cooled at room temperature and 20 mL of water was added dropwise (exothermic reaction). The hot mixture was cooled and the precipitate filtered off. The filtrate was acidified (HCl 3 M) and the organic layer separated. The aqueous layer was treated with 15% NaOH and extracted several times with ethyl ether. The combined organic layers were finally dried and concentrated to yield the crude product, which was distilled under vacuum, yielding 8.7 g of colorless oil, bp 760 130–132 °C: HRMS calcd for $C_9H_{21}N$ 143.27442, found 143.27415. Anal. Calcd for $C_9H_{21}N$: C, 75.44; H, 14.77; N, 9.78. Found: C, 76.32; H, 14.55; N, 10.14.

***N*-*tert*-Butyl-*N*-neopentylbenzamide (26).** To a solution of **30** (6 g, 42 mmol) and triethylamine (90 mL, 62 mmol) in 20 mL of $CHCl_3$, cooled to 0 °C, was added benzoyl chloride (6.5 mL, 50 mmol). A mild exothermic reaction occurs. The mixture was refluxed for 7 h and cooled to room temperature; then water (100 mL) was added. The organic layer was washed several times, dried, and concentrated to afford crude **26** (6.1 g): HRMS calcd for $C_{16}H_{25}ON$ 247.38375, found 247.38413. Anal. Calcd for $C_{16}H_{25}ON$: C, 77.68; H, 10.69; N, 5.66. Found: C, 78.39; H, 10.05; N, 5.18.

X-ray and Dynamic NMR Measurements. The structure of a single crystal of **2** was determined by applying general X-ray crystallographic procedures described elsewhere.[41] Important bond lengths and angles appear in Table II, while Figure 4 illustrates the molecular structure.

Dynamic NMR spectra were obtained on Varian Gemini200 and VXR400 and Bruker CXP300 spectrometers for 0.05 M solutions in solvents specified in Table IV using complete lineshape fitting of calculated[43] and experimental carbon-13 and

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proton spectra as indicated in the text and in the supplementary material. Because of spectral overlap, multiple processes taking place, and viscosity broadening, it was not always possible to measure rate constants over a wide range of temperature, so enthalpy and entropy of activation were determined from Eyring plots for only the phenyl group rotation.

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Supplementary Material Available: Figures A1–A15 showing experimental and calculated spectra for phenyl and *tert*-butyl rotation at the same temperature used to determined the 3:1 ratio of rate constants for these processes and Eyring and Arrhenius plots for phenyl group rotation and tables showing parameters used for spectral simulation, of fractional coordinates, anisotropic thermal parameters, complete lists of bond lengths and interbond angles for X-ray analysis of **2**, and description of data collection and structure refinement (28 pages); observed and calculated structure factors for **2** (7 pages). Ordering information is given on any current masthead page.

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Conformational Studies by Dynamic NMR. 40.[1] Conformational Atropoisomerism in Highly Hindered Naphthylamines

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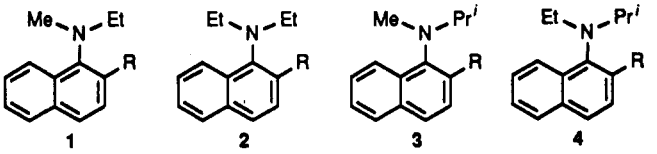
N,N-Dialkyl-1-naphthylamines substituted by alkyl groups R (R = Me, Et, *i*-Pr, *t*-Bu) in position 2 display anisochronous NMR signals owing to their twisted conformational arrangement. These conformers are enantiomerically related (conformational atropoisomers), and variable temperature NMR measurements allowed the enantiomerization barriers to be determined. The barriers increase with the increasing dimension of the substituents (covering the range 15.7–23.0 kcal mol^{-1}), and the observed trend was reproduced by Molecular Mechanics calculations. The calculations also gave indications upon the structure of the conformers that correspond to energy minima. The final choice among the possible conformations could be achieved by comparing the computed interprotonic distances with the results of NOE experiments.

Introduction

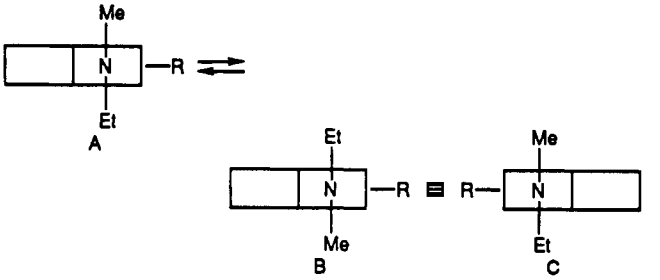
Hindered naphthylamines display conformational atropoisomerism owing to the restriction of the torsional process about the Ar–N bond.[3] It has been shown in fact that *NN*-dialkyl-1-naphthylamines adopt a twisted conformational arrangement both in solution[3] and in the solid state.[4] When two different groups are bonded to the nitrogen atom such a situation gives rise to a pair of conformational enantiomers.[4,5] Dynamic NMR investigations at variable temperature allow one to determine the corresponding free energies of activation for the enantiomerisation process, provided prochiral probes[6,7] (as for instance ethyl or isopropyl group) are introduced in appropriate positions. When such probes are not present, stereomutations can still be observed by NMR if the spectra are taken in the presence of a chiral auxiliary agent.[5,8] In the present study a number of highly hindered 1-naphthylamines were synthesized, and the dependence of their stereodynamics upon the bulkiness of the substituents were investigated by variable-temperature NMR. The conformational ground state of these molecule was also assigned by a combination of NOE (nuclear Overhauser enhancement) experiments and molecular mechanics calculations.

Chart I



a, R = Me; b, R = Et; c, R = *i*-Pr; d, R = *t*-Bu

Scheme I



Results

Dynamic NMR. Within the homogeneous groups of derivatives 1–4 the Ar–N torsional barriers were found to

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