On the Effective Size of Isopropyl and *tert*-Butyl Groups in an Unusual Steric Situation

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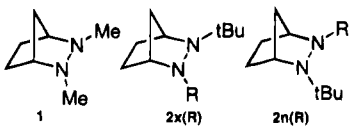
Nonbonded steric interactions involving asymmetric groups such as isopropyl can have unanticipated conformational consequences, of which the most dramatic example is that all-*trans*-hexaisopropylcyclohexane exists exclusively in the hexaaxial conformation.[1] We discuss here *N*-*tert*-butyl-*N'*-isopropyl-2,3-diazanorbornane, for which the isopropyl group is effectively almost as large as the *tert*-butyl group, because forms with the *tert*-butyl and isopropyl group *endo* are almost equally populated.

Anderson and Lehn established in early dynamic NMR studies that 2,3-dimethyl-2,3-diazabicyclo[2.2.1]heptane (**1**) detectably occupies only the enantiomeric pair of conformations having its methyl groups *anti* to each other and that their interconversion by sequential nitrogen inversions becomes slow on the NMR time scale near room temperature.[2] Our group prepared some examples of the 2-*tert*-butyl-3-alkyl derivatives **2(R)**.[3] With their unsymmetrical substitution, the *exo* and *endo tert*-butyl double nitrogen inversion forms (invertomers) **2x(R)** and **2n(R)** are different in energy, and because we assumed significantly smaller steric hindrance on the *exo* face of the norbornyl system, it never occurred to us that the *endo tert*-butyl invertomer would be detectably populated for any compound but the symmetrically substituted **2-(tBu)** case.[3c] This assumption proved to be false when



we prepared **2(iPr)** for comparison with its diazabicyclooctane analogue[4] and discovered that **2x(iPr)** and **2n-(iPr)** have nearly equal populations. A reinvestigation showed that both **2(Et)** and **2(Me)** also have easily detectable amounts of *endo tert*-butyl invertomers present (Table 1). Assigning the minor invertomers as *endo tert*-butyl in all three cases appears reasonable, although the pattern of ^{13}C chemical shift changes between the major and minor invertomers of **2(iPr)** compared to the other cases is complex enough that we do not believe that an unambiguous assignment can be made from the spectra.

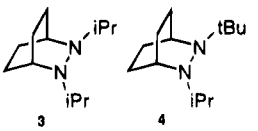
These **2(R)** compounds provide an excellent illustration of the fact that the "effective size" of asymmetric groups depends strongly upon with what they interact. For **2-(R)** as reflected by *exo*:*endo* ratios, tBu ~ iPr ≫ Et > Me (relative $\Delta G°$ values = 0, 0.1, 1.2, and 1.5 kcal/mol, respectively), which is quite different from the familiar order determined from axial:equatorial ratios in alkylcyclohexanes,[5] tBu ≫ iPr > Et ~ Me (relative $\Delta G°$ values = 4.5, 2.1, 1.8, and 1.8 kcal/mol, respectively).

Table 1. Relative Amounts of exo and endo *tert*-Butyl Invertomers Determined by NMR

compound	2x:2n	*T*, °C	$\Delta\Delta G°$
2(iPr)	54:46	−27[a]	0.1_0
2(Et)	88:12	+25[b]	1.1_8
2(Me)	93:7	+25[b]	1.5_3
	96:4	−37[b]	1.8_8

[a] Solvent: CD_2ClCD_2Cl. [b] Solvent: $CDCl_3$.

The most stable conformations about R–N bonds are staggered so that the substituents at C_α of the R group in a projection down the R–N bond are directed approximately *anti* to a, the N–N bond, b, the N–C bond, and c, the N–lp direction (Figure 1). The isopropyl C_α-H will preferentially assume the most hindered position. The a position is clearly the least hindered and will prefer to have a methyl group, but the relative amount of steric hindrance at b, directed toward the N'R' group, and c, directed toward the bicyclic ring, depends upon the size of the R' group. For the diisopropylbicyclooctane derivative **3**, only one type of isopropyl group is detected by NMR at a low enough temperature to freeze out isopropyl group rotation, and we assigned this most stable conformation as bis-cH, calculated by MM2 to be the most stable one by more than 2.6 kcal/mol.[4] In contrast, the *tert*-butyl, isopropyl compound **4** has two different isopropyl rotamers occupied, with the major conformation, assigned as bH, lying 0.8 ± 0.2 kcal/mol lower in energy than the minor one, assigned as the cH conformation. A



turnaround in the most stable isopropyl group rotamer between **3** and **4** is predicted by MM2 calculations, although they get cH **4** lying only 0.3 kcal/mol higher in energy than bH, rather smaller than the experimental value. Because an N(2) *tert*-butyl group turns the N(3) isopropyl hydrogen of **2(iPr)** to the bH position, a methyl group occupies position c, which causes the isopropyl group to have about as large a steric interaction with the bicyclic ring as does the *tert*-butyl group, causing **2x(iPr)** and **2n(iPr)** to be almost equal in energy. The changes in nitrogen pyramidality which occur as steric constraints change are probably important in determining the relative energies of the *exo* and *endo tert*-butyl invertomers of **2(R)**. As shown in Table 2, α_{av}(NR) is calculated to be significantly smaller for the less hindered *exo* RN-alkyl units than for *endo* ones, increases as R becomes larger, and is detectably affected by the N'R' substitutent (the *endo tert*-butyl-substituted nitrogen of **2n(Me)** is 0.5° flatter than that of **2n(tBu)**). The relative energies of the corresponding inversion isomers would presumably be significantly different for the hydrocarbon analogues of these compounds where changes in pyramidality with substitution are smaller.

Experimental Section

2-*tert*-Butyl-3-methyl-2,3-diazabicyclo[2.2.1]heptane (2-(Me)). Preparation as previously reported:[3] ^1H-NMR (500 MHz,

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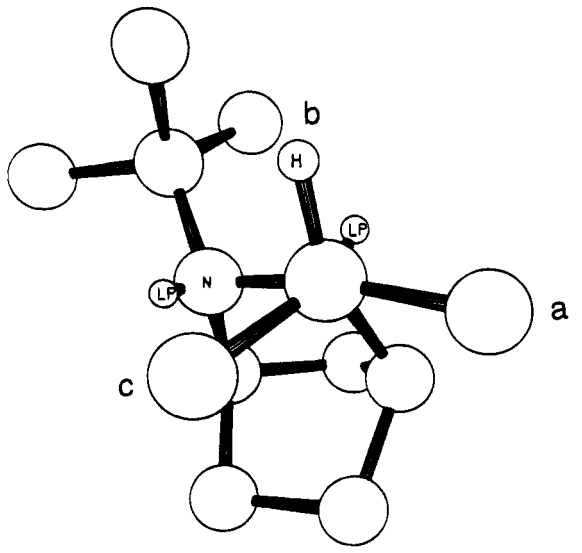

Figure 1. Ortep view of the MM2 structure of the most stable invertomer of **2(iPr)** (**2x(iPr)**, bH, see the text) viewed down the isopropyl–N(3) bond. All hydrogens but the isopropyl $C_\alpha H$ have been omitted for clarity.

Table 2. MM2-Calculated Nitrogen Pyramidalities for the Most Stable Forms of the Invertomers of 2(R)

conformer	orientation	α_{av}	orientation	α_{av}
2x(Me)	tBu-*exo*	111.1	Me-*endo*	110.2
2n(Me)[a]	tBu-*endo*	112.9	Me-*exo*	109.0
	$\Delta\alpha_{av}, x \rightarrow n$	+1.8	$\Delta\alpha_{av}, n \rightarrow x$	−1.2
2x(iPr)	tBu-*exo*	111.1	iPr-*endo*	112.0
2n(iPr)[b]	tBu-*endo*	112.4	iPr-*exo*	110.2
	$\Delta\alpha_{av}, x \rightarrow n$	+1.3	$\Delta\alpha_{av}, n \rightarrow x$	−1.2

[a] Calculated to lie 1.4 kcal/mol higher in steric energy, comparable to the 1.5 kcal/mol $\Delta\Delta G°$ (25 °C) observed experimentally. [b] Calculated to lie 0.7 kcal/mol higher in steric energy, rather larger than the 0.1 kcal/mol $\Delta\Delta G°$ (−27 °C) observed experimentally.

($CDCl_3$, −37 °C): δ major invertomer (94%) 3.42 (H_4), 3.35 (H_1), 2.48 (3H, Me), 2.13 (H_{6n}), 1.98 (H_{7s}), 1.59 (H_{5x}), 1.44 (H_{5n}), 1.25 (H_{7a}), 1.17 (H_{6x}), 1.01 (9H, tBu); minor invertomer (4%) 3.68 (br), 3.13 (br), 2.38 (Me), 1.14 (tBu). ^{13}C-NMR (125 MHz): δ major invertomer (96%) 63.31 (CH, br), 58.44 (CH, br), 57.48 (C_q), 43.30 (NCH_3), 36.71 (C_7H_2), 30.88 (C_5H_2), 27.89 (CH_3, tBu), 21.21 (C_6H_2); minor invertomer (4%) 65.30 (CH, br), 60.43 (CH, br), 55.89 (C_q), 48.89 (NCH_3), 34.61 (CH_2), 28.98 (CH_3, tBu), 26.87 (CH_2), 19.12 (CH_2). The ^{1}H-NMR signals of the major isomer of **2(Me)** were assigned using H,H COSY experiments, and ^{13}C assignments employed DEPT 135 spectra. Sample purity is estimated at >98% because observed impurity peaks are about one-fourth the height of minor isomer peaks in the ^{13}C-NMR.

2-*tert*-Butyl-3-ethyl-2,3-diazabicyclo[2.2.1]heptane (2-(Et)). Preparation as for **2(iPr)** except for extraction with methylene chloride, drying over $CaCl_2$, concentration, and Kugelrohr distillation to give **2(Et)** as a colorless oil (0.38 g, 33%). Empirical formula $C_{11}H_{22}N_2$ established by high-resolution mass spectrometry. ^{1}H-NMR (500 MHz, $CDCl_3$, 25 °C): δ major invertomer (88%) 3.42 (1H, br), 3.33 (1H, br), 2.84–2.27 (1H, m, CH_2CH_3), 2.59–2.52 (1H, m, CH_2CH_3), 2.00–1.95 (1H, m), 1.89–1.87 (1H, m), 1.53–1.48 (1H, m), 1.37–1.31 (1H, m), 1.16 (1H, d, J = 9.6 Hz), 1.12–1.05 (1H, m), 0.97 (9H, tBu), 0.89 (3H, t, J = 7.3 Hz, CH_2CH_3); minor invertomer (12%) 3.58 (1H, br), 3.15 (1H, br), 2.40 (2H, CH_2CH_3), 1.09 (9H, tBu). ^{13}C-NMR (125 MHz): δ major invertomer (88%) 57.87 ($C_{br}H$), 57.76 ($C_{br}H$), 57.49 (C_q), 48.74 (CH_2, Et), 36.08 (CH_2), 31.14 (CH_2), 28.04 (CH_3, tBu), 21.66 (CH_2), 13.00 (CH_3, Et); minor invertomer (12%) 61.74 ($C_{br}H$), 59.74 ($C_{br}H$), 56.05 (C_q), 55.49 (CH_2, Et), 35.31 (CH_2), 28.79 (CH_3, tBu), 27.58 (CH_2), (one CH_2 not located), 14.29 (CH_3 Et). ^{13}C assignments employed DEPT 135 spectra. Sample purity is estimated at 97% because impurity peaks are about one-fifth the size of minor isomer peaks observed in the ^{13}C-NMR.

2-*tert*-Butyl-3-isopropyl-2,3-diazabicyclo[2.2.1]heptane (2(iPr)). A solution of isopropylmagnesium chloride (2 M, 4.2 mL, 8.4 mmol) was added dropwise to a stirred mixture of 2-*tert*-butyl-2-azonia-3-azabicyclo[2.2.1]hept-2-ene tetrafluoroborate[6] (1.02 g, 4.2 mmol) in 20 mL of THF at room temperature. After the mixture was stirred under nitrogen overnight, water (80 mL) was added to quench the reaction, and the solution was extracted with ether (3 × 80 mL). After drying over magnesium sulfate, concentration, Kugelrohr distillation, dissolution in pentane, and filtration through Celite, concentration gave 420.6 mg (50%) of **2(iPr)** as a colorless liquid; the empirical formula $C_{12}H_{24}N_2$ was established by high-resolution mass spectrometry ($CDCl_2CDCl_2$, −27 °C). ^{1}H-NMR (500 MHz; partial, as several peaks of the isomers overlap): δ major invertomer (54%) 3.56 (1H, br s), 3.42 (1H, d, J = 3 Hz), 3.22 (1H, hept, J = 7 Hz, iPr), 0.98 (9H, s, tBu); minor invertomer (56%) 3.59 (1H, br s), 3.27 (1H, d, J = 3 Hz), 2.88 (1H, hept, J = 7 Hz, iPr), 1.14 (9H, s, tBu). ^{13}C-NMR (125 MHz): δ major invertomer (54%) 60.04 ($C_{br}H$), 59.12 (C_q), 57.99 ($C_{br}H$), 57.33 ($C_{iPr}H$), 38.71 (CH_2), 31.59 (CH_2), 30.05 (CH_3[tBu]), 30.05 (CH_2), 24.60 (CH_3[iPr]), 20.27 (CH_3[iPr]); minor invertomer (46%) 61.20 ($C_{br}H$), 60.87 (C_q), 57.71 ($C_{br}H$), 54.79 ($C_{iPr}H$), 39.17 (CH_2), 31.44 (CH_2), 31.28 (CH_3-[tBu]), 29.84 (CH_2), 22.89 (CH_3[iPr]), 19.02 (CH_3[iPr]). ^{13}C assignments employed DEPT 135 spectra.

Molecular mechanics calculations were carried out using Saunders' program[7] to locate energy minima on the Allinger MM2[8] energy surface, using programs written by Peter A. Petillo to the run it in our computer environment (VAX 8650, preparation of input and manipulation of output files using NEWSEL).

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Supplementary Material Available: ^{13}C-NMR spectra of compounds **2(Me)**, **2(Et)**, and **2(iPr)** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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