(DMSO-d_6) δ 9.37 s; MS (FAB, solvent 3-nitrobenzyl alcohol) (m/e, species, %) 301, $M^+ + 3Na^+ - 2$, 40.02; 279, $M^+ + 2Na^+ - 1$, 17.49; 257, $M^+ + Na^+$, 34.59; 235, $M^+ + 1$, 9.67; 153, $CF_2SO_3Na^+$, 2.55; 149, $M^+ + H_2O - SO_3Na$, 100; 103, SO_3Na^+, 1.43; 79, PO_3^+, 13.18; 65, $PO_2H_2^+$ 20.76; 64, PO_2H^+, 8.97; 63, PO_2^+, 39.35.

Preparation of $(HO)_2P(O)CF_2SO_3Na$. (i-$C_3H_7O)_2P(O)CF_2SO_3Na$ (2.54 g, 8 mmol) and concentrated HCl (20 mL) were heated together with stirring for 6 h at 80 °C in a 50-mL boiling flask fitted with a reflux condenser. The mixture was then concentrated to dryness on a rotary evaporator to give the product. The yield was 1.6 g (85%): ^{19}F NMR (D_2O) ϕ -110.5 d (J_{P-F} = 81 Hz); $^{31}P\{H\}$ (D_2O) δ -0.1 t; $^{13}C\{H\}$ (D_2O) δ 120.5 td (J_{P-C} = 179 Hz, J_{F-C} = 295 Hz).

Preparation of $(HO)_2P(O)CF_2SO_2OH$. An aqueous solution of $(HO)_2P(O)CF_2SO_3Na$ (3.48 g, 14.9 mmol) was passed through an Amberlite IR-120 ion-exchange resin (strongly acidic gel-type resin). The volume of the aqueous acid was reduced, and then the crude product was evaporated at reduced pressure at 100-120 °C. The product was dissolved in water, and charcoal (0.3 g) was added. The mixture was stirred at 50-60 °C for 2 h. After the charcoal was removed, the filtrate was evaporated at reduced pressure at 100 °C for 4 h to yield 2.4 g (75.9%) of a white solid, $(HO)_2P(O)CF_2SO_3H$. The solid melts at 76-78 °C. The acid is very hygroscopic: ^{19}F NMR spectrum (DMSO-d_6) ϕ -110.9 d (J_{F-P} = 92.7 Hz); $^{31}P\{H\}$ (DMSO-d_6) δ 0.85 t; ^1H (DMSO-d_6) δ 12.5 s; MS (Cl^+) (m/e, species, %) 213, $M^+ + 1$, 0.62; 149, $M^+ + 1 - PO_2H$, 2.86; 131, $M^+ - (HO)_2P(O)$ or $M^+ - SO_3H$, 0.30; 111, HO_3PCF^+, 9.20; 91, PO_3C^+, 2.03; 81, $(HO)_2P(O)^+$, or SO_3H^+, 2.21; 79, PO_3^+, 2.66; 65, $PO_2H_2^+$, 100; 64, PO_2H^+, 1.66; 59, POC^+, 35.65. Anal. Calcd for $CH_3F_2O_6PS$: C, 5.66; H, 1.41; F, 17.92; S, 15.12. Found: C, 5.77; H, 1.77; F, 17.90; S, 15.04.

Preparation of $(C_2H_5O)_2P(O)CF_2SO_3H$. An aqueous solution of $(C_2H_5O)_2P(O)CF_2SO_3Na$ (4.08 g, 14.1 mmol) was passed through an Amberlite IR-120 ion-exchange resin (strongly acidic gel-type resin). The volume of the aqueous acid was reduced, and then the crude product was evaporated at reduced pressure to yield 3.52 g (93.1%) of a viscous liquid $(C_2H_5O)_2P(O)CF_2SO_3H$: ^{19}F NMR spectrum (DMSO-d_6) ϕ -109.81 d (J_{F-P} = 87.9 Hz); $^{31}P\{H\}$ (DMSO-d_6) δ 1.21 t; ^1H (DMSO-d_6) δ 1.11 t (3 H, J_{H-H} = 6.96 Hz), 4.03 q (1 H), 3.95 q (1 H) (J_{H-P} = 7.14 Hz), δ 10.31 s; MS (EI^+) (m/e, species, %) 269, M + 1, 0.42; 137, $M^+ - CF_2SO_3H$, 8.40; 132, $M^+ + 1 - P(O)(OC_2H_5)_2$, 53.8; 121, $^+P(OC_2H_5)_2$, 9.42; 109, $C_2H_6O_3P^+$, 68.7; 81, SO_3H^+, 100; 65, $PO_2H_2^+$, 91.28; 64, PO_2H^+, 50.33.

Titration. Titration of the acid (IV) was monitored utilizing an Orion Model 701A digital Ionalyzer and Corning combination pH electrode. Sodium hydroxide was standardized with primary standard potassium acid phthalate. Tetrabutylammonium hydroxide in toluene/methanol solution was prepared from tetrabutylammonium iodide[11] and standardized against primary standard benzoic acid in dimethyl formamide.

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Registry No. Ia, 118576-78-6; Ib, 118576-80-0; IIa, 118576-79-7; IIb, 118576-81-1; II (R = H), 118576-82-2; $(C_2H_5O)_2P(O)CF_2Br$, 65094-22-6; $(C_2H_5O)_2P(O)CF_2I$, 80077-69-6; (i-$C_3H_7O)_2P(O)CF_2I$, 118576-72-0; (i-$C_3H_7O)_2P(O)CF_2Br$, 65094-24-8; (i-$C_3H_7O)_2P(O)CF_2CdBr$, 118576-83-3; $[(C_2H_5O)_2P(O)CF_2SO_2]_2Cd$, 118576-76-4; $[(i\text{-}C_3H_7O)_2P(O)CF_2SO_2]_2Cd$, 118576-75-3; $[(i\text{-}C_3H_7O)_2P(O)CF_2SO_3]_2Cd$, 118576-77-5; $(HO)_2P(O)CF_2SO_2OH$, 118576-73-1; $(C_2H_5O)_2P(O)CF_2SO_3H$, 118576-74-2.

(11) USP/NF XX(XV) 1980, 1113. United States Pharmacopeial Convention.

The Nitrogen Inversion Barrier of 7-Methyl-7-azabicyclo[2.2.1]heptane and the "Bicyclic Effect"

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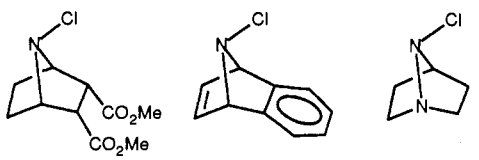
Abstract: The free energy of activation for nitrogen inversion of the title compound was determined to be 13.77 (4) kcal/mol at 25 °C in $CDCl_3$ by dynamic ^{13}C NMR and that for the 7-ethyl compound to be 13.17 (4) kcal/mol under the same conditions. The change in α(av) (the average of the three bond angles at nitrogen) during nitrogen inversion is used to assist comparison of inversion barriers for amines with different substituents attached. Comparison with literature data and AM1 calculations indicate that the barrier increase for 7-methyl-7-azabicyclo[2.2.1]heptane N inversion relative to an α-unbranched monocyclic compound of the same pyramidality at nitrogen is on the order of 3.5 kcal/mol, while the less strained 1-bridge-azabicyclo[3.3.1]nonyl and -[3.2.1]octyl systems show barrier increases of about 1.5 kcal/mol. This represents an estimate of the size of Lehn's "bicyclic effect".

7-Azabicyclo[2.2.1]heptane (7-azanorbornane) derivatives have especially high nitrogen inversion barriers. Lehn[1] reported a dynamic ^1H NMR $\Delta G^{\ddagger}_i$ of 21 (1) kcal/mol at 140 (10) °C for chloroamine **1**, and Rautenstrauch[2] determined a 23.5 kcal/mol barrier at 23 °C for **2** by direct equilibration. CNC bond angle restriction clearly causes higher nitrogen inversion barriers,[1,3] and restriction of the $C_1N_7C_4$ angle by the bicyclic ring system is a factor causing the high $\Delta G^{\ddagger}_i$ values observed. Lehn suggested[4] that there is also an unexplained "bicyclic effect" raising nitrogen inversion barriers in 7-azanorbornane derivatives, because their inversion barriers are substantially higher than might be expected from the CNC angle imposed by the bicyclic framework. For example, Lambert and co-workers[5] observed $\Delta G^{\ddagger}_i$ of ca. 13.4 kcal/mol at -20 °C for *N*-chloroazetidine, which has a smaller endocyclic CNC angle imposed by its four-membered ring than that of 7-azanorbornane derivatives. More recently, Malpass and



1 **2** **3**

(1) Lehn, J. M. Fortschr. *Chem. Forsch.* **1970**, *15*, 311-377.
(2) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1969**, 1122.
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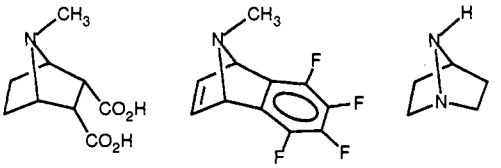
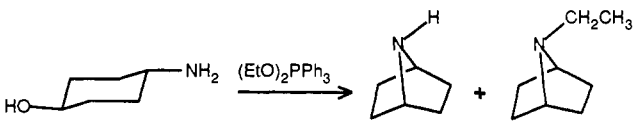
co-workers[6] measured a $\Delta G^{\ddagger}_{i}$ of 22.0 (3) kcal/mol at 167 °C for chlorohydrazine **3** and argued that neither the chlorine substitution nor the second nitrogen was the principal source of the high barrier and supported Lehn's "bicyclic effect". Evidence for high barriers in 7-azanorbornanes with other 7-substituents has been somewhat conflicting. The 19.5 kcal/mol barrier for an *N*-methyl derivative cited in Lehn's review[1] was for **4**, which presumably exists at least partially as the N-protonated zwitterion, which cannot invert. Gribble and co-workers[7] found a barrier of 14 kcal/mol for the *N*-methyl fluorinate benzo derivative **5**. The anomalously low barrier reported[6] for the 7-H hydrazine derivative **6** will be corrected upwards.[8] We have measured inversion barriers for 7-alkyl derivatives of the saturated 7-azanorbornane system to more quantitatively consider the size of Lehn's "bicyclic effect".



4 **5** **6**

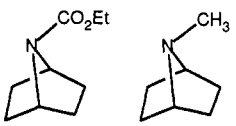
Results

We employed diethoxytriphenylphosphorane,[9] which Evans and co-workers showed closes vicinal amino alcohols to aziridines,[9b] to convert **7** to **8** in a single operation. Fraser and Swingle's earlier



7 **8** **9**

conversion[10] of **7** to **8** using carbobenzyloxy amino group protection and tosylate hydroxyl activation required four steps, proceeding in 38% overall yield. A cyclic aminophosphorane intermediate cannot form from **7**, so the cyclic phosphorane intermediate proposed in azridine formation[9b] is not a necessary requirement for getting primary amino alcohols to cyclize. When enough diethoxyphosphorane was employed to completely consume **7**, we also observed formation of the ethyl derivative **9**. Because we desired both the methyl and ethyl derivatives for NMR studies, we used approximately 2 mol of diethoxyphosphorane/mol of **7**, which gave about a 1:1 mixture of **8** and **9**. Treatment of the mixture with ethyl chloroformate in ether efficiently precipitated **9** as its hydrochloride salt, leaving **10** in solution for subsequent reduction to the desired methyl derivative **11** with LAH. ^{13}C



10 **11**

NMR spectra in $CDCl_3$ for **11** show two ethylene bridge CH_2 signals at low temperature, which coalesce near room temperature. Data collected at seven temperatures between 10 and 42 °C were analyzed by digital simulation, giving a nitrogen inversion barrier, $\Delta G^{\ddagger}_{i}$ (25 °C), 13.77 (4) kcal/mol, $\Delta H^{\ddagger}_{i}$ 15.2 (13) kcal/mol, and $\Delta S^{\ddagger}_{i}$ 4.8 (42) cal/deg mol (eu). For **9**, data at seven temperatures between −11 and 42 °C gave $\Delta G^{\ddagger}_{i}$ (25 °C) 13.17 (4) kcal/mol, $\Delta H^{\ddagger}_{i}$ 14.0 (10) kcal/mol, and $\Delta S^{\ddagger}_{i}$ 4.8 (42) eu.

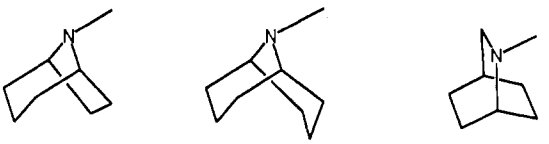
Table I. Comparison of Nitrogen Inversion Barriers in Some Bicyclic Methylamines

compd	$\Delta G^{\ddagger}_{i}$(−50 °C),[a] kcal/mol	reference
11	14.1	this work
12	9.2	13
13	7.9	14
14	6.1	15

[a] Estimated with a $\Delta S^{\ddagger}_{i}$ value of 5 eu (see text).

Discussion: Inversion Barriers for Bicycloalkyl Methylamines

The barrier for nitrogen inversion of **11** measured here is compared with literature values for bicyclic methylamines which have less CNC bond restriction, **12–14**, in Table I. Only barriers



12 **13** **14**

measured by ^{13}C NMR were used in Table I; they are significantly more accurate than earlier values[1] estimated with ^{1}H NMR for **13** and **14** because of small chemical shift differences and complexity problems. Accuracy for $\Delta G^{\ddagger}_{i}$ measurements by NMR is well known to be far better at the coalescence temperature than at other temperatures because of systematic errors which lead to inaccurate $\Delta S^{\ddagger}_{i}$ values. Such problems are probably present in the data of Table I, because the entropies of activation reported for the series **11–14** are respectively 4.8 (42), 18 (5), 8.5 (25), and 5.3 (68) eu, determined from data sets showing coalescence temperatures of +25, −50, −90, and −127 °C. Only **12** has two conformations of different energy, and we suspect that the reason for its anomalous $\Delta S^{\ddagger}_{i}$ value involves problems arising from neglect of temperature extrapolation of the chemical shifts and equilibrium constant (see ref 13). The N inversion barrier quoted is for the more stable equatorial methyl conformation shown above. We have chosen to compare free energy barriers at −50 °C because −50 °C is the only temperature for which $\Delta G^{\ddagger}_{i}$ is likely to be reliably known for **12** and it is also near the middle of the temperature range for the four compounds. We have used a $\Delta S^{\ddagger}_{i}$ of 5 eu, the value Lehn chose to use in his review,[1] to make the extrapolation from the measured $\Delta G^{\ddagger}_{i}$ value at the coalescence temperature.

The 0.6 kcal/mol lower barrier observed for the 7-ethyl compound **11** than for the methyl derivative **9** is reasonably consistent with the about 1.0 kcal/mol lower barrier found[14] for 9-ethyl-9-azabicyclo[3.3.1]nonane than for its methyl analogue **13** and the 0.8 kcal/mol lower barrier for Malpass's ethyldazanorbornane **15** than for the methyl compound **16**.[15] The barrier observed by Malpass[15] for **16** [14.35 (17) kcal/mol] is about 0.6 kcal/mol higher than that found here for **11**. The same structural change, replacement of CH at position 1 by N, raises the observed barrier by about 1.5 kcal/mol in going from **14** to hydrazine **17**.[13] The barrier for **11** is also similar to that for the 7-methyl-7-azanorbornadiene derivative **5**. Neither breaking the symmetry plane through position 7 by replacing CH by N nor introducing 2,3;5,6 unsaturation has a very large effect on 7-azanorbornane N inversion barriers.

(6) Davies, J. W.; Malpass, J. R.; Moss, R. E. *Tetrahedron Lett.*, **1985**, *26*, 4533.
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(8) Nitrogen inversion barrier determination for NH compounds is especially difficult because acidic impurities provide a pathway for isomerization which does not involve nitrogen inversion. Dr. Malpass has informed us that special purification efforts have significantly raised the observed barrier for **6** from the 6.8 kcal/mol reported[6] (private communication).
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(14) (a) Nelsen, S. F.; Steffek, D. J.; Cunkle, G. T.; Gannett, P. M. *J. Am. Chem. Soc.* **1982**, *104*, 6641. (b) Nelsen, S. F.; Cunkle, G. T.; Evans, D. H.; Haller, K. J.; Kaftory, M.; Kirste, B.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 3825.
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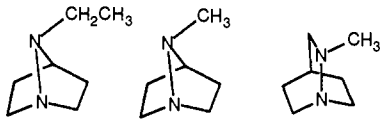
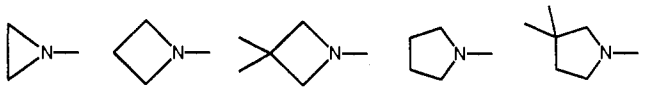


15 16 17

The inversion barrier for **11** is higher than those of the other compounds of Table I. It is about 6 kcal/mol less than that for *N*-methylaziridine,[1] **18**, which has $\Delta G^{\ddagger}_{i}$ 19.4 kcal/mol at 115 °C (20.2 at −50 °C with $\Delta S^{\ddagger}_{i}$ of 5 eu), but 3.9 kcal/mol higher than that for *N*-methylazetidine, **19**, at 10.0 kcal/mol at −69 °C.[5] Proton NMR data are also available[1,5] for **20–22**, as well as several



18 19 20 21 22

of the *N*-chloroamine analogues of the *N*-methylamines we have been discussing, which we will disignate with suffix **C** after the methylamine compound number. To consider how restriction of the CNC angle affects the N inversion barrier, we compare the barriers measured by NMR for **11–14** and **18–22** with those on their *N*-chloroamine analogues in Figure 1, displaying changes from the barrier observed for the 9-azabicyclo[3.3.1]nonane compounds **13** and **13C**. Because we also want to compare experimental with calculated values, $\Delta H^{\ddagger}_{i}$ values have been used. For the methylamines, they were obtained from the experimental $\Delta G^{\ddagger}_{i}(T_c)$ values with $\Delta S^{\ddagger}_{i}$ of 5 eu, for the reasons described above. We have used a $\Delta S^{\ddagger}_{i}$ value of zero in estimating $\Delta H^{\ddagger}_{i}$ for the chloroamines. *N*-Chloroamines do not have one source of positive entropy of activation that *N*-methylamines have, because the chloro group is cylindrically symmetrical, and for two cases studied over a wide temperature range by ^{13}C NMR, experimental $\Delta S^{\ddagger}_{i}$ values were significantly smaller, +1.7 eu for **13C**[14] and −2.5 eu for **14C**.[16] We do not really know how large the experimental error in the $\Delta H^{\ddagger}_{i}$ values used is, and note that even the relatively small structural change from a chlorine to a methyl group does not always keep the same order for the various R_2N groups. Changes in barrier between methylamines and chloroamines are especially large for the azetidines and pyrrolidines, which have more conformational freedom than the other compounds considered.

Discussion: Calculation of R_2NX Inversion Barriers

The biggest problem in thinking quantitatively about how nitrogen inversion barriers change as the alkyl groups are changed has always been the lack of a reasonable way of comparing compounds with different substitution. Calculations which could focus clearly on the geometry changes involved in reaching the transition state would help. Unfortunately, it is not easy to calculate inversion barriers accurately. The electronic effects causing nitrogens to be pyramidal instead of planar are somewhat subtle, and rather high level ab initio calculations need to be carried out to obtain reasonable inversion barriers. It is still too time-consuming to do high enough level calculations on modestly large compounds such as those considered here for this to yet be a reasonable approach to correlating experimental data. Jennings and Worley[17] have discussed application of semiempirical MNDO calculations and earlier methods to a wide variety of nitrogen inversion considerations. MNDO is in fact of little use for consideration of alkylamine inversion barriers because it greatly overestimates nonbonded steric effects and predicts trimethylamine to be planar at nitrogen. Dewar's group has subsequently introduced the AM1 semiempirical Hamiltonian and computational package.[18] Because AM1 has substantially reduced the unreasonably large nonbonded interactions which plagued earlier methods, we have examined the utility of AM1 calculations for considering the problem at hand by carrying out calculations on methylamines **11–14** and **18–22**, as well as the related chloroamines (designated with a suffix **C**) and NH substituted compounds (designated with a suffix **H**). Barriers derived from NMR data, calculated barriers, and some geometrical information are given for the methylamines in Table II. This information for the NCl and NH compounds appears in the supplementary material.

Table II. Comparison of NMR with Calculated Nitrogen Inversion Barriers and Calculated Pyramidality at N for R_2NMe

compd	$\Delta H^{\ddagger}_{i}$[a] NMR	$\Delta H^{\ddagger}_{i}$[b] AM1	CNC angle[c] AM1 [MM2]	α(av)[d] AM1 [MM2]
11	15.3	10.0	94.9 [95.3]	109.0 [109.0]
12	10.3	8.4	100.8 [101.9]	109.3 [109.3]
13	9.0	5.9	109.0 [109.5]	112.4 [111.8]
14	7.2	5.2	109.8 [110.1]	112.5 [111.8]
18	21.3	16.7	61.7[e]	99.6[e]
19	11.3	8.1	91.8 [91.8]	108.3 [106.4]
20	9.0	8.2	92.1 [94.8]	108.0 [107.8]
21	8.7	4.9	108.8 [104.0]	112.6 [109.7]
22	8.2	4.9	109.1 [103.8]	112.4 [110.4]

[a] In kcal/mol, from $\Delta G^{\ddagger}_{i}$ at coalescence using $\Delta S^{\ddagger}_{i}$ of 5 eu. [b] In kcal/mol, heat of formation of optimized planar nitrogen species minus that of the ground state. [c] For the endocyclic CNC angle, in deg; number in brackets is from MM2. [d] Average of the three CNC angles at nitrogen, in deg; number in brackets is from MM2. [e] Aziridine parameters have not been reported. With the azetidine parameters,[22b] the CNC angle is 61.7° and α(av) 98.61°.

Figure 2 shows a comparison of the calculated barriers done in the same way as Figure 1, and Figure 3 shows the same information as a plot of observed versus calculated barriers. There is a substantial amount of scatter in the plots, and it is not clear how much comes from the experimental, and how much from the calculated data. Clearly our assumption that $\Delta S^{\ddagger}_{i}$ is 5 eu for all dialkylmethylamines but zero for chloroamines is not accurate and introduces a basically unknown amount of error into the "experimental" numbers. Some assumption about the activation entropy must be made, because it is not possible to accurately estimate how $\Delta S^{\ddagger}_{i}$ changes with structure. The major pattern of barrier changes is rather similar, although there is clearly a problem with the azetidines. AM1 incorrectly predicts the methylamines **19** and **20** to have rather similar barriers and chloroamines **19C** and **20C** to be harder to invert than **13C**. We suspect that the problem involves the degree of puckering calculated for four-membered rings. AM1 calculates azetidines to be nearly planar, optimizing **19** with a 3.6° CN,CC dihedral angle in the four-membered ring. MM2 (see below) obtains a 20.0° angle for **19** and significantly less puckering for **20**, where this angle is 8.8°. AM1 does successfully predict a significantly larger barrier or the 7-azanorbornane **11** than for azetidines **19** and **20** in both the methylamine and chloroamine series, which is experimentally true and, we believe, the original reason for proposing a "bicyclic effect".

We consider the comparison between calculated and experimental nitrogen inversion barriers in Figures 1–3 to be good enough to merit more detailed consideration of the calculated barriers, in an attempt to better understand how changing the alkyl substituents affects inversion barrier. This requires devising how to compare inversion barriers for compounds having different substitution with the geometry changes that the substitution causes. We are not aware that a reasonable way to do this has been suggested. The primary cause of different barriers for R_2NX compounds of different ring size is restriction of the endocyclic CNC angle, but all three CNC angles change during nitrogen inversion. It is also not entirely reasonable to directly compare barriers for the bis-secondary alkyl group substituted **11** with the unbranched monocyclic compounds. Nonbonded interactions in both the ground state and transition state for N inversion have to somehow be taken into account. No single geometric parameter can really represent the geometry change between the pyramidal amine and the planar transition state perfectly. We have chosen

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(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

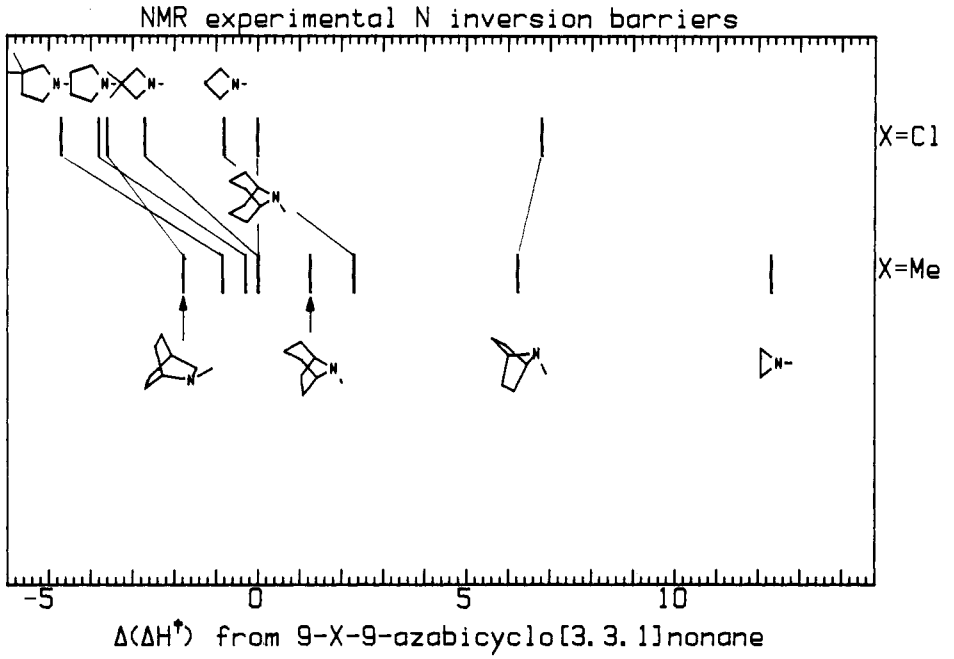

Figure 1. Effects of alkyl group changes on nitrogen inversion barriers determined from NMR measurements for R_2NCl and R_2NMe, displayed as changes in $\Delta H^{\ddagger}_i$ from that for the 9-azabicyclo[3.3.1]nonane derivative.

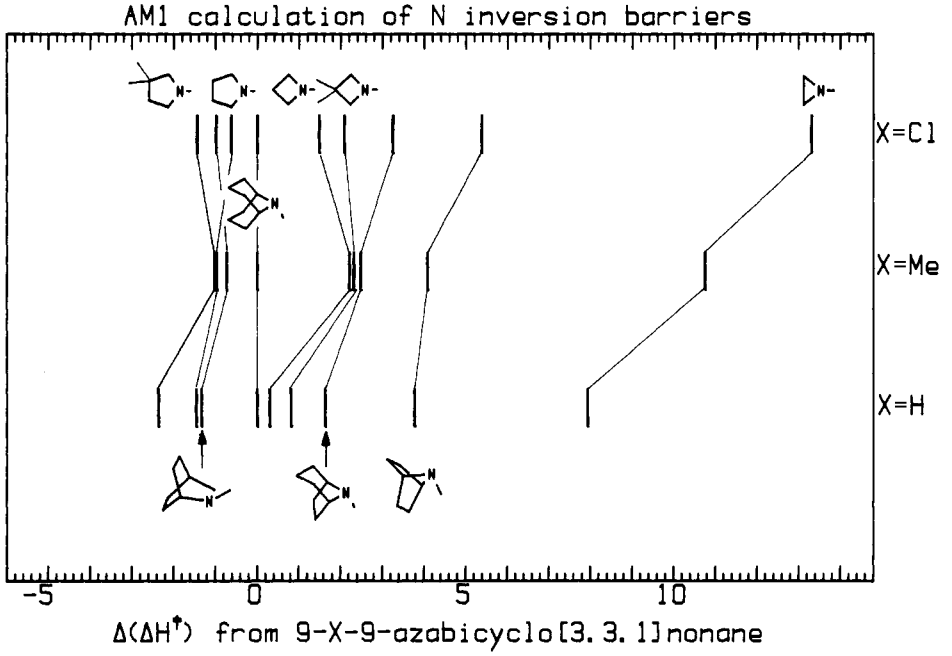

Figure 2. As Figure 1, using $\Delta H^{\ddagger}_i$ values calculated by AM1, for R_2NCl, R_2NMe, and R_2NH.

to employ the average of the three bond angles at N, α(av), to compare different compounds.[19] We argue from the plot of calculated dialkylmethylamine nitrogen inversion barriers versus the change in α(av) during inversion [$\Delta\alpha$(av) = 120° − α(av) for the optimized amine structure] shown in Figure 4 that $\Delta\alpha$(av) is a reasonably good single geometric parameter for comparing nitrogen inversion barriers. There is unquestionably a substantial correlation between $\Delta H^{\ddagger}_i$ and $\Delta\alpha$(av). The line drawn in Figure 4 is a linear regression ignoring the point for **11**. This line has a correlation coefficient r = 0.99 and an average deviation of 0.4 kcal/mol in $\Delta H^{\ddagger}_i$, with a total range of 11.8 kcal/mol in $\Delta H^{\ddagger}_i$. There is no theoretical reason for a linear correlation of barrier with $\Delta\alpha$(av), nor do the calculated values actually lie on the regression line, but we suggest that this plot does effectively reveal some structural effects on calculated $\Delta H^{\ddagger}_i$. The primary alkyl group substituted monocyclic compounds (shown as circles) show an upward curvature when $\Delta\alpha$(av) increases as the ring size is reduced; although with effectively only three points for the five-, four-, and three-membered rings, this curve is not especially well defined.[20] The bicyclic compounds, which have secondary alkyl substituents at N and are shown as squares in Figure 4, all lie above the line. The point for the mono-secondary alkyl group substituted compound **14** is closer to the line than are the points

(19) α(av) has previously proven to correlate nearly linearly with calculated vertical ionization potential as nitrogen atoms are flattened (Nelsen, S. F.; Kessel, C. R.; Brien, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 791; Nelsen, S. F. *J. Org. Chem.* **1984**, *49*, 1891) and with observed $^1J_{CH}$ values over a wide range of carbon pyramidality (Szalontai, G. *Tetrahedron* **1983**, *39*, 1783). α(av) appears to usefully represent changes in hybridization as pyramidality changes.

(20) Nevertheless, a second-degree polynomial least-squares fit to the data of the five α-unbranched monocyclic compounds of Figure 4 (the circles) gives the equation: $\Delta H^{\ddagger}_i$ = 1.083 + 0.364$\Delta\alpha$(av) + 0.01966[$\Delta\alpha$(av)]^2.

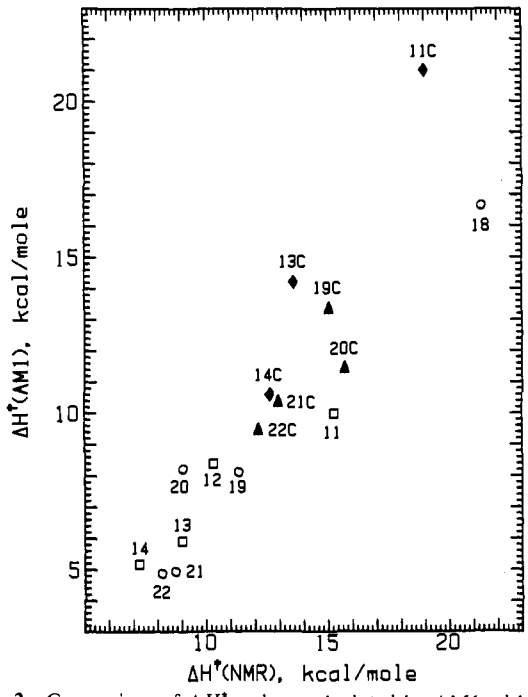

Figure 3. Comparison of $\Delta H^{\ddagger}_{i}$ values calculated by AM1 with those measured by NMR for R_2NMe (open symbols; circles are monocyclic and squares are bicyclic compounds) and chloroamines (filled symbols; triangles are monocyclic and diamonds are bicyclic compounds.)

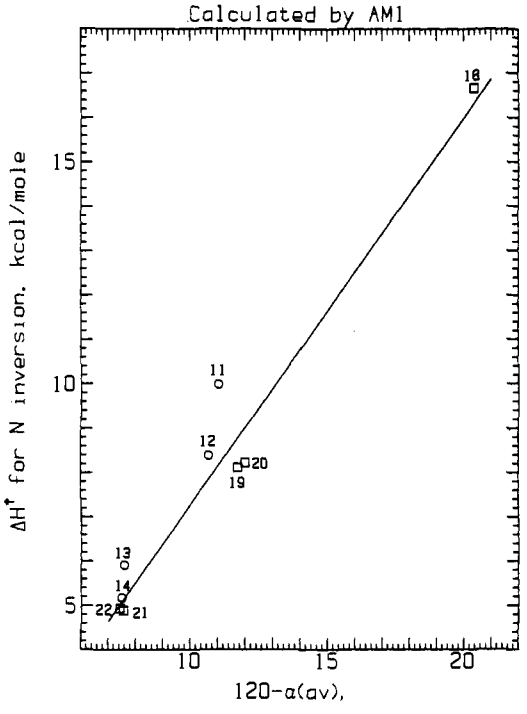

Figure 4. Plot of AM1 calculations of $\Delta H^{\ddagger}_{i}$ versus change in α(av) between ground state and inversion transition state. Squares are bicyclic R_2N and circles are monocyclic R_2N.

for the compounds with two secondary N substituents. $\Delta H^{\ddagger}_{i}$ for **14** lies 0.26 (3) kcal/mol above that of the pyrrolidines **21** and **22**, which have similar α(av) values. Increasing the degree of branching at the carbon next to nitrogen consistently increases the calculated barrier at a given α(av). Because the nitrogen lone pair orbital mixes significantly with the sigma combination orbitals of the alkyl groups, it seems qualitatively reasonable that attachment of secondary alkyl substituents, which weaken the CN bonds, would affect the inversion barrier. The calculated barrier-raising effect of the 7-azabicyclo[2.2.1]heptyl system **11** (2.5 kcal/mol above the curve through the monocyclic points[20]) is substantially larger than that of its homologues **12** and **13** (1.2 and 0.9 kcal/mol above the curve). The calculated N inversion barriers are smaller than experimental ones; the average ratio of the experimental to the calculated entries in Table II is 1.4, although how close the calculated value is to the experimental one depends somewhat upon structure. Compound **11** shows the largest deviation from the curve through the monocyclic compounds, but all the secondary alkyl substituted bicyclic amines show higher barriers in the plot versus $\Delta\alpha$(av) than do the primary alkyl substituted monocyclic ones.[21] We suggest that the AM1 calculations, through comparing the results with the changes in α(av) and the calculated barriers with experimental ones, allow reasonable estimation of the size of Lehn's "bicyclic effect" for R_2NMe. The bis-secondary substituted bicyclic compounds **12** and **13** have inversion barriers about 1.5 kcal/mol higher than an unbranched monocyclic compound of the same $\Delta\alpha$(av) value would have, and the 7-azanorbornane **11** shows a larger barrier increase of about 3.5 kcal/mol.

A completely different calculational approach to considering changes in N inversion barriers for various alkyl substituents would be to use molecular mechanics instead of quantum mechanical calculations. Profeta and Allinger have quite successfully parameterized MM2 for aliphatic amines,[22a] and we do not doubt that the relative energies and geometries of the ground states might be better treated by MM2 than by quantum mechanical calculations. The CNC bond angles and α(av) values calculated by MM2 have been included in Table II for comparison with the values calculated by AM1. It will be noted that rather large differences are obtained for the less constrained nitrogens (especially the azetidines, which have rings that are too planar by AM1), but that the differences are rather small for the bicyclic systems. Unfortunately, Profeta and Allinger's MM2 parameterization cannot be directly extended to N inversion transition states, because the lone pair is treated as a rather small, quite soft pseudoatom, which most be on one side or the other of the nitrogen atom. Geometries which are flat at nitrogen cannot be handled by this approach.

Discussion: Electronic Effects in 7-Azabicyclo[2.2.1]heptanes

Even though AM1 is able to correctly calculate the observed effect of barrier increases for 7-azanorbornane derivatives, this gives no direct insight into the origin of the effect. Lehn tentatively suggested in 1970 that repulsion between the nitrogen lone pair at position 7 and the bonding electrons in the two carbon bridges might be the source of the barrier raising.[4] Three years later, Hoffmann, Mollere, and Heilbronner[23] pointed out that there is indeed a most unusual electronic effect involving position 7 of norbornyl systems. They showed that 7-oxa- and 7-methylenenorbornane are unusually difficult to ionize in the gas phase and suggested orbital symmetry as an origin for the effect. The highest several sigma MO's of the boat cyclohexane portion of the norbornyl framework have the wrong symmetry to interact with a p orbital centered at position 7. This lack of mixing of the upper σ hydrocarbon MO's with the π orbital at position 7, which is imposed by orbital symmetry, destabilizes species in which the π orbital at position 7 is not filled because the filled σ orbitals get less stabilization than is "normal". This orbital symmetry effect does not lead us to predict special difficulty for nitrogen inversion in 7-azanorbornanes because the lone pair orbital is filled.

Mixing of the N lone pair with the substituent σ and σ^* orbitals occurs in the pyramidal ground state, but the N–C bond contributions to this mixing are required by symmetry to disappear at the transition state. Contracting the CNC angle by decreasing

(21) Calculations on the R_2NCl and R_NH compounds (see supplementary material) give similar conclusions, but discussion has been eliminated to save space.

(22) (a) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907. (b) MM2 = Molecular Mechanics II, Allinger, N. L.; Yah, Y. H. *QCPE* 395, corrected to the amine parameters of ref 22a. (c) Structures were input using MMHELP, Molecular Mechanics Input Assist (*QCPE* 476), Collidge, M. B.; Petillo, P. A.; Weisman, G. R. *QCPE Bull.* **1984**, *4*, 46.

(23) Hoffmann, R.; Mollere, P. D.; Heilbronner, E. *J. Am. Chem. Soc.* **1973**, *95*, 4860.

ring size increases pyramidality at N, which should increase the amount of lone pair, σ^* mixing in the ground state for N inversion relative to less pyramidal compounds. If this mixing were significantly larger for the secondary alkyl substituted bicyclic examples than for the primary alkyl substituted monocyclic compounds, ground-state stabilization which is lost at the transition state for N inversion would increase the N inversion barrier for the bicyclic compounds as the nitrogens become more pyramidal. In an attempt to discover whether effects on the ground state are sufficient to rationalize the calculated barriers, we examined the calculated CN bond lengths as a function of structure on the idea that if lone pair, σ^* mixing were important enough to lead to significant stabilization of the ground state, it might lengthen the CN bonds detectably. There is a notably linear correlation of calculated $\Delta H^{\ddagger}_{i}$ with endocyclic NC bond length for **11–14** and **19–22**. For these eight compounds, the correlation coefficient, r, obtained is 0.99, and the average deviation of calculated $\Delta H^{\ddagger}_{i}$ from the least-squares line is 0.18 kcal/mol.[24] Not surprisingly because of the extensive rehybridization at carbon as well as nitrogen involved for this compound, *N*-methylaziridine (**18**) does not fit the correlation. However, the correlation is only slightly worse at the planar transition state for N inversion, $r = 0.95$, average deviation 0.46 kcal/mol. We do not presently see a way of quantitating the relative importance of ground-state and transition-state effects. Lone pair, σ framework mixing also depends on alkyl group orientation, and the C_α–C_β bonds of primary alkyl monocyclic groups are in poorer geometry for overlap than are those of bicyclic alkyl groups, which might be another factor causing the "bicyclic effect".

Conclusions

AM1 calculations give N inversion barriers for trialkylamines which are somewhat too low, but which reflect changes in barrier as the alkyl substituents are changed encouragingly well. The change in the average of the bond angles at N between the pyramidal ground state and the planar transition state is a useful geometric parameter to consider in comparing N inversion barriers for compounds with different substituents. Such a comparison indicates that there is an increase in the N inversion barrier for bis-α-branched 1-bridge-azabicyclo[3.3.1]nonyl and -[3.2.1]octyl systems on the order of 1.5 kcal/mol compared to monocyclic compounds, and that an additional increment of about 2 kcal/mol occurs for the more pyramidal 7-azanorbornyl derivatives. Consideration of how alkyl substitution affects the calculated N inversion barrier is consistent with increased ground-state stabilization caused by larger lone pair, alkyl group σ^* orbital mixing for secondary than for primary-alkyl substituents being a factor in causing the "bicyclic effect".

Experimental Section

7-Azabicyclo[2.2.1]heptane Hydrochloride (8·HCl) and 7-Ethyl-7-azabicyclo[2.2.1]heptane Hydrochloride (9·HCl). A 5.6-mL sample of an approximately 1.54 M solution of diethoxytriphenylphosphorane in toluene[9a] was added to a flame-dried 50-mL round-bottom flask containing 0.656 g (5.7 mmol) of **7**[10] stirring under nitrogen in 4 mL of toluene. The solution was heated at 68 °C for 2.5 days with a rubber septum wired to the top of a reflux condenser; loss of the volatile products during this long reaction proved to be a problem in open systems. Toluene and the products were slowly distilled in vacuo into a nitrogen-flushed flask cooled to −78 °C, 5 mL of ether was added, and dry HCl gas was bubbled through the solution in the absence of air, producing a very hygroscopic white powder from which the solvent was decanted. After washing several times with dry ether and drying by blowing a stream of dry nitrogen over the powder, 0.368 g of a 1.2:1 mixture of the hydrochlorides of **8** and **9** respectively was obtained (26% and 18% yields).

7-(Carboxyethyl)-7-azabicyclo[2.2.1]heptane (10) and 7-Ethyl-7-azabicyclo[2.2.1]heptane Hydrochloride (9·HCl). To 0.452 g of a mixture of **8**·HCl and **9**·HCl from the above reaction was added 8 mL of 20% aqueous NaOH, and the solution was extracted six times with 25 mL of ether. Once dried with potassium carbonate, the ether solution was treated with 1.52 g (1.40 mmol) of ethyl chloroformate, rapidly producing **9**·HCl as a flocculent white precipitate which was collected by filtration (0.220 g, 1.36 mmol) NMR: ($CDCl_3$) δ 4.00 (br s, 2 H), 3.05 (br q, 2 H), 2.59 (br d, 2 H), 2.05 (br d, 2 H), 1.79 (m, 2 H), 1.65 (m, 2 H), 1.50 (t, 3 H). Concentration of the filtrate gave **10** as a white solid (0.210 g, 1.30 mmol). NMR: ($CDCl_3$) δ 4.60 (br m, 2 H), 4.30 (q, 2 H), 1.79 (br m, 4 H), 1.40 (d, J = 8.5 Hz, 4 H), 1.24 (t, 3 H).

7-Methyl-7-azabicyclo[2.2.1]heptane Hydrochloride (11·HCl). A solution of 0.210 g (1.3 mmol) of **10** from the above reaction in 10 mL of ether was added to a stirring suspension of 0.40 g (10.5 mmol) of LAH in 50 mL of ether, refluxed 12 h, and quenched with 0.4 mL of H_2O, 0.4 mL of 10% NaOH, and 1.2 mL of H_2O. The resulting salts were filtered through a pad of Celite and rinsed with ether. The ether solutions were combined and dried over potassium carbonate, and **11**·HCl was precipitated by bubbling HCl through the solution, yielding 0.180 g (1.22 mmol, 94%). NMR: ($CDCl_3$) δ 5.8 (br s, NH), 3.91 (br s, 2 H), 3.91 (br s, 2 H), 2.76 (s, 3 H), 2.55 (br d, 2 H), 2.13 (br d, 2 H), 1.80 (br d, 2 H), 1.68 (br d, 1 H).

NMR Solutions. The NMR solution of **11** for dynamic studies was produced by shaking 0.137 g of **11**·HCl with 0.3 mL of $CDCl_3$ and 0.29 g of KOH in 0.5 mL of H_2O, removing the $CDCl_3$ layer by syringe, and extracting five times with 0.1-mL portions of $CDCl_3$. The combined solutions were dried by stirring over BaO and K_2CO_3 for 48 h with careful exclusion of air, and the solvent and compound were distilled into an NMR tube, cooled to −78 °C on a vacuum manifold, and the NMR tube sealed under vacuum. The sample of **9** was prepared similarly from 0.063 g of **9**·HCl and a total of 1.4 mL of $CDCl_3$. Dynamic NMR data were recorded on a Brucker AM-500 and analyzed by digital simulation.[16] For **11**, data at 9.7, 15.1, 20.3, 25.8, 30.8, 36.4, and 42.0 °C gave $\Delta G^{\ddagger}$ (25°C) 13.77 (4), $\Delta H^{\ddagger}$ 15.2 (13), and $\Delta S^{\ddagger}$ 4.8 (42). For 9, data at 9.7, 15.1, 20.3, 25.8, 30.8, 36.4, 42.0, and 58.0 °C gave $\Delta G^{\ddagger}$ (25°C) 13.16 (4), $\Delta H^{\ddagger}$ 14.0 (14), and $\Delta S^{\ddagger}$ 2.3 (34).

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Registry No. **7**, 27489-62-9; **8**·HCl, 27514-07-4; **9**, 116350-35-7; **9**·HCl, 116350-36-8; **10**, 116350-37-9; **11**, 55258-02-1; **11**·HCl, 27514-10-9; **11C**, 116005-43-7; **11H**, 279-40-3; **12**, 529-17-9; **12C**, 74327-95-0; **12H**, 280-05-7; **13**, 491-25-8; **13C**, 73322-95-9; **13H**, 280-97-7; **14**, 55100-40-8; **14C**, 5697-97-2; **14H**, 280-38-6; **18**, 1072-44-2; **18C**, 10165-13-6; **18H**, 151-56-4; **19**, 4923-79-9; **19C**, 32115-53-0; **19H**, 503-29-7; **20**, 16047-91-9; **20C**, 19816-93-4; **20H**, 19816-92-3; **21**, 120-94-5; **21C**, 19733-68-7; **21H**, 123-75-1; **22**, 16911-20-9; **22C**, 29886-71-3; **22H**, 3437-30-7.

Supplementary Material Available: AM1 calculated barriers for nitrogen inversion of chloroamines **11C–14C** and **18C–11C** (Table III) and **11H–14H** and **18H–22H** (Table IV) (2 pages). Ordering information is given on any current masthead page.

(24) We employed the NCH_2 bond length of **14**, the only compound in this series with a choice between the NCH_2R and $NCHR_2$ bonds. A very large deviation, −1.05 kcal/mol, occurs if the N–CH bond length is used.