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In-Line Proximity Effects in Extended 7-Azanorbornanes. 2. A Major Reduction of *N*-Inversion Barriers in Symmetrically Flanked Systems

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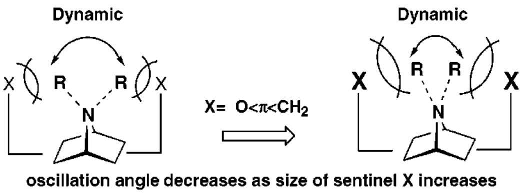
ABSTRACT



Through-space compression effects from a pair of flanking (sentinel) groups X are shown to cause a flattening of the bridging nitrogen in symmetrically fused 7-azanorbornanes which is evaluated by a substantial reduction of the nitrogen inversion barrier as measured by low-temperature ^{1}H NMR spectroscopy. This effect is attributed to destabilization of the ground state of the amine.

Interest in the 7-azanorbornane (7-azabicyclo[2.2.1]heptane) skeleton has received substantial recent stimulation as a result of the isolation of the first natural derivative,[1] and this has catalyzed renewed interest in the fundamental properties of this ring system. Pre-eminent among these is the unusually high barrier to inversion at nitrogen (the term “bicyclic effect" was originally coined by Lehn[2] to describe this effect) which continues to stimulate investigations.[3]

We have recently synthesized a series of azanorbornane derivatives in which the central tertiary amine bridge is flanked by two additional norbornyl or heteronorbornyl bridges (collectively referred to as sentinel bridges), and these offer a unique opportunity to investigate the pressures imposed on the central nitrogen as a consequence of through-space effects (rather than by substituents directly attached to nitrogen[4,5]). In particular, we expected the central nitrogen to be significantly flattened, aware that this would be a high-energy process as the remaining CN bonds of the amine are locked in a rigid norbornane ring system.

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(1) Epibatidine, a compound with potent analgesic activity, is a chloropyridyl derivative of 7-azabicyclo[2.2.1]heptane and was discovered in 1992: Spande, T. F.; Garraffo,H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478. References to the very wide range of syntheses of epibatidine can be found in, for example, the following: Aoyogi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397−8406. Palmgren, A.; Larsson, A. L. E.; Bäckvall, J.-E.; Helquist, P. *J. Org. Chem.* **1999**, *64*, 836−842.

(2) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311−377.

(3) (a) For a view based largely on transition state strain, see: Bushweller, C. H.; Brown, J. H.; DiMeglio, C. M.; Gribble, G. W.; Eaton, J. T.; LeHoullier, C. S.; Olson, E. R. *J. Org. Chem.* **1995**, *60*, 268−271. (b) Belostotskii, A. M.; Gottlieb, H. E.; Hassner, A. *J. Am. Chem. Soc.* **1996**, *118*, 7783−7789. For consideration of contributions to the inversion process in azabicycles from torsional strain, see: (c) Forsyth, D. A.; Zhang, W.; Hanley, J. A. *J. Org. Chem.* **1996**, *61*, 1284−1289. See also references in footnote 13.

(4) For example, triisopropylamine, where serious flattening of the ground state occurs as a result of interactions between three spatially demanding groups attached *directly* to nitrogen: (a) Bock, H.; Goebel, I.; Havlas, S. L.; Oberhammer, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 187−190. (b) Anderson, J. E.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1996**, *61*, 1290−1296. (c) Wong, T. C.; Collazo, L. R.; Guziec F. S., Jr. *Tetrahedron* **1995**, *51*, 649−656.

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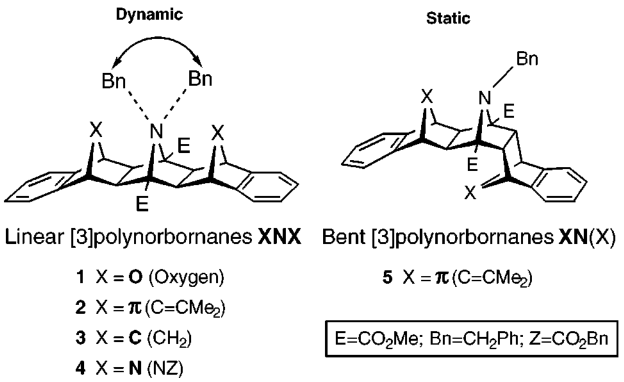

Figure 1. Polynorbornanes **1**−**5** in linear and bent geometries.

The linear [3]polynorbornanes shown in Figure 1 were synthesized[6] and characterized as described in the accompanying paper and are referred to as XNX.[7] This work also includes a wider selection of compounds having different flanking bridges XNY together with "bent" analogues. We have chosen "bent" compound **5** which has two terminal isopropylidene bridges for comparison.

For compounds **1**−**4**, we predicted that the presence of the two flanking (sentinel) bridges would lead to an increase in α(av) angle.[8] This provides a convenient measure of the pyramidalization at the central nitrogen bridge. This flattening of the central nitrogen is confirmed by an X-ray crystal structure for CNC[9] (Figure 2) which shows an α(av) angle of 114.9°, a figure which is close to the AM1-calculated value of 116.1°. This α(av) angle is larger than the calculated (AM1) values for reference compound **5** (α(av) 109.0°) and *N*-benzyl-7-azanorbornane (α(av) 108.7°).

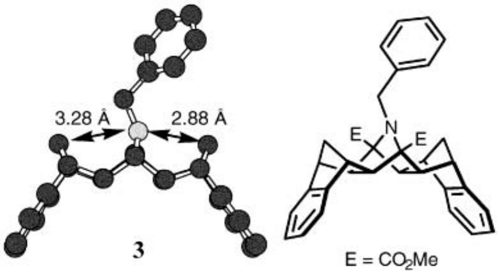

Figure 2. X-ray crystallographic structure of CNC **3** (esters and hydrogens removed for clarity).

This increase in α(av) for CNC compared with the α(av) angle in *N*-benzyl-7-azanorbornane is illustrated in Figure 3, an effect which must result in an increase in the s-character in the C−N bonds of the central nitrogen (increased p-character of the lone pair). We chose the measurement of nitrogen inversion barriers as a convenient method for evaluation of geometric changes at the central nitrogen in these cases.

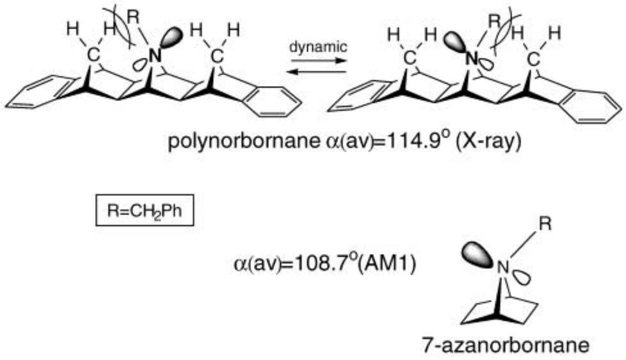

Figure 3. Increase in α(av) angle in the *N*-benzyl[3]polynorbornane CNC **3** caused by the sentinel methylene bridges in comparison with *N*-benzyl-7-azanorbornane.

Nitrogen inversion barriers for compounds **1**, **2**, and **3** were calculated using VT ^{1}H NMR spectroscopic data.[10] The NMR spectra for **4** were too complicated for confident analysis as a result of the additional process of slow rotation about both N−CO bonds of the two *N*-benzyloxycarbonyl groups which also gives rise to a mixture of stereoisomers at low temperatures. The inversion barriers for **1**−**3** are shown in Figure 4 together with comparison values for simpler *N*-benzyl-7-azanorbornanes taken from the literature.[3a,11,12] A sizable reduction in $\Delta G^{\ddagger}$ is evident in all three cases. In

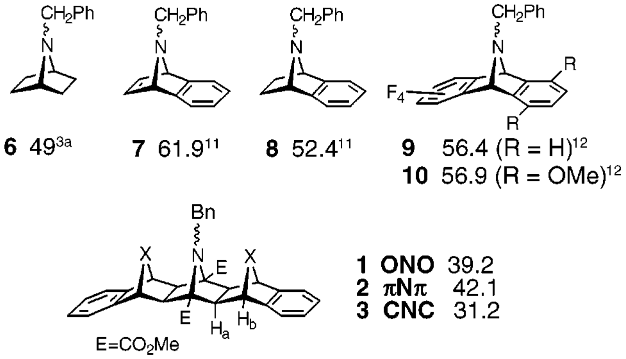

Figure 4. Comparative barriers to inversion at nitrogen $\Delta G^{\ddagger}_{300}$ (kJ mol^{-1}). Calculated using $\Delta S^{\ddagger} = 5$ J mol^{-1} K^{-1} after Nelsen.[13a]

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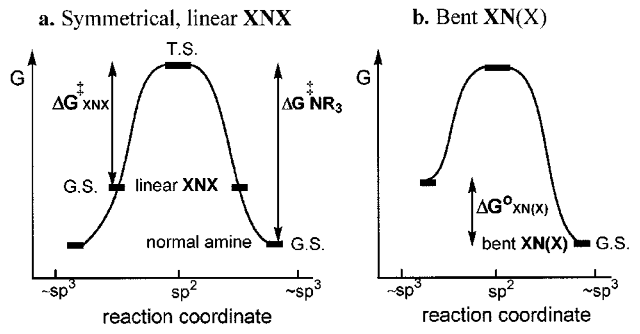
(5) Ground-state destabilization (flattening at nitrogen) has been proposed in other cases where the nitrogen bears a bulky alkyl group, e.g., *N-tert*-butyl-9-azabicyclo[3.3.1]nonan-3-one (on the basis of pK_a measurements and compression effects in the ^{13}C NMR spectrum): Wiseman, J. R.; Krabbenhoft, H. O.; Lee, R. E. *J. Org. Chem.* **1977**, *42*, 629−632. No conclusions concerning *N*-inversion were possible in this work. See also: Nelsen, S. F. *J. Org. Chem.* **1984**, *49*, 1891−1897. (b) The inversion barrier is also lowered substantially in *N-tert*-butyl-7-azanorbornane.[3b]

(6) The synthesis of these compounds is based on a substantial extension of methodology developed earlier (Butler, D. N.; Malpass, J. R.; Margetic, D.; Russell, R. A.; Sun, G.; Warrener, R. N. *Synlett* **1998**, 588−589) which is described in the accompanying Letter.[7]

comparison with the established examples, the inversion barrier for ONO is already substantially reduced but the presence of sterically demanding methylene bridges in CNC (cf. Figure 3) reduces $\Delta G^{\ddagger}$ considerably more when compared with the reference compounds.[3a,11,12]

Factors which distort the central nitrogen toward planarity must destabilize the ground state and effectively cause movement along the reaction profile toward the energy maximum, thus reducing the nitrogen inversion barrier. This is illustrated diagrammatically in Figure 5a for a strained amine having two isoenergetic invertomer ground states (linear XNX) and for a “normal” tertiary amine. It is entirely to be expected that compound **3** (having two methylene bridges) should suffer the greatest ground-state destabilization and hence have the lowest value of $\Delta G^{\ddagger}_{\text{inv}}$.


a. Symmetrical, linear **XNX**

b. Bent **XN**(X)

Figure 5. Inversion at bridging nitrogen.

The uneven balance of effects in the case of an *N*-bridge having an unsymmetrical environment (Figure 5b) leads to destablization of one invertomer to such an extent that it is effectively inaccessible, thus “fixing” the *N*-substituent in the single lower-energy conformation. This interpretation was confirmed for πN(π) **5** by VT NMR analysis which showed no decoalescence or evidence of a minor invertomer at temperatures down to −100 °C.

The free energy of activation for the nitrogen inversion process is governed by the relative energy of both the nominally sp^3 ground state and the sp^2 transition state (Figure 5a). Factors which increase or decrease the energy of the *transition state* for inversion are well-documented for cyclic and bicyclic amines and can lead, respectively, to a very substantial increase or decrease in the barrier to inversion at nitrogen.[2,3] While the possible additional involvement of ground-state stabilization effects in raising the barrier in this unique bicyclic system was recognized by Nelsen[13a] and supported by one of us,[13b] *de*stabilization effects normally appear to play a relatively minor role.[13c]

There is evidence from calculations (AM1) and from the X-ray data for **3** (Figure 2) that the angles between the three bridges widen to some extent, presumably to minimize repulsions.[9,14] Nevertheless, the reduction of the inversion barriers indicates that this deformation is not sufficient to allow the central nitrogen in symmetrical [3]polynorbornanes to escape the consequences of the buttressing effect of the neighboring bridges; the linear backbone clearly retains sufficient rigidity for meaningful investigation of interbridge effects. The contributions made by the neighboring bridges on the transition state for inversion are not easy to predict and have been neglected in the treatment above. While steric interactions between the outer bridges and the *N*-substituent are reduced at the transition state, at this stage we cannot quantify the importance of interactions between the orbitals on the terminal bridges and the lone pair of electrons in the central nitrogen p-orbital. In any event, they are clearly of secondary importance, leading only to augmentation or attenuation of the larger ground-state effects which lead to flattening of the central nitrogen and hence the substantial reduction of the inversion barrier which is common to compounds **1**−**3**.

The $\Delta G^{\ddagger}_{\text{inv}}$ values for **1**−**3** are compared with calculated α(av) angles in Figure 6 (which also includes an α(av) angle derived from crystallographic data for CNC). As expected, a smaller $\Delta G^{\ddagger}_{\text{inv}}$ value corresponds to a larger α(av), i.e. flattening of the nitrogen of the central bridge.[15]

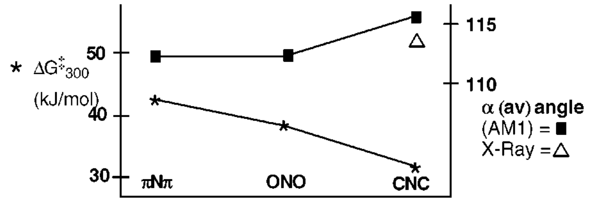


Figure 6. Inversion barriers $\Delta G^{\ddagger}_{300}$ and angles α(av) for πNπ, ONO, and CNC.

While compound **3** shows an exceptional lowering of the inversion barrier, the fact that variants **1** (ONO) and **2** (πNπ) also show major effects suggests that the influence of enforced n/n and n/π interactions deserves further investigation in addition to n/σ in variant **3** (CNC). Proximity effects have been discussed previously in the 7-azanorbornyl ring system and include n−π interactions between the lone pair

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(7) Butler, D. N.; Hammond, M. A. L.; Johnston, M. R.; Sun, G.; Malpass, J. R.; Fawcett, J.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 721−724.

(8) The angle α(av) defined as the average of the sum of the bond angles around the nitrogen of the central bridge.[3b]

(9) It should also be noted that the nitrogen atom of the central bridge is not symmetrically positioned between the flanking methylene groups (Figure 2). This feature is common to all [3]polynorbornanes having a central *N*-benzyl-substituted bridge that we have studied.[7]

(10) Inversion barriers were calculated using the coalesence method which uses the expression $k_c = \pi(\Delta\nu)/\sqrt{2}$ to approximate inversion rate at the coalesence temperature T_c (errors in k_c associated with this method are on the order of 20%). The inversion barrier $\Delta G^{\ddagger}$ was determined at the coalesence temperature using the Eyring equation and converted to 300 K using $\Delta S^{\ddagger} = 5$ J mol^{-1} K^{-1} from Nelsen.[13a] Thus, for ONO a $\Delta\nu$ of 46 Hz for H$_b$, T_c −70 °C, gave $k_c = 102$ s^{-1} and $\Delta G^{\ddagger}_{203} = 41.3$ kJ mol^{-1}. In comparison, πNπ had $\Delta\nu = 174$ Hz for H$_a$, T_c −47 °C, and $k_c = 386$ s^{-1} yielding $\Delta G^{\ddagger}_{226} = 43.6$ kJ mol^{-1}. CNC had $\Delta\nu = 134$ Hz for H$_a$ and T_c −98 °C giving $k_c = 297$ s^{-1} and $\Delta G^{\ddagger}_{175} = 33.8$ kJ mol^{-1}.

(11) Deloughry, W. J.; Sutherland, I. O. *Chem. Commun.* **1971**, 1104−1105.

(12) Davies, J. W.; Durrant, M. L.; Walker, M. P.; Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1992**, *48*, 861−884.

and etheno bridges and benzo bridges in 7-azabenzonorbornadienes.[16] Such relatively distant π-bonds are known to induce small changes in invertomer ratios[12] in this ring system, but these interactions are of modest consequence compared to those observed here in the three-bridged systems.

Compounds **1**−**3** suffer substantial variations in ground-state shape (hybridization) for symmetrical tertiary amines as a result of through-space interactions from adjacent groups which are not attached *directly* to the nitrogen; indeed the central nitrogen is separated from the bridging methylene CH by five bonds in **3**. These results strongly support a direct relationship between nitrogen hybridization in the ground state and $\Delta G^{\ddagger}_{\mathrm{inv}}$. Further variation of the X bridges offers a fascinating range of compounds for deeper study of proximity effects on nitrogen.

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(13) (a) The suggestion that additional contributions from ground-state stabilization in 7-azanorbornanes might be important was made by Nelsen, S. F.; Ippoliti, J. T.; Frigo, T. B.; Petillo, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 1776−1781. See also footnote 4e in Durrant, M. L.; Malpass J. R. *Tetrahedron* **1995**, *51*, 7063−7076 and the discussion in Davies, J. W.; Durrant, M. L.; Walker, M. P.; Malpass, J. R. *Tetrahedron* **1992**, *48*, 4379−4398. Barriers to inversion at nitrogen can be almost as high in 7-azanorbornanes as in aziridines (where the angle strain is greater). Additional delocalization of electron density from nitrogen into the bicyclic framework is supported by the unusual deshielding of the bridging nitrogen in these systems[13b] (in contrast with the substantial *shielding* of the nitrogen in aziridines). Such an effect would raise the energy required to reach the sp^2 transition state, in which the nitrogen lone pair occupies a p-orbital. If this stabilization of the ground state does indeed operate, it will counter the *de*stabilizing effects proposed in the present work and may therefore be expected to moderate them to some extent. (b) Belkacemi, D.; Davies, J. W.; Malpass, J. R.; Naylor, A.; Smith, C. R. *Tetrahedron* **1992**, *48*, 10161−10176. (c) 7-Azanorbornanes bearing *N*-ethyl, *N*-isopropyl, *N*-benzyl, and *N*-isobutyl substituents cover a range of only $\Delta G^{\ddagger}_{300} = 8.5$ kJ mol^{-1}.

(14) A similar effect is observed in [*n*]polynorbornanes where the radius of curvature of the frame changes as the CH_2 is replaced by N and O, and this effect (C > N > O) is in the same order as that observed here. Warrener, R. N.; Margetic, D.; Sun, G.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111−4114.

(15) We are currently completing a wider study establishing that ^{15}N NMR spectroscopy is a useful tool for probing changes of hybridization in these systems, and this work will be published separately.

(16) Martin, H.-D.; Mayer, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 283−313. Altenbach, H.-J.; Constant, D.; Martin, H.-D.; Müller, M.; Vogel, E. *Chem. Ber.* **1991**, *124*, 791−801 and references therein.