

A third type of alkylamines possessing high nitrogen inversion–rotation barriers

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ABSTRACT: A new type of alkylamines possessing high nitrogen inversion–rotation (NIR) barriers is described (in general, these are hindered cyclic amines). The increase in barrier values for these amines is caused by an increase in steric interactions in the NIR transition state due to restrictions for *N*-substituent rotation (usually steric repulsion of *N*-substituents is decreased on going to a planar NIR transition state of alkylamines). Since these compounds may be essentially different in structure, a comparison between the NIR barriers of homologs is proposed as a criterion for the assignment of amines to this type. According to this criterion, the NIR barriers are drastically increased (3–5 kcal mol^{−1}) on going from NMe or NH (usual amines) to more bulky *N*-alkylhomologs (amines of the third type). Structures of some of these amines were predicted and their NIR barriers were estimated by MM3. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: molecular mechanics; inversion–rotation barriers; alkylamines

INTRODUCTION

Nitrogen inversion–rotation (NIR) barriers for *most* alkylamines in aprotic solvents do not exceed the 9 kcal mol^{−1} limit^{1–3} (although many authors consider this as nitrogen inversion, in most cases an NIR process is actually occurring^{3,4}). Substantially higher NIR barriers were reported for different methyl-substituted *N*-methylpiperidines in aqueous^{5a,b} and organic solutions,^{5c} but they rather relate to other intramolecular conformational transformations.⁴ Also, experimental values for azetidines (9–10 kcal mol^{−1})⁶ should be considered as kinetic characteristics of a concerted ring inversion–NIR process (and not NIR).⁷

Thus, when NIR barriers are >11 kcal mol^{−1}, in the absence of stabilization of a nitrogen pyramid via a strong N···H bond (e.g. an intramolecular H-bond⁸), they may be defined as high NIR barriers. Two types of compounds with high NIR barriers are known among a variety of alkylamines: (1) aziridines (with barriers of >16 kcal mol^{−1})⁶ and (2) azanorbornanes (with barriers of >13 kcal mol^{−1}).^{9,10} In both cases specific effects cause this increase: abnormal angle strain in the aziridine case⁸ and strain together with the ‘bicyclic effect’ in the azanorbornane case.^{9,10} In general, azanorbornanes belong to the class of polycyclic amines whose backbone disallows a concerted ring inversion–nitrogen inversion–process.⁷ A drastic increase in NIR barriers is predicted for such systems.⁷

However, high NIR barriers (12.1 and 11.7 kcal mol^{−1})^{11,12} were indicated by NMR for other bicyclic amines, which do not belong to either of these two types, namely azabicyclononane **1a** and triptycylamine **2a**, respectively (see Fig. 1). For piperidines **3** and

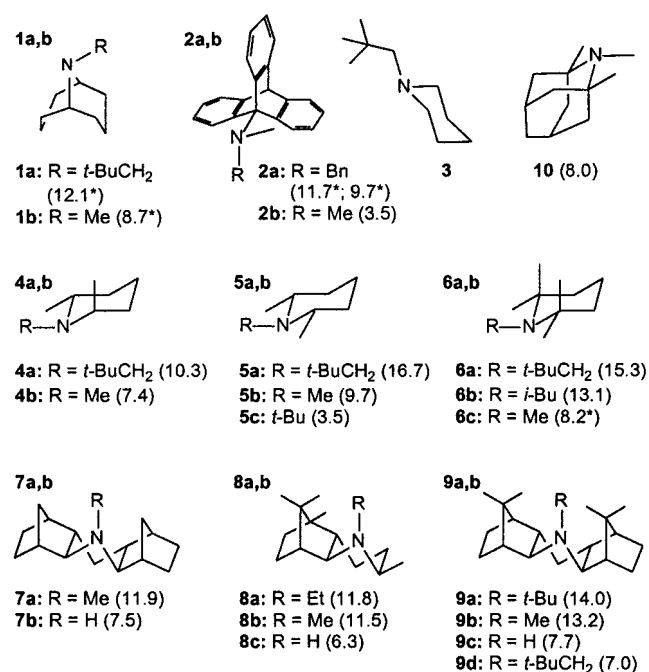


Figure 1. Amines **1a,b–10** and corresponding NIR barrier values (kcal mol^{−1}, in parentheses). For **9d** and the NH compounds these are the barriers of isolated N inversion. Experimental barriers are marked with asterisks

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6a the MM3 force field estimated the NIR barriers as^{4,7} 12.1 and 15.3 kcal mol⁻¹ (for the problems of the assignment of the NMR-measured barrier for **3**,^{13a} see Ref. 4). The high barrier for **1a** was explained via a large energy contribution of the rotational component of NIR.¹¹ While **2a** possesses an additional NIR barrier of lower energy (9.6 kcal mol⁻¹),¹² the measured high NIR barrier for **1a** is the only NIR barrier for this system. Hence amines **1a**, **3** and **6a** can be classified as belonging to a *third* type of alkylamines with a high NIR barrier. This type may be defined as alkylamines for which (a) an increased height of the NIR barrier is caused by an increased contribution of steric interactions of the *N*-substituents in the NIR transition state and (b) this barrier is the lowest NIR barrier among the NIR barriers inherent to the lowest energy stable conformer.

Indeed, when an *N*-alkyl substituent of an amine rotates during NIR, an energy-lowering reorientation (sequential rotation, conrotation or disrotation) of other substituents obviously occurs to avoid tight steric contacts. These contacts are usually minimal in the NIR transition state since the distance between the α -carbon atoms of the *N*-substituents is maximal for a planar nitrogen geometry. A situation is possible in which this reorientation is restricted. For instance, in the small and medium size saturated azacycles and more so in bicycles, the C—N rotation of two endocyclic fragments is essentially limited, whereas the third, exocyclic *N*-substituent can rotate freely. Hence repulsion of the *N*-substituents may increase even in the lowest energy NIR transition state relative to this repulsion in the stable pyramidal conformation.

The above definition considers the lowest energy conformer although it does not necessarily undergo NIR most rapidly. For instance, the higher energy twist conformers of piperidines possess lower NIR barriers than the minimal energy chair conformer.^{4,7} Our choice is based on a practical convenience: experimental NIR barriers relate to conformational transformations of the minimal energy conformers.

It is difficult to define *a priori* structural features of this amine type since the above-mentioned 'high-energy' combination of *N*-substituents may be different for various amines. Neopentylamines **1a**, **3** and **6a** turn out to be the only examples of the third type of alkylamines. Nevertheless, the presence of an *N*-neopentyl substituent in an amine system does not necessarily lead to high NIR values, *e.g.* the highest NMR-measured values lie in the 8.3–9.7 kcal mol⁻¹ range for the open-chain tertiary mono-, di- and trineopentyl amines.^{13b}

It was demonstrated recently that, unlike some other computational methods (*e.g.* MM2- or AM1-based calculations; for a criticism see Refs. 10 and 16), the MM3 force field^{14,15} provides a good estimation of NIR barriers.^{7,10,16} For instance, restriction of selected atom motion in the MM2 block diagonal matrix minimization is used for modeling of transition states with an assumed

geometry (see, *e.g.*, Ref. 11 for the NIR transition state) but the still used MM2 program has no tool to prove whether this structure is a transition state and obviously whether it is the first-order transition state. In contrast, convenient features of the MM3 package, namely full matrix minimization option as well as normal mode vibrational analysis, permit one to find transition states on conformational pathways and also to determine their order^{10,16,17} and to establish formal genetic relationships between these transition states and the corresponding conformers.^{4,7} Therefore, in order to prove 'the third type of amines' concept and to reveal characteristic features for these amines, we have undertaken an MM3-assisted search and analysis of other systems of this type.

RESULTS AND DISCUSSION

Finding of NIR transition states using the simple methodology (a) (construction of a planar nitrogen-containing fragment followed by full matrix minimization;¹⁰ see Experimental) turned out not to be straight forward in some cases (*e.g.* for amines **2b** and **6b**). Furthermore, since more than one NIR barrier may be present for an amine (*e.g.* for amine **2a**¹²), this approach becomes problematic for the finding of the lowest energy transition state. Therefore, we employed also two other MM3-based methodologies for calculation of NIR barriers: rotational procedure (b) and conformational search followed by full matrix minimization (c)^{7,16} (see Experimental for the details). The last calculation methodology is necessary also for the finding of lowest energy stable conformers (*e.g.* for amines **4b**, **5a**, **6b**, **11–13** and **16a,b**). Four- and five-membered azacycles have been not considered because those are the 'no NIR systems' or belong to amines of type (2) when these rings are structural components of nitrogen-bridged polycycles (see above and also Ref. 16).

We succeeded in finding new high NIR barrier systems, namely hindered amines **5a**, **6b** and **7a**, **8a,b**, **9a,b** and **16a**. Some were as high as 16 kcal mol⁻¹ (see Figs 1 and 2 for calculated barrier values). However, no simple structure–high barrier relationship may be deduced from these data. We can only maintain that trialkylamines of type (3) should *usually* have a mono- or polycyclic backbone which is α -branched relative to the amine nitrogen. Indeed, most of the high-barrier systems considered possess this branching while usual NIR values were measured for different cyclic and bicyclic alkylamines without this structural feature.^{18–20} We reported recently about secure meshing for rotation of the *syn*-periplanar-oriented *tert*-butyl groups in norbornane systems.²¹ However, even this spatial proximity of rotating groups is not essential for NIR in bis-*endo*-substituted norbornanes **11** and **12** (amines with only one α -branching): the calculated barriers are similar to a low value for the *exo-endo*-bis-substituted com-

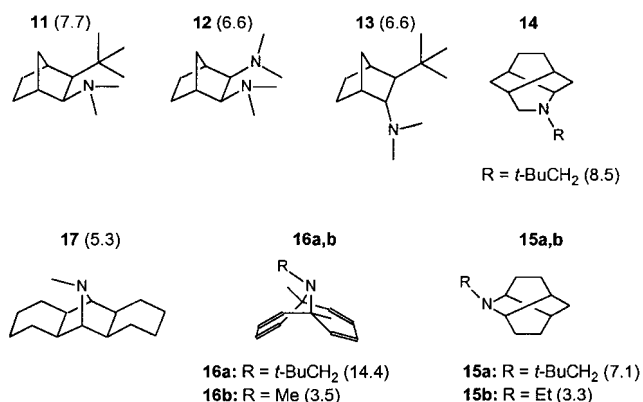


Figure 2. Amines **11–17** and calculated NIR barrier values (kcal mol⁻¹, shown in parentheses)

pound **13** (see Fig. 2). Also, no concerted NIR–NIR and no concerted NIR–ISR (*tert*-butyl) processes were found for diamine **12** and amine **11**, respectively. Only an *N*-neopentyl compound, unbranched piperidine **3**,^{13a} belongs to type (3) of alkylamines. On the other hand, NIR barriers for some α -branched cycles, *N*-neopentylazastitanes **13a** and **14**, are estimated as ‘usual’ values. One finds also that:

(a) A neopentyl substituent is often a ‘high-barrier inducer’ (e.g. piperidines **1a**, **3**, **5a** and **6a** and bicycle **16a**). One notes that the corresponding *N*-Me compounds **1b**, **5b** and **6c**⁵ possess much lower barriers. In contrast, the corresponding values for neopentyl compounds **4a** and **13a** are not unduly high although they are higher than for *N*-Me and *N*-Et analogs **4b** and **13b**, respectively. For neopentyl compound **9d** NIR does not occur and pyramidal inversion is an isolated process^{5,16} (without C–N rotation) with a barrier of 7.0 kcal mol⁻¹.

(b) Although α -branching for two of the *N*-substituents is essential to provide a high NIR barrier (see above), branching for the third substituent may be α (amine **9a**) or β (amines **1a**, **4a**, **5a**, **6b** and **16a**) or may be absent (e.g. amines **7**, **8a,b** and **9b** with a primary *N*-substituent).

(c) System rigidity does not determine the height of the barrier. Whereas rigid *N*-Me piperidines **7a**, **8b** and **9a** with diequatorial 2,6-substituents belong to the high-barrier systems, the calculated NIR barrier for the even more rigid *N*-methylazaadamantane **10** with diequatorial methyl groups is similar to the values for flexible *N*-methylpiperidines **5b** and **6c**.

(d) A piperidine cycle is not an attribute of an amine system of type (3) (e.g. see Fig. 2 for the calculated barrier for azabicyclo[4.4.1]undecatetraene system **16a**).

Therefore, we can conclude that sole backbone structure (atom connection order) does not determine the NIR barrier height. Steric repulsion of *N*-substituents in the NIR transition state depends on, e.g., their stereochemistry. For instance, *N*-neopentylpiperidines **1a** and **5a** which contain *cis*-2,6-substituents of diaxial and diequatorial orientation, respectively, possess high

NIR barriers. *trans*-2,6-Substituted analogs **4a** and **13a** with equatorial–axial and dipseudoaxial orientations, respectively, have appreciably lower barriers. Nevertheless, *cis*-stereochemistry of α -substituents together with the presence of a bulky *N*-substituent also cannot be a characteristic structural feature for amines of type (3): e.g. no NIR was found for diequatorially substituted *cis*-piperidine **9d** (see above). Hence structural criteria for the third type of amines are problematic.

This situation is similar to the case of type (2) alkylamines which also may be defined in structural terms only approximately. The 7-azabicyclo[2.2.1]heptane backbone does not provide slow NIR: *tert*-butylazanorbornane possesses the corresponding barrier of 6.1 kcal mol⁻¹ at room temperature.¹⁰ Since a *tert*-butyl substituent is a known ‘NIR barrier reducer’,^{1,10} we give here an example of an *N*-methylazanorbornane of low NIR barrier (see Fig. 2 for **17**).

Therefore, we propose a ‘non-structural’ criterion for amines of type (3) which is based on comparison of the NIR barrier of a high NIR barrier system with that of a less hindered analog. It is well known for alkylamines^{1,10} that an increase in steric hindrance lowers NIR barriers (e.g. for *N*-methylamine **5b** and *N*-*tert*-butylamine **5c**). However, for amine pairs **1a–1b**, **5a–5b**, **6b–6c**, **6a–6b**, **8a–8b**, **9a–9b** and **16a–16b** (more hindered system–less hindered system) the barrier values *rise* with increase in the bulk of the *N*-substituent. This phenomenon should take place when intramolecular repulsive steric interactions for an amine are increased in the NIR transition state. Since this corresponds to the above definition of the third type of amine systems, a decrease in NIR barriers on going from a more hindered system with a high barrier to a less hindered system with a lower barrier appears to be a reasonable criterion for the third type of amines. Thus, amines **1a**, **5a**, **6b** and **7a**, **8a,b**, **9a,b** and **16a** belong to type (3) of amines. This situation (a higher barrier corresponds to a more hindered system) may also occur within the ‘usual’ NIR barrier range (e.g. amines **13a** and **13b** and the Me₃N case mentioned below).

It is convenient to compare a high NIR barrier amine containing an *N*-alkyl substituent with those of the *N*-Me or NH analog in order to prove the attribution of this amine to type (3). According to the above-mentioned criterion, *N*-Me and NH amines possess lower NIR (or nitrogen inversion in the case of NH compounds) barriers than their *N*-alkyl homologs of type (3). Moreover, the barriers for these NH compounds have ‘usual’ values for inversion barriers. For instance, the calculated barriers for the NH analogs **7b**, **8c** and **9c** of the *N*-Me-containing high-barrier systems **7a**, **8b** and **9b** lie in the range 6.3–7.7 kcal mol⁻¹ (see Fig. 1). The calculated geometry of the corresponding NH and *N*-Me compounds is similar in the stable conformation and in the transition state. Therefore, the 4.0–5.5 kcal mol⁻¹ increase in the NIR values for the high-barrier tertiary amines **7a**, **8b** and **9b** with respect to the secondary analogs is caused only by

an increase in steric interactions with the more bulky *N*-substituent.

Flattening of a nitrogen pyramid, which rises with increase in crowding, was mentioned as an NIR rate-accelerating factor.^{1,22} The insufficiency of only this explanation is revealed even under consideration of the simplest methylamines (their experimental barriers are reviewed in Ref. 22): more flattened Me₃N possesses about a twofold higher NIR barrier than Me₂NH and MeNH₂.²² Hence, the ~ 4 kcal mol⁻¹ discrepancy on going from Me₂NH and MeNH₂ to Me₃N is caused by synchronous rotation of three methyl groups during NIR in Me₃N (this concerted rotation is revealed when the stable conformation–the NIR transition state pathway for Me₃N, is modeled by MM3 via stepwise flattening of the nitrogen-containing fragment followed by minimization in each step²³).

Now we can also explain why no *amine structure–NIR barrier height* relationship can be evaluated for alkylamines. The case of amines of type (3) and also Me₃N and amines **15a** and **15b** demonstrate how large may be the rotation contribution in the NIR barriers. It is obvious that for other alkylamines rotation of *N*-substituents also contributes to the barrier, although to a smaller extent. In other words, the difference in the NIR barrier heights for alkylamines is determined both by the nitrogen pyramidal-ity in stable conformations of these amines and steric interactions of *N*-substituents, which appeared due to their rotation during NIR, in the corresponding NIR transition states. While the tendency of the first NIR rate-accelerating factor (the pyramidal-ity decrease) is simply predictable via amine structure (see above), there is no trend for the rotation contribution. This second factor is case-specific, as the example of alkylamines of type (3) shows.

EXPERIMENTAL

The 1994 version of the MM3 program^{14,15} was used for molecular mechanics calculations. The Vibplot program from the MM3 package was employed for normal-mode vibrational analysis. The minimum energy stable conformers were found via MM3-supported conformational search (option 8). Transition states were found as described in (a)–(c). Their belonging to NIR (or to other transition states) and their orders were proved by normal-mode vibrational analysis as follows: coordinates derived by the Vibplot program from the eigenvectors (produced by option 5 of the MM3 program) of vibrational modes with imaginary frequency were employed as starting coordinates for full minimization (option 3). For structure comparison the molecular graphics program (Xmol) was used.

(a) Amine structures with a planar amino fragment were built by the following algorithm: orientation of the molecule to place the N atom and two cyclic C- α atoms in

the *xy*-plane; change of the *z*-coordinate of the third C- α atom to zero and block diagonal minimization of this structure with restricted motion along the *z*-coordinate for the N atom and three C- α atoms; full matrix minimization (option 3).

(b) For calculation of NIR barriers via a rotational procedure the Driver option was used (NDRIVE = -1). The exocyclic *N*-substituent was rotated gradually in the range -180 to 180° (1° rotation step). Full matrix minimization (option 3) was further employed for the high-energy points of rotation (NIR transition states were distinguished from the C–N rotation transition states via normal mode vibrational analysis; see above for details).

(c) Stochastic search followed by full matrix minimization (option 9) was used for locating the NIR transition states and corresponding stable conformations. Stochastic search (400 pushes for amine **12** and 200 pushes for other amines) was performed starting from arbitrary amine conformations. Establishment of the formal relationship between conformers and transition states was performed via normal-mode vibrational analysis (see above).

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