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CONFORMATIONAL STUDIES BY DYNAMIC NMR—25[1]

STEREOMUTATIONS IN TRIALKYLAMINES

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Abstract—The trend toward steric acceleration for N-inversion and steric deceleration for C–N rotation has been verified in an homogeneous series of tertiary isopropylamines. Unambiguous evidence has been obtained that in a crowded amine (3-pentyl diisopropylamine) the barrier to rotation becomes higher than that to inversion. It has also been shown that this amine adopts an eclipsed, rather than a staggered dynamic conformation.

INTRODUCTION

The dichotomy concerning inversion vs rotation in amines and their derivatives has given rise to discussions and investigations. In a series of outstanding papers Bushweller *et al.*[2–6] have shown that in simple trialkylamines the barrier to N-inversion is higher than that to C–N rotation. They also reported[3b] that in the case of amines containing the t-Bu group the dynamic process that renders diastereotopic the Me's of a t-Bu has the same barrier to N-inversion (determined by monitoring the Et or benzyl groups). The suggestion was thus advanced that there is an unique inversion-rotation pathway for Bu^t-N rotation and N-inversion.

However, Jackson and Jennings pointed out[7] that the barrier to isolated Bu^t-N rotation cannot be determined by NMR in presence of rapid N-inversion since, when both processes are possible, the Me's of t-Bu become diastereotopic only when both motions (N-inversion and Bu^t-N rotation) are slow in the NMR time scale. They also showed[7] that the transition state for a Bu^t-N rotation has an energy higher than that available to a N-inversion pathway; in view of the fact that dynamic NMR can only measure the barrier of the lowest of the two processes, that of the highest one (i.e. Bu^t-N rotation) cannot be determined. Therefore, the $\Delta G^{\ddagger}$ value one determines when monitoring the Me signals of a t-Bu is not that of a rotation but, essentially, that of N-inversion. Indeed the N-inversion pathway that reaches a transition state with a lower energy than rotation (Scheme B of Ref. 7) could be also interpreted as a N-inversion accompanied by a large amplitude vibration of 30° ("libration") about the Bu^t-N bond (Fig. 2 of Ref. 3*b*). This probably explains why this process is referred to either as "coupled inversion-rotation" or, simply, "N-inversion". Whatever the name given to this pathway, there is little doubt that isolated Bu^t-N rotation has an higher barrier, that cannot be thus determined in presence of concomitant N-inversion.[6,7]

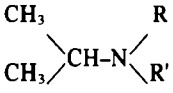
Consequently, since C-N rotational barriers for groups less bulky than t-Bu are lower[6] than N-inversion, and Bu^t-N rotation barriers in alkyl amines, although larger, cannot be determined *via* NMR, meaningful measurements of CN rotational barriers higher than inversion were not available.

In some cases[8,9] the observation of diastereotopic hydrogens in aliphatic amines was attributed to restricted rotation, even though the possibility that the phenomenon had been generated by slow N-inversion could not be excluded. Recently, however, it has been reported[10] that a particularly crowded amine ($Bu_2^tCHNMe_2$) displays, at room temperature, a dynamic process with a quite high barrier ($\Delta G^{\ddagger} = 18.5$ kcal mol^{-1}). Although this molecule does not contain a probe sensitive to N-inversion, the observed asymmetry is consistent with a N-inversion process with a barrier lower than rotation; the observed barrier has thus been assigned to C-N rotation. It has in fact been recognized[11–18] that when the bulkiness of the N bonded groups increases, the barrier to inversion should decrease (steric acceleration) since the energy of the pyramidal ground state becomes closer to that of the planar transition state. Opposite to this trend is that of C-N rotation, since the bulkier the substituent, the more difficult should be the passage through the transition state (steric deceleration): the amine of Ref. 10 is a good example of the dramatic increase in the rotational barrier in an extremely crowded situation. This model only applies to an omogeneous series of compounds, as trialkylamines. In fact dialkylamines, although less crowded, do not exhibit, at NMR, effects due to slow N-inversion, having a lower $\Delta G^{\ddagger}_{inv}$ than trialkylamines.[19] For instance, in the case of Pr^i_2NH, not even at −160° could we detect diastereotopic Me's due to a prochiral N. In the class of trialkylamines the case[10] of $Bu^t_2CHNMe_2$ strongly supports the model of steric deceleration for rotation and acceleration for N-inversion: we also think that this finding should not be considered an isolated example due to an abnormally crowded situation and it should be possible to find other

amines having barrier to rotation higher than inversion. To test this prediction one has to select an amine with a symmetry which displays different spectral features in the case of inversion with respect to rotation: in this way the conflicting interpretations between the two possibilities[8,9,20] will be avoided. The choice of suitable derivatives was restricted in the past by the complexity of the low temperature proton NMR spectra of many aliphatic amines. In some cases the problem was circumvented in an elegant way by selective deuteration accompanied by deuteron decoupling.[3,5] An alternative approach is the use of ^{13}C NMR that gives spectra simple enough to be unambiguously interpreted. This technique has the advantage of having shifts with larger internal differences that permit observation of the dynamic phenomenon at temperatures higher than ^{1}H NMR. This feature makes the C-13 line shape less affected by the dependence of the line width on the solvent viscosity. As a consequence the determinations of $\Delta G^{\neq}$ and other kinetic parameters at very low temperature become more reliable. The ^{13}C NMR has however a limitation in that it requires the presence of isopropyls or other CHR_2 moieties as probes for monitoring slow N-inversion; ^{1}H NMR, on the other hand, is also sensitive to the presence of pairs of geminal protons (CH_2R). We applied ^{13}C NMR to some isopropyl amines to show that, depending on the steric hindrance, the barrier to inversion can be either higher or lower than C-N rotation.

RESULTS AND DISCUSSION

For this purpose we first reexamined with ^{13}C NMR three isopropyl amines (**1–3**) where the N-inversion barriers could be measured by monitoring the diastereotopic Me's of the i-Pr groups.



R	R'	
Me	Et	**1**
Me	Pr^{i}	**2**
Et	Pr^{i}	**3**
Me	Bu^{t}	**4**
$CHEt_2$	Pr^{i}	**5**

It was confirmed that the effect of C-N rotation is detectable[6] only at much lower temperature† thus proving that in **1–3** N-inversion is slower than Pr^{i}-N rotation. Furthermore it was proved (Table 1) that the more hindered the amine, the lower the N-inversion barrier (steric acceleration). When an even bulkier amine was examined (Pr^{i}NMeBu^{t}, **4**) diastereotopic Me's were observed *both* in the i-Pr and t-Bu groups in the same temperature range (Fig. 1). This means that, in addition to N-inversion that makes the i-Pr methyls non equivalent, there is also restricted the Bu^{t}-N rotation that makes the three t-Bu methyls non equivalent‡. Although these effects were not detected[3] by ^{1}H NMR on **4** itself, our finding agrees with the observations reported for very similar t-butylamines.[3] The barrier we measured monitoring the Me signals of t-Bu (Table 1) is in fact equal to that we obtained monitoring the signals of the i-Pr methyls (6.5 kcal mol^{-1}). Although, as explained in the introduction, we could not obtain the barrier to isolated CN rotation, its value is certainly larger than that of N-inversion. The increased bulkiness of **4** thus increases the barrier to CN rotation with respect to **1–3** (steric deceleration) and, at the same time, reduces that to N-inversion (steric acceleration). However, when we investigated the low temperature C-13 spectrum of a bulkier derivative (3-pentyl, diisopropylamine **5**) a completely different behaviour was observed. The Me, and the CH as well, of the i-Pr groups become diastereotopic

†It was detectable in **1** as a selective broadening, below −130°, of the doublets of the isopropyl Me's; we were however unable to reach the temperature that splits further the signals[7] and we thus failed to measure the barrier for Pr^{i}-N rotation.

‡Of the three methyl signals expected for a "locked" ter-butyl only two were detected with a 2:1 intensity ratio (Fig. 1). Two methyls have accidentally coincident shifts.

Table 1. Free energy of activation ($\Delta G^{\neq}$, kcal mol^{-1}) for the dynamic processes occurring in amines **1–5**

Compound		$\Delta G^{\neq}$ (this work)	Literature
Pr^{i}-NMeEt	1	7.7$_5$ ± .1 (inv.) < 6.0 (rot.)	7.5 ± .2 (inv.)[4,6] 5.6 ± .2 (rot.)[6]
Pr^{i}-NMePr^{i}	2	6.9$_5$ ± .1 (inv.)	6.0 ± .2 (inv.)[4]
Pr^{i}-NEtPr^{i}	3	6.8 ± .1 (inv.)	6.5 ± .2 (inv.)
Pr^{i}-NMeBu^{t}	4	6.5 ± .1 (inv.) > 6.5 ± .1 (rot.)	5.5 ± .2[3b]
Pr^{i}-NPr^{i}CHEt$_2$	5	< 6.0 (inv.) 9.2 ± .1 (rot.)[a]	- -

a. $\Delta H^{\neq}$ = 9.1$_5$ ± .4 kcal mol^{-1}; $\Delta S^{\neq}$ = −0.4 ± 3 cal mol^{-1} degree^{-1}

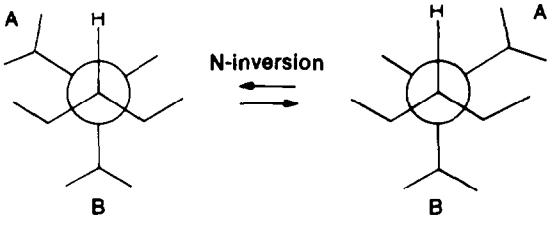
at −115°, whereas all the carbons of the 3-pentyl group remain homotopic (Fig. 1 and Table 2). This feature cannot be explained with a slow N-inversion since a prochiral N cannot make the CH of two isopropyls diastereotopic. On the contrary restricted C-N rotation of the 3-pentyl group can differentiate all the isopropylic carbons.

To do so, however, the amine **5** must assume a conformation having the CH bond of 3-pentyl eclipsed (or nearly so) with respect to the N-C bond of one of the two isopropyls (**5a**). A staggered conformation (**5b**) would not produce diastereotopic isopropyls.

(**5a**) (**5b**)

Scheme 1. Newman projection along the 3-pentyl C-N bond of Pr^i_2 $NCHEt_2$ (**5**). Owing to the fast N-inversion the two isopropyls are drawn as lying in the dynamic averaged plane of the sp^3 nitrogen.

The picture **5a** in Scheme 1 might be interpreted as the dynamic average between the two following situations, where the fast N-inversion occurs keeping the two isopropyl diastereotopic A and B:



It is also worth outlining that the chemical shift difference (Table 2) between the i-Pr methyls in **5** is much smaller ($\Delta\nu = 6$ Hz) than that produced in **1–4** by N-inversion ($\Delta\nu$ ranging within 85 Hz of **3** and 116 Hz of **2**): a further proof of the different origin of the phenomenon. The free energy of activation obtained monitoring the CH signals is the same as that obtained monitoring the Me signals ($\Delta G^{\neq} = 9.2$ kcal mol^{-1}), as expected if both groups experience the same dynamic process. A complete line shape analysis yielded a negligible entropy ($\Delta S^{\neq} = -0.4 \pm 3$ cal mol^{-1} degree^{-1}) and a $\Delta H^{\neq} = 9.1_5 \pm 0.4$ kcal mol^{-1}. When the temperature is furtherly lowered to −155° the appearence of the spectrum does not change. Since the CH are still different, the occurence of slow N-inversion at lower temperature would have split further each of the i-Pr methyl signals,[21] with a $\Delta\nu$ similar to that of **1–4**. Four diastereotopic Me's would in fact be expected in **5** if both C–N pentyl rotation and N-inversion had been slow in the NMR time scale. For, if slow C-N rotation keep the CH and the pair of equivalent Me's in a i-Pr different from those of the other i-Pr, slow N-inversion would make, in addition, the Me's *within* each i-Pr diastereotropic. The occurence of only the first kind of splitting in **5** thus proves that we have found a clear cut example of a trialkylamine where C-N rotation has an higher barrier than N-inversion.

EXPERIMENTAL

Derivatives **2** and **5** were commercially available. Amine **1** was obtained from isopropylethylamine by reaction[22] with H_2CO and HCOOH. Isopropylethylamine was prepared from isopropylamine by reaction with Ac_2O followed by reduction with LAH.[23] Derivative **3** was the product of alkylation of diisopropylamine with MeI and **4** was prepared from t-butylisopropylamine with the method of Ref. 22.

NMR spectra

The samples were prepared condensing, with liquid N_2, the gaseous solvent (CHF_2Cl) into the 10 mm NMR tubes containing the product. The samples were then sealed in vacuum and introduced in the precooled probe of the spectrometer. The ^{13}C spectra were run at 25.16 MHz in the FT mode with a Varian XL-100 instrument using TMS-d_{12} as a deuterium source for internal lock. For temps lower than −150° an external F-19 lock

Table 2. ^{13}C Chemical shifts (ppm with respect to TMS) of amines **1–5** in CHF_2Cl at 25.16 MHz. The values are given at temperatures above the coalescence (averaged signals) and below the coalescence point

Compound	Temperature	NCH(Pr^i)	CH_2	NCH_3	CH_3(Pr^i)	CH_3 (other)	C (other)
1	−80°	54.2	48.2	35.8	17.8	13.65	-
	−120°	54.3	48.2	35.8	19.4; 15.6_5	13.7_5	-
2	−80°	50.7	-	31.6	19.5	-	-
	−140°	50.5	-	32.0	22.1; 17.5	-	-
3	−60°	50.2	41.0	-	20.5	18.1	-
	−145°	50.8	41.6	-	22.0; 18.6	19.2	-
4	−110°	47.2	-	28.4	21.5	27.5	55.9
	−150°	47.0	-	28.5	23.5; 19.4	30.5; 21.3	55.8
5	−80°	44.8	26.7	-	23.1	12.9	58.6
	−120°	45.3; 44.3	26.5_5	-	23.3; 23.1	12.9	58.4_5

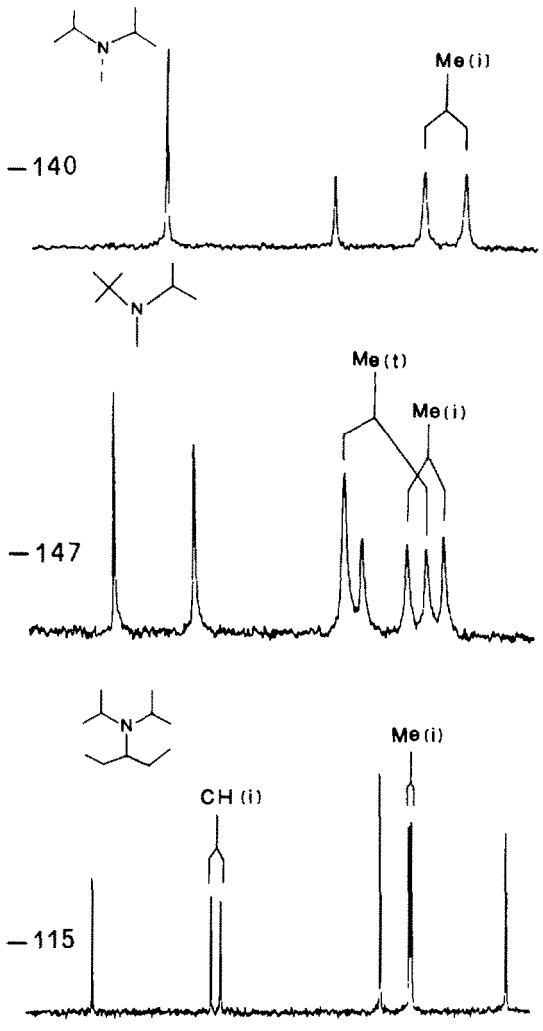


Fig. 1. ^{13}C NMR spectra of Pr^i_2NMe (2) at −140° showing the effect of N-inversion, of Bu^tNMePr^i (4) at −147° showing the effect of both N inversion and C–N rotation and of $Pr^i_2NCHEt_2$ (5) at −115° showing the effect of C–N rotation. The signals that are singlets at high temperature and split at low temperature are indicated. The symbols (i) and (t) refer to the carbons belonging, respectively, to isopropyl and terbutyl groups.

device was employed. The temp was monitored with a thermocouple inserted in a dummy tube before or after each series of few hundreths accumulation. Whereas the $\Delta G^{\neq}$ obtained for 1 and 3 were close to those measured[3] *via* H-1 NMR, those of 2 and 4 were significantly different (Table 1). We thus repeated these measurements many times and simulated the line shape at different temps. It is possible that the difference is, in part, due to the different solvents employed. Since however we used the same solvent throughout, our values should be internally consistent. Simulation programs were run on a Apple II computer provided with a plotter and were checked with the DNMR program[24] run on the computing Center of the University of Bologna.

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