The Barrier to Pyramidal Inversion of Nitrogen in Dibenzylmethylamine[1]

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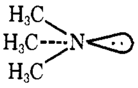
Received July 18, 1970

Abstract: The first direct experimental measurement of the barrier to nitrogen inversion in a simple acyclic alkylamine, dibenzylmethylamine, has been made using the dynamic nmr method. The magnitude of the barrier ($\Delta F^{\ddagger} = 6.7 \pm 0.2$ kcal/mol in vinyl chloride solution at $-135°$) agrees well with that calculated theoretically.

One of the long-standing problems of stereochemistry is that of determining barriers to pyramidal inversion of nitrogen in amines. While failures to separate enantiomorphs had indicated at an early stage that the barriers must be low, no quantitative estimates were reported prior to the discovery that the barriers in aziridines are large enough for study by the dynamic nmr method,[3] lying in the range 15–20 kcal/mol.[4,5]

Attempts to determine the barriers in acyclic amines by analogous procedures have so far failed, indicating that they must be very much less than those in aziridines; Kincaid and Henriques[6] had predicted this to be the case on the basis of calculations of barrier heights, using experimental vibration frequencies and assumed potential functions for inversion. More recent calculations of this kind have led[7] to estimates of 7.5 and 34 kcal/mol, respectively, for the barriers in trimethylamine (**1**) and aziridine (**2**).



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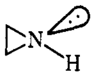

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The only experimental estimates of barrier heights so far reported are those of Saunders and Yamada,[8] who used an elegant indirect method to determine the activation energies for inversion in several tertiary amines. The values found by them (10–11 kcal/mol) are considerably greater than the calculated[7] value, particularly since the results for aziridine imply that the latter is probably too high; however, Saunders and Yamada carried out their measurements in aqueous solution where the barrier to inversion must be augmented to an unknown extent by hydrogen bonding of water to the lone pair electrons of nitrogen; unfortunately, this technique cannot be extended to aprotic solvents.

Recently it has been shown that the barrier to inversion in **2** increases dramatically[9] if the imino hydrogen is replaced by an electronegative substituent (Cl, NH_2, F, or CF_3); similar substituents on nitrogen in acyclic amines also increase the barriers sufficiently for them to be determined by the dynamic nmr method.[10] The magnitude of this effect cannot, however, be estimated quantitatively since the barriers to inversion in the parent amines are still unknown.

Recent work in these laboratories has led to the development of a semiempirical SCF–MO treatment of barrier heights[11] which gave results in good agreement with experiment for aziridines and hydrazines. This made the need for reliable measurements of barrier height for simple amines more urgent, to check the values predicted by our theoretical approach.

In a brief preliminary report[12] we described the first direct measurement of such a barrier by the dynamic nmr method for a simple tertiary amine, *i.e.*, dibenzylmethylamine; here we report our results in detail.[13]

Experimental Section

Dibenzylmethylamine (obtained from Matheson, Coleman, and Bell) was fractionally distilled *in vacuo* and stored over calcium hydride.

Nmr Spectra. The spectra were determined on a Varian Associates HA-100 spectrometer equipped with a modified variable-temperature accessory (-150 to 200°). The sample was ~10% w/v in vinyl chloride and was degassed and sealed *in vacuo* with a

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(1) This work was supported by the Air Force Office of Scientific Research through Grant No. AF-AFOSR-1050-67, and by the Robert A. Welch Foundation.

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(3) For a recent review of this method, see G. Binsch, *Top. Stereochem.*, **3**, 97 (1968).

(4) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 5126 (1956); **80**, 5203 (1958); H. S. Gutowsky, *Ann. N. Y. Acad. Sci.*, **70**, 786 (1958); A. Loewenstein, J. F. Neumer, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3599 (1960); T. J. Bardos, C. Szantay, and C. K. Navada, *ibid.*, **87**, 5796 (1965); M. Jautelat and J. D. Roberts, *ibid.*, **91**, 642 (1969).

(5) Some of the activation energies quoted in ref 4 lie outside this range, probably because of errors in the method of deriving exchange rates from the spectra (see ref 3).

(6) J. F. Kincaid and F. C. Henriques, Jr., *J. Amer. Chem. Soc.*, **62**, 1474 (1940).

(7) R. E. Weston, Jr., *ibid.*, **76**, 2645 (1954); G. W. Koeppl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *ibid.*, **89**, 3396 (1967).

(8) M. Saunders, *Proc. Int. Conf., 2nd Stockholm, 1966*, 85 (1967); M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, **85**, 1882 (1963).

(9) S. J. Brois, *ibid.*, **90**, 506 (1968); S. J. Brois, *Tetrahedron Lett.*, 5997 (1968); D. Felix and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **7**, 224 (1968); R. S. Atkinson, *Chem. Commun.*, 676 (1968); R. G. Kostyanovsky, I. I. Tchervin, A. A. Fomichov, and Z. E. Samojlova, *Tetrahedron Lett.*, 4021 (1969).

(10) F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967); M. J. S. Dewar and W. B. Jennings, *J. Amer. Chem. Soc.*, **91**, 3655 (1969); J. E. Anderson, D. L. Griffith, and J. D. Roberts, *ibid.*, **91**, 6371 (1969); M. G. Barlow and K. W. Cheung, *Chem. Commun.*, 870 (1969); S. K. Brauman and M. E. Hill, *J. Chem. Soc. B*, 1091 (1969).

(11) M. J. S. Dewar and M. Shanshal, *J. Amer. Chem. Soc.*, **91**, 3654 (1969).

(12) M. J. S. Dewar and W. B. Jennings, *Tetrahedron Lett.*, 339 (1970).

(13) C. H. Bushweller and J. W. O'Neill [*J. Amer. Chem. Soc.*, **92**, 2159 (1970)] have recently also reported measurement of the barrier in dibenzylmethylamine. The barrier quoted by these authors ($\Delta F^{\ddagger} =$ 6.0 kcal/mol at $-146°$), which was obtained at 60 MHz using an approximate analysis of the spectrum at coalescence, is somewhat lower than that obtained in the present study at $-135°$.

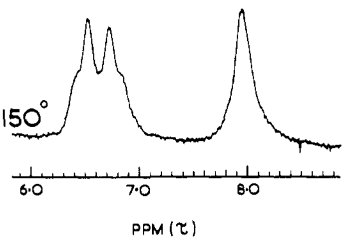
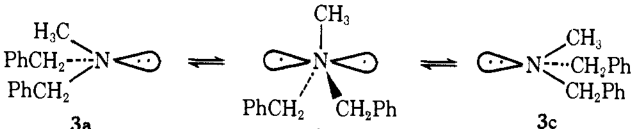


Figure 1. 100-MHz proton nmr spectrum of dibenzylmethylamine in vinyl chloride solution at −150°.

few per cent tetramethylsilane as internal lock. Probe temperatures were measured by inserting a copper–constantan thermocouple into a sample tube containing 0.5 ml of an isohexane mixture.[14] Theoretical spectra for the collapse of an AB quartet were calculated on the University of Texas CDC 6600 digital computer using a program (CURVE 1) devised by Jonas, Allerhand, and Gutowsky.[15] The program iterates the exchange rate to afford the best least-squares fit of the theoretical spectra to the inputed experimental spectrum.

Results and Discussion

The NCH_3 and NCH_2 signals in the nmr spectrum of a solution of dibenzylmethylamine in vinyl chloride broadened considerably on cooling below −100°. Below −120° the methylene signal collapsed rapidly and at −150° split into a broad AB quartet with $\Delta\nu_{AB} = 30$ Hz and $J_{AB} \cong 11$ Hz (Figure 1) indicating that the geminal CH_2 protons had become anisochronous. At this temperature the NCH_3 signal, though broad (line width at half-height, $W \cong 18$ Hz), retained its Lorentzian line shape. These observations are best interpreted in terms of a slowly inverting nitrogen atom on the nmr time scale at −150°.[16]



3a 3b 3c

Rapid inversion of the nitrogen pyramid in dibenzylmethylamine (*i.e.*, **3a** ⇌ **3c**) renders the diastereotopic[17] methylene protons within each prochiral[18] benzyl group enantiotopic on the nmr time scale and therefore chemical shift equivalent (in achiral solvents). The exchange rate in the region of coalescence was determined by the complete line shape method with computer matching of the calculated and experimental spectra. The values of $\Delta\nu_{AB}$ and J_{AB} estimated at −150° were adjusted slightly to optimize the fit between the calculated and experimental spectra. Considerable difficulty was experienced in the choice of the natural line width (W) used to calculate an "effective" spin-spin relaxation time (T_2) owing to the considerable line broadening at low temperature. The line width employed in the calculation was varied between the minimum value (estimated in the region of fast exchange) and the maximum value estimated from the spectrum at −150°. The final parameters, $\Delta\nu_{AB} = 30.5$ Hz, $J_{AB} = 11.9$ Hz, and $W = 6$ Hz, afforded a near perfect fit to the spectra (Figure 2) and gave the rate constant for nitrogen inversion as 65 sec^{-1} at −135°. Application of the Eyring equation, assuming a transmission coefficient of unity,[19] gave $\Delta F^{\ddagger} = 6.7 \pm 0.2$ kcal/mol at −135°.[20] The entropy of activation for nitrogen inversion should be very small and therefore the $\Delta F^{\ddagger}$ value should approximate closely to the enthalpy of activation.[21] The large and uncertain line widths in the low-temperature spectra of dibenzylmethylamine made it impossible to determine the exchange rate over a sufficiently wide temperature range to justify confidence in the derived entropy of activation. The problem is particularly acute at very low temperatures owing to the enhanced temperature sensitivity of the exchange rate and to the problem of accurate temperature measurement and control.

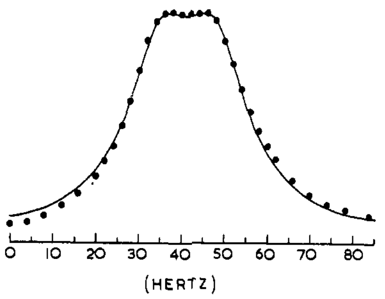
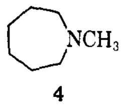


Figure 2. Nmr spectrum of the NCH_2 signal of dibenzylmethylamine at coalescence (−135°). The curve is the "best fit" computed spectrum (k = 65 sec^{-1}) to the digitized experimental spectrum (●).

The measured barrier is in close agreement with the values calculated by the valency force model[7] (7.5 kcal/mol) or the MINDO SCF–MO method[11] (6.5 kcal/mol), and also with that (6.0 kcal/mol) reported in a preliminary communication by Bushweller and O'Neill.[13] The difference between these values and that reported by Saunders and Yamada[8] indicates that the barrier to inversion of an amine in aqueous solution is increased by *ca.* 4 kcal/mol through hydrogen bonding to the solvent.

Two groups of workers have very recently measured the barriers to nitrogen inversion in some cyclic amines containing five, six, and seven-membered rings.[22] The



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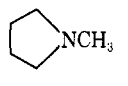

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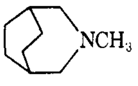

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seven-membered ring compound **4** has a barrier of 6.4 ± 0.5 kcal/mol (in $CHClF_2$ solution)[22b] which is similar to the inversion barrier of acyclic nitrogen (see

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(14) The thermocouple was calibrated using the boiling point of water and the sublimation temperature of carbon dioxide as reference points; see R. B. Scott in "Temperature, Its Measurement and Control in Science and Industry," Reinhold, New York, N. Y., 1941, p 206.

(15) J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965).

(16) Rotation around the N–CH_2 bonds is considered to be rapid even at −150°. The C–N torsional barrier has been measured for some amines and is in the range 2–4.5 kcal/mol, *i.e.*, considerably lower than the barrier obtained in this study; see J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1968).

(17) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

(18) K. R. Hanson, *J. Amer. Chem. Soc.*, **88**, 2731 (1966).

(19) The tunnelling frequency should be low for a tertiary amine as there are no protons attached to the nitrogen atom.

(20) The quoted error in $\Delta F^{\ddagger}$ allows for an error in temperature measurement of up to ±4°.

(21) This has been shown to be the case for nitrogen inversion in oxaziridines (see F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1086 (1969)) and for inversion in dibenzylhydrazine (M. J. S. Dewar and W. B. Jennings, unpublished results).

(22) (a) J. B. Lambert and W. J. Oliver, Jr., *J. Amer. Chem. Soc.*, **91**, 7774 (1969); (b) J. M. Lehn and J. Wagner, *Chem. Commun.*, 414 (1970).

above). However, the barriers in *N*-methylpyrrolidine (**5**) and in the bicyclic compound **6** are significantly higher (8-9 kcal/mol),[22] probably because of the ring strain associated with a cyclic sp^2 hybridized nitrogen atom in the transition state for nitrogen inversion.

An interesting feature of the low-temperature nmr spectra of dibenzylmethylamine (Figure 1) is the large and unequal line broadening of the NCH_3 and NCH_2 signals. Thus at $-135°$ the NCH_3 signal has a line width of 11 Hz whereas the NCH_2 signal has a natural width of ~6 Hz (see above). The solvent signal remained comparatively sharp down to $-150°$. Anderson, Griffith, and Roberts[23] observed similar effects in the spectra of benzyltrimethylhydrazine and attributed the excess broadening to incomplete quadrupole-induced relaxation of the nitrogen atoms at low temperature. A similar quadrupole effect has recently been suggested as an explanation of the line broadening of the NCH_3 signal in dibenzylmethylamine at low temperatures.[13] These proposals are surprising since quadrupole-induced relaxation of the ^{14}N nucleus becomes more facile at low temperatures as a result of the longer correlation time. This results in broadening of the ^{14}N nmr signals but *narrowing* of adjacent proton signals due to the effective removal of any coupling between the nitrogen and hydrogen nuclei. The theory has been discussed by Pople,[24] and has been verified experimentally.[25] We therefore prefer to attribute the excess line broadening of the NCH_3 and NCH_2 signals of dibenzylmethylamine at low temperatures to effects resulting from the slowing down of molecular motions such as tumbling and rotation around the C–C and C–N bonds.

Acknowledgment. The Varian HA-100 instrument was purchased with funds provided by the National Science Foundation (Grant No. GP-6940). We thank Professor H. S. Gutowsky for a listing of the computer program CURVE 1, and Dr. B. Shoulders for helpful discussions.

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(23) J. E. Anderson, D. L. Griffith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 6371 (1969).

(24) J. A. Pople, *Mol. Phys.*, **1**, 168 (1958).

(25) R. M. Moriarty, J. P. Kim, S. J. Druck, and E. Lustig, *Tetrahedron*, **25**, 1261 (1969).

Stereochemistry of Tropane Quaternization

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Received June 18, 1970

Abstract: Chemical correlation of major products of *N*-alkoxycarbonylmethylation of tropane, tropine, pseudotropine, and tropinone with that of $3\alpha,6\beta$-tropanediol **7f** of unequivocal geometry has proven the preferred equatorial steric course for all these quaternizations. Pseudotropine-*N*-acetic acid by X-ray investigation also proved to be the N_b isomer, **12d**. Furthermore, conversion of *N*-ethoxycarbonylmethyltropinium bromide (**3b**) into N_b-ethylmethylnortropinium bromide having structure **2**, known from X-ray studies, clearly indicated consistence of preferred equatorial course in ethylation, hydroxyethylation, chloroethylation, and alkoxycarbonylmethylation throughout the tropane series. Critical survey of correlation of N–Me nmr signals with stereochemistry is presented, also supported by correlation between the main product of deuteriomethylation of tropine and of $3\alpha,6\beta$-tropanediol with that of methoxycarbonylmethylation of the same two amines. Amine oxide formation from scopolamine was shown by X-ray to give preferentially the N_b oxide.

This and a forthcoming paper[4] by Bottini, *et al.*, present conclusive experimental evidence for preferred equatorial quaternization with different reagents throughout the tropane series.

It has long been known[5] that quaternization of tropine with ethyl iodoacetate resulted in isolation of one product. The geometry of the N stereoisomer that had formed stereospecifically,[6a] as we now know rather stereoselectively, from $3\alpha,6\beta$-tropanediol with the same reagent, proved by its conversion into lactone salt **7f** to be the N_b-carboxymethyl derivative.

Reversal of sequence of quaternization with noramines, which means methylation in the last step, rendered the N_a-carboxymethyl N stereoisomers unable to undergo cyclization,[6a,b] indicating preferential equatorial course of quaternization. Selectivity of reaction of ethyl iodoacetate was confirmed with tropine,

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(3) (a) Agricultural Research Service, USDA; (b) deceased Dec 1970.

(4) U. O. de la Camp, A. T. Bottini, C. C. Thut, J. Gal, and A. G. Bellettini, submitted for publication; A. T. Bottini in "Selective Organic Transformations," Vol. I, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 89–143. We thank Professor Bottini for informing us of their results prior to publication.

(5) M. Scholtz and K. Bode, *Arch. Pharm.*, **242**, 568 (1904).

(6) (a) G. Fodor, J. Toth, and I. Vincze, *Helv. Chim. Acta*, **37**, 907 (1954); (b) G. Fodor, J. Toth, and I. Vincze, *J. Chem. Soc.*, 3504 (1955), also introducing notation N_a for axial and N_b for equatorial groups; (c) G. Fodor, K. Koczka, and J. Lestyan, *Magy. Kem. Foly.*, **59**, 242 (1953); *J. Chem. Soc.*, 1411 (1956); (d) G. Fodor, Ö. Kovacs, and M. Halmos, *ibid.*, 873 (1956); (e) for α,β notations suggested by R. S. Cahn see G. Fodor and K. Nador, *ibid.*, 721 (1953).

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