Conformational Studies by Dynamic Nuclear Magnetic Resonance. Part 8.[1] Effect of Aromatic Substituents on the Stereodynamics of Hindered Hydrazones

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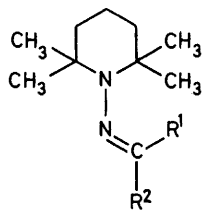
^{1}H and ^{13}C n.m.r. measurements show that hydrazones containing the 2,2,6,6-tetramethylpiperidin-1-yl (TMP) ring (*i.e.* TMP–N=CR^{1}R^2) have the –N=C< plane 90° twisted with respect to the dynamically averaged plane of the TMP ring itself. Restricted rotation occurs around the N–N bond, allowing the determination of the torsional barriers by means of line shape analysis of the variable temperature n.m.r. spectra. Steric and conjugative effects upon the barrier when R^2 is an aromatic substituent (phenyl, naphthyl, pyridyl, thienyl, furyl) are discussed.

In a previous Part [2] it was shown that aliphatic hydrazones containing the 2,2,6,6-tetramethylpiperidin-1-yl (TMP) ring show non-equivalence of the methyl groups in positions 2 and 6, owing to restricted rotation about the N–N bond. It was also inferred that this peculiar behaviour (hydrazones without the TMP ring do not exhibit such an effect [2]) depends on the unusual perpendicular conformation assumed by these molecules: the dynamically averaged plane of TMP is 90° twisted with respect to the plane containing the –N=C< group. In the aromatic series we performed further experiments which unambiguously show that such a conformation is adopted not only in the solid state (as proved by a *X*-ray determination [2,3]) but also in solution. The effects of the aromatic rings upon the rotational barrier are also discussed.

RESULTS AND DISCUSSION

The hydrazones (1)—(12) were examined. In all the cases only one of the two possible isomers (R^2 *cis* or R^2 *trans*) has been obtained. Since the *X*-ray investigation [2,3] on (1) did show, as one would have



(1)—(9) R^1 = Me; R^2

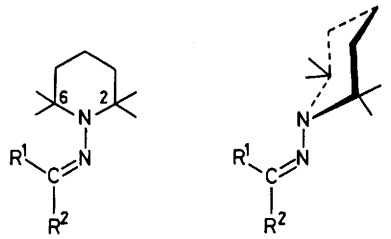
(1) Ph
(2) 4-pyridyl
(3) 3-pyridyl
(4) 2-pyridyl
(5) 2-thienyl
(6) 2-furyl

(10)—(12) R^1 = H; R^2

(7) β-naphthyl
(8) –CH:CH[CMe$_2$]$_4$
(9) –CH[CMe$_2$]$_5$
(10) Ph
(11) β-naphthyl
(12) α-naphthyl

anticipated from steric considerations, that the *trans*-configuration is adopted, the latter was also assumed for all the derivatives (2)—(12). The R^2 *trans*-configuration was found to be the more stable even when both isomers could be obtained.[4]

As previously mentioned, two possible conformations can in principle be expected for each configuration; the plane of TMP ring (dynamically created by fast ring reversal and nitrogen inversion †) can either be coplanar, or 90° twisted with respect to the plane identified by the –N=C< group. When the N–N rotation is slow on the



n.m.r. time scale, the pair of methyl groups bonded to C-2 (*i.e. anti* to R^1) should be different from the pair bonded to C-6 (*i.e. syn* to R^1), if the molecular conformation is planar. On the other hand, if the perpendicular conformation is adopted, the two equatorial methyl groups (*i.e.* one of the groups at C-2 and one at C-6) will be different from the two axial groups, owing to the bent structure of the CNN function.‡ Should the first case occur, the line widths of the signals of the two non-equivalent pairs of methyl groups would be identical, since each pair contains an axial *and* an equatorial methyl. On the contrary, in the second case the line widths could be different, since the long range couplings

† Recently Anet *et al.*[5] showed that *N*-2,2,6-tetramethylpiperidine has a nitrogen inversion barrier of 9 kcal mol^{-1}. Owing to the impossibility of our derivatives adopting conformations that, as in ref. 5, can release the strain of two axial methyl groups, this barrier is expected to be even lower. The same argument applies to the ring reversal barrier.[2,6]

‡ It is known that inversion of the *sp*^{2} nitrogen in CNN, which would destroy the asymmetry of the bent structure, is very slow [2,7] even at high temperatures (≥200°).

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[7] C. I. Stassinopoulu, C. Zioudrou, and G. J. Karabatsos, *Tetrahedron*, 1976, **32**, 1147; N. P. Marullo and E. H. Wagener, *Tetrahedron Letters*, 1969, 2555; Y. Shvo and A. Nahlieli, *ibid.*, 1970, 4273.

of the equatorial methyl with the methylene groups are not the same, in principle, as those of the axial groups. In Figure 1 (upper) the 100 MHz ^{1}H n.m.r. spectrum of

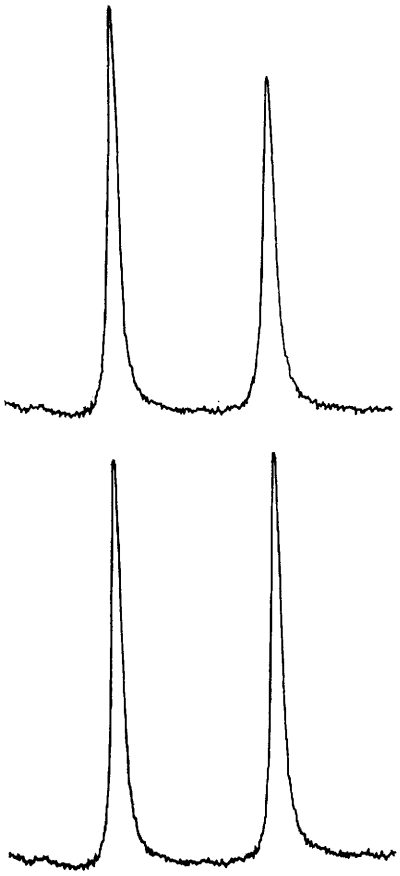
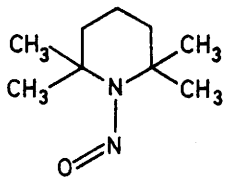


FIGURE 1 100 MHz N.m.r. spectrum of the four piperidyl methyl of hydrazone (4) at −38 °C in CS_2, before (upper) and during (lower) decoupling at the frequency of the methylene signals

(3) is reported at −38 °C in CS_2; only the signals corresponding to the piperidyl methyl groups are displayed. Although the integrated intensities are exactly equal (each signal corresponds to two methyl groups), their different heights clearly show that the upfield peak has a larger line width. Furthermore, since the axial–axial coupling is likely to be the larger, it may be inferred that the high field signal is that of the axial methyl groups. Irradiation of all the methylene signals makes the two methyl lines equally sharp (Figure 1, lower), thus proving that the broadening is due to the CH_2–C–CH_3 long range couplings. The perpendicular conformation is therefore indicated.

A second, independent assessment, comes from ^{13}C spectroscopy; in a planar conformation we would expect the two pairs of methyl groups, as well as C-2 and -6 and C-3 and -5, to be non-equivalent. This is indeed the case for the *N*-nitroso-derivative [2] (13), whose ^{13}C spectrum is shown in Figure 2 (upper). On the contrary, in the ^{13}C spectrum of (3) (Figure 2, lower) only the signals of the two pairs of methyl groups are non-equivalent, whereas a single line is observed for both C-2 and -6 and C-3 and -5. Obviously this can only happen when the plane of −N=C< is perpendicular to the piperidyl ring. No doubt is thus left that the



(13)

perpendicular conformation detected in the solid [2] is also present in solution.

The ^{1}H n.m.r. spectra of compounds (1)—(9) and (12) display non-equivalence of the piperidyl methyls at

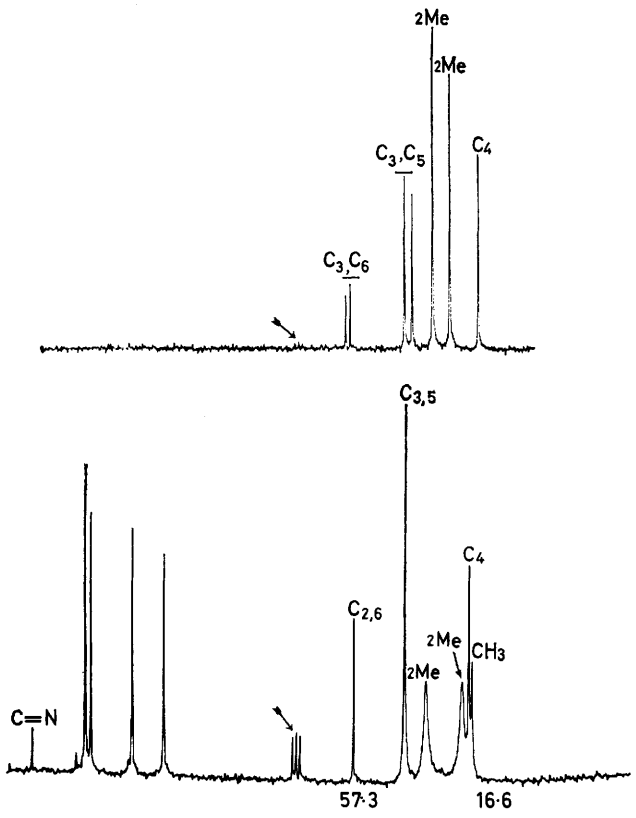


FIGURE 2 25.15 MHz Fourier transform ^{13}C n.m.r. spectrum of (13) (upper) and (3) (lower) at room temperature in $CDCl_3$; the arrowed triplets are due to the solvent. The piperidyl methyl signals of (13) are sharp owing to the larger rotational barrier, whereas those of (3) are already broadened by the exchange. The different signals for C-2 and -6 as well as for C-3 and -5 are clearly visible in (13) (planar) whilst they are equivalent in (3) (perpendicular)

appropriate temperatures: on raising the temperature the signals coalesce into a single broad line which further sharpens at higher temperatures, the trend being reversible.

Total line shape (t.l.s.) analysis of the spectral patterns affords the thermodynamic parameters (Tables 1—3) involved in N–N rotation: a typical sequence of computed and experimental spectra is reported in Figure 3.

As observed in many other cases,[2,8,9] the $\Delta S^{\ddagger}$ values determined for derivatives (2)—(4) (Table 1) are negligible within experimental error. Therefore $\Delta H^{\ddagger}$ is equal to $\Delta G^{\ddagger}$ and, being more accurately determinable,[8,9] the latter is used throughout as the measure of the rotational barrier. Furthermore, it was observed for derivatives (2)—(4) that the $\Delta G^{\ddagger}$ values obtained from the t.l.s. analysis are equal to those computed at the coalescence points by the Gutowsky–Holm approximation.[10] The latter method has thus been used for the remaining compounds, since all the requirements for employing the approximation were fulfilled.

TABLE 1

Thermodynamic parameters for motional averaging about the N–N bond in hydrazones (2)—(4). The data were obtained at 60 MHz in $CDCl_3$; the chemical shift differences ($\Delta\nu$) refer to the pair of equatorial and axial methyls in the TMP ring

Compound	$\Delta G^{\ddagger}$ [a]	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [b]	$E_a^{\ddagger}$ [a]	log A	t_c/°C	$\Delta\nu$/Hz
(2)	$14.1 \pm 0_5$	14.1 ± 0.8	0.1 ± 3	14.6 ± 0.8	13.2 ± 0.7	6.5	26.2
(4)	$13.9 \pm 0_5$	14.1 ± 0.6	0.9 ± 0.2	14.6 ± 0.6	13.4 ± 0.5	0.5	24.0
(3)	$14.9 \pm 0_5$	15.6 ± 0.6	2.5 ± 2.5	16.2 ± 0.6	13.8 ± 0.5	22	25.5

[a] kcal mol^{-1} [b] cal mol^{-1} K^{-1}.

TABLE 2

Free activation energies (kcal mol^{-1}) for motional averaging about the N–N bond of hydrazones (1), (8), and (9). The data were obtained at 60 MHz: the chemical shift differences ($\Delta\nu$) refer to the pair of equatorial and axial methyls in the TMP ring

Compound	$\Delta G^{\ddagger}$	t_c/°C	$\Delta\nu$/Hz	Solvent
(1)	15.6 ± 0.1	36	25.2	$CDCl_3$
(8)	16.5 ± 0.1	53.5	25.2	C_2Cl_4
(9)	17.0 ± 0.1	61	22.8	C_2Cl_4

TABLE 3

Free activation energies (kcal mol^{-1}) for motional averaging about the N–N bond of hydrazones (5)—(7) and (12). Unless otherwise specified the data were obtained at 60 MHz; the chemical shift differences ($\Delta\nu$) refer to the pairs of equatorial and axial methyls in the TMP ring

Compound	$\Delta G^{\ddagger}$	t_c/°C	$\Delta\nu$/Hz	Solvent
(12)	8.5 ± 0.1	−104	15.0	CHF_2Cl
	8.4 ± 0.1	−102.5 [a]	25.5 [a]	CHF_2Cl
(7)	16.0 ± 0.1	+42.5	24.6	$CDCl_3$
(6)	14.3 ± 0.1	+8.5	24.6	$CDCl_3$
(5)	14.4 ± 0.1	+12	23.4	$CDCl_3$

[a] At 100 MHz.

Owing to the perpendicular conformation of these hindered hydrazones, the larger the size of R^1 and R^2, the larger the expected rotational barrier about the N–N bond. This has been verified when both R^1 and R^2 are aliphatic functions,[2] but the same feature is also detectable in the aromatic derivatives. The barrier of (12) is 8.4 kcal mol^{-1} (Table 3) whereas in (11) it is so low that it could not be determined even at the lowest attainable temperature (−140 °C) at 100 MHz (hence $\Delta G^{\ddagger} \leqslant 6.5$ kcal mol^{-1}). Most likely the hindrance of the α-naphthyl group in (12) to the N–N rotation is larger by far than that of β-naphthyl in (11), owing to the proximity of the *peri*-hydrogen atom to the TMP group. On the contrary, the β-naphthyl group has a steric effect only slightly larger than that of phenyl in (10) which, accordingly, does not exhibit restricted rotation, even at −140 °C. This parallel behaviour of (10) and (11) is

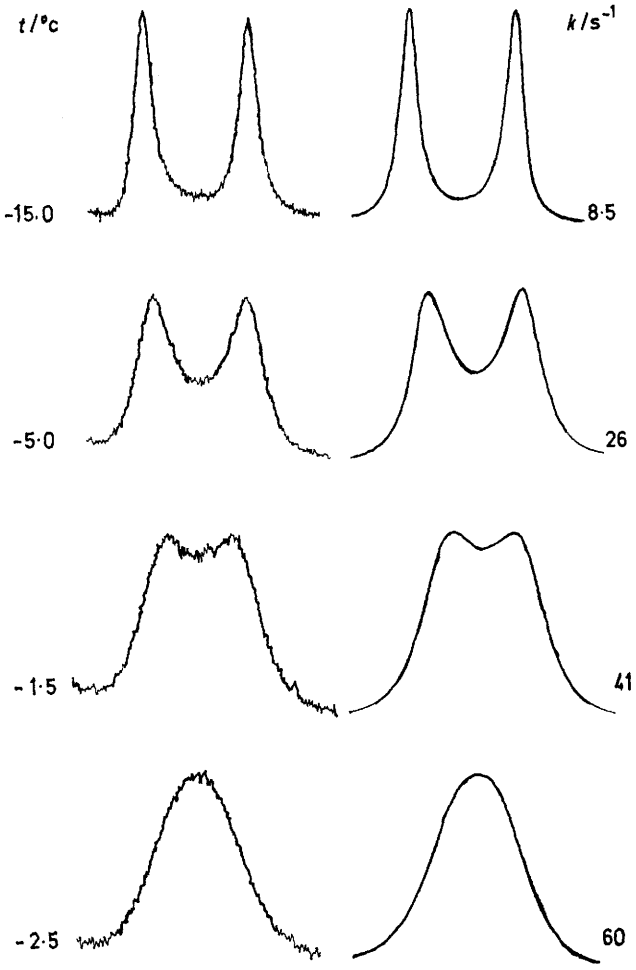


FIGURE 3 Example of motional averaging in hindered aromatic hydrazones. Experimental (left) and computer simulated 60 MHz signals of the four piperidyl methyl groups of hydrazone (2) at four different temperatures

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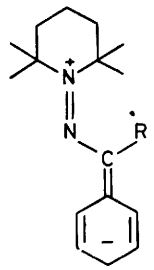
confirmed by observations on the derivatives with $R^1 = CH_3$, where the barrier is high enough to be determined for both $R^2 = C_6H_5$ (1) and $R^2 = \beta$-naphthyl (7); the value of the latter (16.0 kcal mol^{-1}) is only slightly larger than that of the former (15.6 kcal mol^{-1}),* as shown in Tables 3 and 2 respectively.

Although steric hindrance plays the most important role in determining the torsional barriers of these hydrazones, electronic properties too have some effect. Actually, the aromatic derivatives investigated have barriers usually lower than those of the analogous aliphatic compounds.[2] However, since the dimension of aliphatic and aromatic groups are often not comparable, we investigated derivatives (8) and (9) which have steric requirements as similar as possible to those of (1). The rotational barrier of (9) was found to be higher than that of (8), which in turn is higher than that of (1), as shown in Table 2. It seems quite clear that, given similar steric effects, the larger the conjugative ability, the smaller the rotational barrier.

A further indication of this trend is provided by the three hydrazones (2)—(4) containing the pyridine ring. There is no doubt that the steric hindrance is very similar in these three isomers, particularly if one considers the *para*- (2) and the *meta*-derivative (3). Nonetheless compound (3), where *meta*-substitution is expected to reduce the conjugative ability with respect to the *ortho*- (4) and *para*-derivative (2), has a larger torsional barrier (Table 1). It is thus demonstrated that, given similar steric effects, an increase of the conjugative ability of the substituents reduces the N–N rotational barrier, either in aromatic relative to olefinic and aliphatic compounds, or within the aromatic series itself.

To understand this conclusion it has to be considered that these hindered hydrazones have the >C=N= plane 90° twisted with respect to the ' virtual ' plane dynamically created in the TMP ring. Accordingly stabilization of mesomeric structures [*e.g.* (A)] are forbidden in the ground (perpendicular) state. In fact the p_z orbital of

(A)



the iminyl (sp^2) nitrogen lies in a plane perpendicular to the lone pair electron of the amino (sp^3) nitrogen and the conjugation cannot stabilize the ground state.

On the contrary the mesomeric structure (A) is allowed in the transition (planar) state since the p_z orbital is now parallel to the lone pair electrons. Therefore, whereas the ground state of the aromatic compound has a total energy comparable with that of aliphatic hydrazones of similar size, the transition state is stabilized by conjugation, and the N–N rotational barrier thus lowered.

This interpretation, however, can give only a qualitative picture of the observed trend of $\Delta G^{\ddagger}$ values. When different steric *and* conjugative properties have to be taken into account (as in comparing, for instance, the smaller five-membered with the six-membered aromatic rings) a delicate balance of both properties is obviously present. Under these circumstances the lack of quantitative evaluation of steric and conjugative effects prevents an interpretation of the barriers measured, for instance, in the thienyl (5) and furyl (6) derivatives (Table 3).

* Unfortunately the value for $R^2 = \alpha$-naphthyl could not be measured, in that we were not able to synthesize the compound by the same method, an indirect indication of the much larger steric hindrance of α-naphthyl with respect to β-naphthyl derivatives.

EXPERIMENTAL

Preparation of Compounds.—Hydrazone (1) was obtained according to ref. 2. Hydrazones (2)—(12) were prepared by condensation [2,11] of 2,2,6,6-tetramethylpiperidin-1-ylhydrazine [12] (TMP-NH_2) with the appropriate carbonyl compounds. The following preparation of 2,2,6,6-tetramethyl-1-[1-(4-pyridyl)ethylideneamino]piperidine (2) is typical. A mixture consisting of 4-acetylpyridine (0.8 g) and 2,2,6,6-tetramethylpiperidylhydrazine (1 g) was refluxed at 50 °C for 6 h. On cooling to room temperature a precipitate was obtained which was then filtered and crystallized (0.4 g) from aqueous ethanol, m.p. 76—77 °C. The n.m.r. spectrum, elemental analysis, and molecular weight (mass spectrometry) were as expected. Solid hydrazones were: (3), m.p. 84—85 °C; (6), m.p. 66—67 °C; (7), m.p. 116—117 °C; (10), m.p. 34.5—35.5 °C; (11), m.p. 100—101 °C; (12), m.p. 100—101 °C. Liquid hydrazones were: (4), b.p. 137 °C at 5 mmHg; (5), b.p. 119 °C at 4 mmHg; (8), b.p. 122 °C at 6 mmHg; (9), 93 °C at 8 mmHg.

All the compounds had the expected molecular weights (mass spectrometry) and appropriate n.m.r. spectra.

Spectral Measurements.—N.m.r. spectra were recorded at 60 or 100 MHz on JEOL C60 HL and PS 100 spectrometers respectively. After each spectrum was recorded, the temperature was measured by placing a thermocouple in a dummy tube. When CHF_2Cl was used as solvent, ordinary n.m.r. tubes were sealed under vacuum at liquid nitrogen temperature. The dynamic n.m.r. computer program [13] (run on the CDC 7600 machine of the University of Bologna) was used for line shape analysis. ^{13}C Spectra (Figure 2) were run in the Fourier transform mode at 25.15 MHz. Assignments of the signals were made by off resonance experiments and by analogy with related molecules.[14] No attempt was made to distinguish between C-2 and -6 or C-3 and -5 in (13).

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