

## CONFORMATIONAL STUDIES OF SOME 2-PHENYLPROPYL DERIVATIVES BY NMR SPECTROSCOPY AND USE OF LANTHANIDE SHIFT REAGENTS

S. L. SPASSOV and R. STEFANOVA

*Institute of Organic Chemistry, Bulgarian Academy of Sciences, 1113 Sofia (Bulgaria)*

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### ABSTRACT

The conformational distribution of  $\text{CH}_3\text{CH}(\text{Ph})\text{CH}_2\text{X}$  ( $\text{X} = \text{OH}, \text{OCH}_3, \text{NH}_2, \text{Cl}$ ) has been studied by NMR and IR spectroscopy. The results are interpreted in favour of the conformers with methoxy- or chloro-groups *anti* to the phenyl group, but the amino group *anti* to the methyl group. For the alcohol both forms are about equally populated. It is suggested that intra-molecular hydrogen bonding might be affecting the conformational equilibria when  $\text{X} = \text{OH}, \text{NH}_2$ .

### INTRODUCTION

The present work was a continuation of our conformational studies of 1,1,2-trisubstituted ethanes containing methyl and phenyl groups as well as polar substituents [1–3]. Its purpose was also to examine the applicability of the qualitative conformational approach [3] based on lanthanide-induced shifts (LIS) for a larger number of compounds.

The compounds under investigation were of the type  $\text{CH}_3\text{CH}(\text{Ph})\text{CH}_2\text{X}$  and included 2-phenylpropanol (1,  $\text{X} = \text{OH}$ ), 2-phenylpropyl methyl ether (2,  $\text{X} = \text{OCH}_3$ ), 2-phenylpropylamine (3,  $\text{X} = \text{NH}_2$ ), and 2-phenylpropyl chloride (4,  $\text{X} = \text{Cl}$ ). Vicinal coupling constants and LIS were both used as sources of conformational evidence.

The literature data relevant to the conformation of compounds 1–4 are scarce. An IR study of 1 has revealed the existence of an intramolecular  $\text{OH} \cdots \text{Ph}$  bond in dilute carbon tetrachloride solution as well as in the gas phase [4]. Empirical potential energy calculations for 3 have indicated the preference of a folded conformation (the amino group nearest to the ring) in vacuo and in neutral aqueous solution, whereas for the cation in aqueous solution an extended form (the amino group far from the ring) is favoured [5].

### RESULTS AND DISCUSSION

The NMR spectra of compounds 1–4 were measured at 100 MHz in chloroform-d solution (Fig. 1). Under these conditions 3 gave overlapping

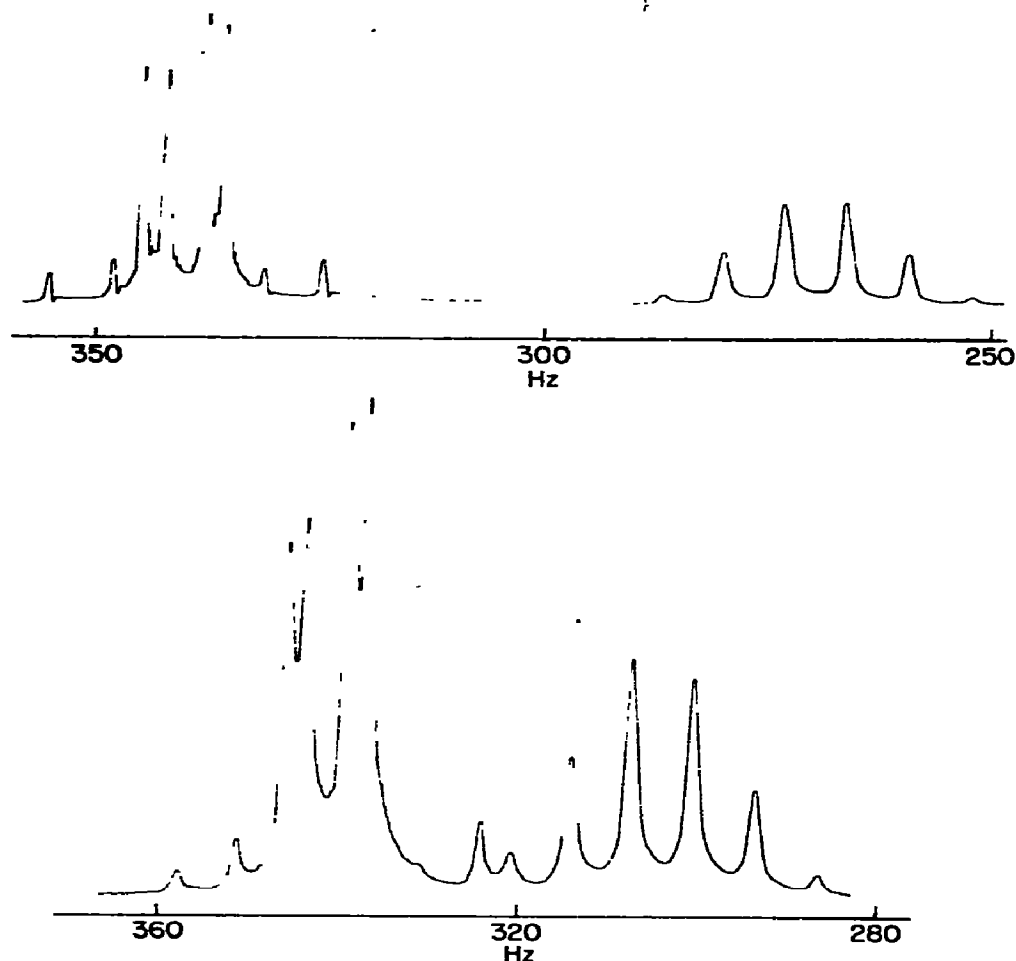


Fig. 1. 100 MHz spectra in  $\text{CDCl}_3$  of the  $\text{CH}_2\text{—CH}$  protons in: (top)  $\text{CH}_3\text{CH(Ph)CH}_2\text{OH}$  1; (bottom)  $\text{CH}_3\text{CH(Ph)CH}_2\text{NH}_2$  plus 0.02 mol/mol  $\text{Eu(fod)}_3$ .

$\text{CH}_2\text{—}$  and  $\text{CH—}$  signals, so a small amount of shift reagent was used in order to facilitate the analysis. The analysis of the spectra was performed by use of the program LAOCOON-3 adapted for an ICL-1904A computer, treating the aliphatic protons as  $\text{ABCD}_3$  systems. The final parameters are shown in Table 1.

Since the assignment of the geminal methylene protons is arbitrary and does not follow from the spectrum analysis, two sets of staggered conformations for the compounds 1–4 must be considered (Fig. 2). From steric considerations as well as from the values of the vicinal couplings observed one may expect the two major conformers to be I and II. On the basis of the approximate Karplus rule procedure [2, 3] one may further conclude that if conformer I is favoured over II the correct assignment will be (a) for  $J_{\text{AC}} > J_{\text{BC}}$ , and (b) for  $J_{\text{AC}} < J_{\text{BC}}$ . In the alternative case (II favoured over I) the assignment must be reversed. The experimental result for 1 ( $J_{\text{AC}} \approx J_{\text{BC}}$ ) implies that forms I and II are about equally populated.

TABLE 1

NMR parameters<sup>a</sup> of  $\text{CH}_3\text{CH}(\text{Ph})\text{CH}_2\text{X}$  (in Hz at 100 MHz with respect to internal TMS; ca. 0.4 molar solutions in  $\text{CDCl}_3$ )

Compound X	1 OH	2 $\text{OCH}_3$	3 <sup>b</sup> $\text{NH}_2$	4 Cl
$\nu_A$	$344.18 \pm 0.01$	$338.51 \pm 0.03$	$343.87 \pm 0.07$	$359.39 \pm 0.01$
$\nu_B$	$336.73 \pm 0.01$	$329.42 \pm 0.03$	$336.78 \pm 0.08$	$349.06 \pm 0.02$
$\nu_C$	$270.48 \pm 0.02$	$291.51 \pm 0.06$	$303.88 \pm 0.09$	$300.74 \pm 0.02$
$\nu_D$	$111.63 \pm 0.01$	$123.30 \pm 0.03$	$106.11 \pm 0.04$	$138.28 \pm 0.01$
$J_{AB}$	$-10.62 \pm 0.01$	$-9.12 \pm 0.04$	$-12.77 \pm 0.05$	$-10.61 \pm 0.01$
$J_{AC}$	$6.90 \pm 0.02$	$6.36 \pm 0.05$	$5.80 \pm 0.11$	$5.98 \pm 0.03$
$J_{BC}$	$6.84 \pm 0.02$	$7.57 \pm 0.07$	$8.30 \pm 0.02$	$8.00 \pm 0.04$
$J_{AD}$	$-0.02 \pm 0.01$	$-0.03 \pm 0.03$	$-0.02 \pm 0.06$	$-0.04 \pm 0.01$
$J_{BD}$	$-0.03 \pm 0.01$	$-0.06 \pm 0.03$	$-0.16 \pm 0.03$	$-0.05 \pm 0.02$
$J_{CD}$	$7.04 \pm 0.01$	$6.81 \pm 0.04$	$6.63 \pm 0.05$	$6.96 \pm 0.01$

<sup>a</sup>Abbreviations used: A, B  $\text{CH}_2$  protons; C  $\text{CH}$  proton; D  $\text{CH}_3$  protons. <sup>b</sup>Plus 0.02 mol  $\text{Eu}(\text{fod})_3/\text{mol}$  substrate.

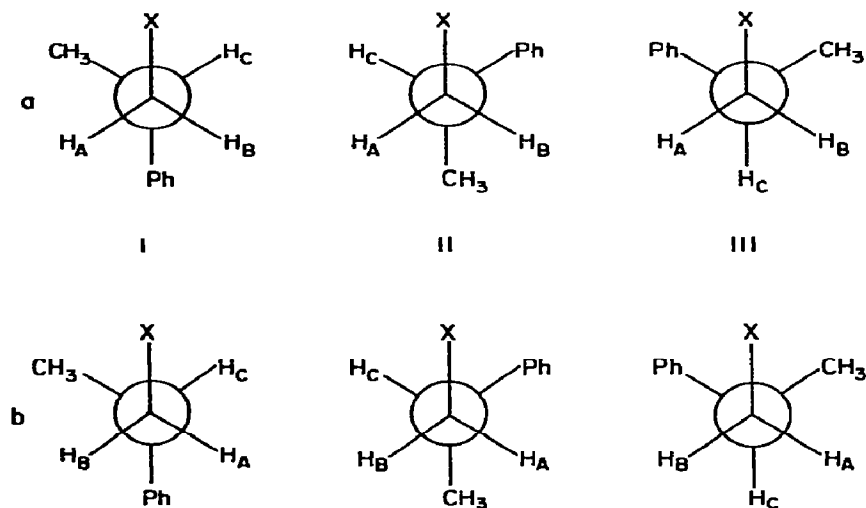


Fig. 2. Staggered conformations of 2-phenylpropyl derivatives.

An attempt was made to estimate the conformational preference for 1 and 3 by applying the qualitative LIS approach described earlier [3], using isobutanol (1a), 2,2-diphenylethanol (1b), isobutylamine (3a), and 2,2-diphenylethylamine (3b) as model compounds.

The induced shifts were obtained in the usual way by successive addition of  $\text{Eu}(\text{fod})_3$  or  $\text{Pr}(\text{fod})_3$  to solutions of the compounds studied in chloroform-*d*. The shifts were linearly dependent on the LSR/substrate ratio up to a value of ca. 0.5 mol/mol (correlation coefficients better than 0.999). The values of the induced shifts  $G$  are collected in Table 2, together with some data already available in the literature. The induced shifts of the geminal methylene

TABLE 2

Induced shifts  $G$  (extrapolated to molar ratio  $\text{Ln}(\text{fod})_3/\text{substrate}$  1:1; concentration of substrate ca. 0.4 molar in  $\text{CDCl}_3$ )

Comp.	$\text{Ln}^a$	$G_{\text{CH}_2}$	$G_{\text{CH}}$	$G_{\text{CH}_3}$	$G_{\text{O-Ph}}$	$G_{\text{m,p-Ph}}$	$G_{\text{CH}_3}/G_{\text{CH}_2}$	$G_{\text{O-Ph}}/G_{\text{CH}}$
1 <sup>b</sup>	Eu	24.9 (22.2, 23.1)	15.1 (13.5)	7.8 (7.3)	8.1	2.9	0.31 (0.32)	0.33
1a <sup>b</sup>	Eu	24.4 (26.4)	15.6 (15.8)	9.9 (9.8)	—	—	0.41 (0.37)	—
1b	Eu	27.3	17.5	—	8.2	2.9	—	0.30
3	Eu	24.1	14.7	7.7	7.2	2.6	0.32	0.30
3a <sup>b</sup>	Eu	26.1 (35.2)	16.2 (20.2)	9.1 (11.8)	—	—	0.35 (0.33)	—
3b	Eu	28.0	16.9	—	7.2	2.6	—	0.26
3	Pr	43.0	24.8	12.6	12.4	—	0.29	0.29
3a	Pr	43.2	23.9	14.3	—	—	0.33	—
3b	Pr	46.5	28.0	—	13.5	5.5	—	0.29

<sup>a</sup>As usual, Eu gave downfield shifts, and Pr upfield shifts. <sup>b</sup>The values in parentheses have been obtained previously using  $\text{Eu}(\text{dpm})_3$ : ref. [6] for compound 1, and ref. [7] for 1a and 3a.

protons were practically identical, indicating that the latter are symmetrically located with respect to the lanthanide.

Earlier work [3, 7] has indicated a similar geometry of the LSR complexes within a series of structurally and conformationally related compounds. This justifies to some extent the comparison of the induced shifts of like groups for the purposes of a qualitative conformational analysis. For comparison of the induced shifts of the methyl and *o*-phenyl protons we preferred to use the ratios  $G_{\text{CH}_3}/G_{\text{CH}_2}$  and  $G_{\text{O-Ph}}/G_{\text{CH}_2}$ , respectively in order to reduce the errors due to differences in geometry and complexation factors. As the data in Table 2 show, these ratios are remarkably independent of variations in the experimental conditions and LSR used in the different studies. Taking into account the fact that 1 exhibits a smaller  $G_{\text{CH}_3}/G_{\text{CH}_2}$  value than 1a, and a larger  $G_{\text{O-Ph}}/G_{\text{CH}_2}$  value than 1b and considering the proximity of the respective protons to the complexation site in the different conformers, one may conclude that conformation II should be favoured over I for 1; the same is true also for 3.

Although the shifts produced by  $\text{Pr}(\text{fod})_3$  are larger, its use may be less reliable due to the known tendency of this reagent to dimerize and form both 1:1 as well as 1:2 adducts [8].

Examination of the IR spectra taken at low concentrations in carbon tetrachloride solution (Fig. 3) revealed that 1b exists mainly (but not entirely) as an intramolecularly  $\text{OH} \cdots \text{Ph}$  bonded species. On the other hand for 1 the intensities of the free and bonded OH bands at 3645 and 3610  $\text{cm}^{-1}$  were approximately equal, in agreement with a previous report [4]. Assuming a smaller amount of conformer III, the IR evidence corresponds

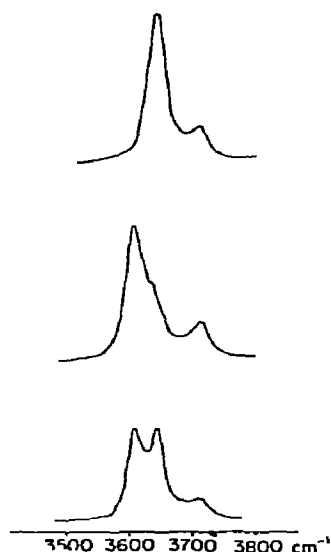


Fig. 3. Infrared OH—stretching bands of compounds 1 (bottom), 1a (top) and 1b (middle). Solutions  $10^{-3}$  molar in  $\text{CCl}_4$ .

well to that obtained on the basis of the vicinal couplings, i.e. approximately equal amounts of I and II should be present. On the other hand the LIS evidence, as stated above, is in favour of form II. This could be attributed to some contribution of form III, in which the hydroxyl group (and hence the lanthanide) is expected to be closer to the phenyl than to the methyl group as a result of the intramolecular hydrogen bonding.

In the ester 2, the elimination of the intramolecular bond should tend to destabilize conformations II and III. Thus the increased difference between the vicinal coupling constants  $J_{AC}$  and  $J_{BC}$  could be interpreted in terms of I becoming the predominant form.

The predominance of II over I for the amine 3 indicated by the LIS data is in agreement with the results from theoretical calculations [5]. It is also indirectly supported by the results obtained for amphetamine,  $\text{PhCH}_2\text{CH}(\text{CH}_3)\text{NH}_2$  for which case the conformation with *anti*-phenyl and methyl groups (possessing the same *gauche*-interactions as II) was found to be the dominant one in chloroform solution [9].

Exact analysis of the spectrum of 2-phenylpropyl bromide has shown [10] that both vicinal coupling constants are equal (6.6 Hz), thus indicating equal populations of conformers I and II. This apparently is not true for the case of the chloro-analogue 4 (Table 1). Studies of 1,2-disubstituted ethanes have shown that the conformations with methyl and chloro groups *gauche*, and phenyl and chloro groups *anti* to each other are favoured [11]. On this basis it is reasonable to assume that the predominant form of 4 is I.

Thus, the assignment of the geminal protons should correspond to Fig. 2(a) for the case of compound 3, and to Fig. 2(b) for 1, 2 and 4.

The chemical shift data for the methylene protons (Table 1) show that the proton B exhibiting the larger vicinal coupling is more shielded than A.

Inspection of Fig. 2 reveals that this is in agreement with the shielding effect of *gauche*-phenyl or methyl groups usually observed in similar systems [2].

A semiquantitative estimate of the conformational populations could be achieved in the usual way [1, 2], assuming certain values for the vicinal couplings in the individual conformers. Applying the approach of Abraham et al. [12], one calculates the *gauche*-coupling constant in forms I and II ( $J_g$ ), and in form III ( $J'_g$ ); the respective values are shown in Table 3. The *anti*-coupling constant ( $J_t$ ) in I and II was estimated similarly on the basis of literature data [11]. The results of the calculations are shown in Table 3.

As expected, form III is the least populated one but its amount is not negligible. The results for I and II together with earlier data [3] indicate that in systems of the type  $\text{CH}_3\text{CH}(\text{Ph})\text{CH}_2\text{X}$  the conformation with phenyl and X groups *anti* to each other is the favoured one, except in cases where X is a proton-donating group (OH,  $\text{NH}_2$ ). This leads to the conclusion that intramolecular hydrogen bonding might be of importance in determining the conformational equilibria in such systems [13].

In conclusion, the results obtained in the present study seem to indicate that, in spite of its very approximate nature [14], the qualitative LIS approach [3] might be of some use, particularly in combination with other techniques.

## EXPERIMENTAL

The NMR spectra were measured on JEOL PS-100 (100 MHz) and JNM-C-60S (60 MHz) spectrometers at normal probe temperature. The IR spectra were taken on a C. Zeiss-Jena UR-10 spectrometer.

Compounds 1, 1a, 3, 3a, and 3b, as well as the shift reagents were obtained commercially. The alcohol 1b, b.p.  $164^\circ\text{C}/8\text{ mm}$ , was synthesized according to ref. 15. The ether 2, b.p.  $184\text{--}185^\circ\text{C}/760\text{ mm}$ ,  $n_D^{20} = 1.4949$  was prepared from the parent alcohol 1 through methylation with methyl iodide/sodium in tetrahydrofuran and purified by column chromatography. Compound 4, and purified by column chromatography. Compound 4, b.p.  $77^\circ\text{C}/5\text{ mm}$ , was made from 1 upon treatment with thionyl chloride [16].

TABLE 3

Conformational populations of  $\text{CH}_3\text{CH}(\text{Ph})\text{CH}_2\text{X}$

Compound	X	$J_t$	$J_g$	$J'_g$	Conformational population (mol fraction)		
					I	II	III
1	OH	11.5	4.5	1.8	0.40	0.42	0.18
2	$\text{OCH}_3$	11.5	4.5	1.8	0.50	0.34	0.16
3	$\text{NH}_2$	12	4.1	2.2	0.26	0.57	0.17
4	Cl	12	4.3	2.0	0.59	0.30	0.11

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