The Conformational Analysis of 1-*p*-Tolyl-2-phenyl-1-propanols, 1-*p*-Tolyl-2-phenylethanol, and 1-*p*-Tolyl-2-phenyl-1-propanone by Means of NMR Spectroscopy

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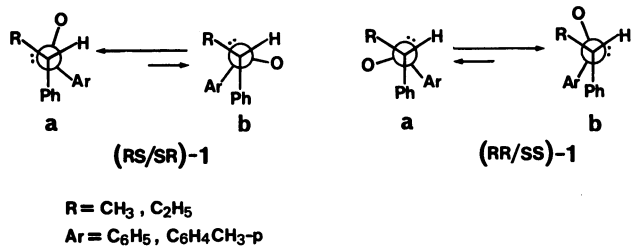
The conformations of the diastereomers of 1-*p*-tolyl-2-phenyl-1-propanols[(*RS*/*SR*)-**3** and (*RR*/*SS*)-**3**], 1-*p*-tolyl-2-phenylethanol (**4**), and 1-*p*-tolyl-2-phenyl-1-propanone (**5**) were studied by means of NMR spectroscopy, mostly with the aid of the computer-simulation of the lanthanoid-induced shifts. It has been suggested that the rotamers in which the tolyl group lies close to the phenyl group are preferred in the conformational equilibria of (*RS*/*SR*)-**3**, **4**, and **5**. For (*RR*/*SS*)-**3**, the most stable rotamer (in $CDCl_3$) has been suggested to have the tolyl group *anti* to the phenyl group and *gauche* to the methyl group. The results have been discussed in view of the general occurrence of the folded conformation.

Our recent nuclear magnetic resonance studies of several diastereomeric 1-phenylalkyl aryl sulfoxides, (*RS*/*SR*)- or (*RR*/*SS*)-$C_6H_5CH(R)$–SO–Ar (**1**),[1] have demonstrated that the conformational equilibria of these compounds are like those illustrated in Scheme 1. That is to say, it has been found that the rotamers in which the aromatic group(Ar) is positioned *gauche* to the phenyl group (Ph) (**a** and **b** rotamers) are most populated in the conformational equilibria of these compounds.



Scheme 1.

This phenomenon (favored *gauche* interactions) is interesting in relation to a similar one hitherto observed for the compounds of the following type: $C_6H_5CH(CH_3)$–X–R (**2**) [X=S,[14] SO,[1,10] CH_2,[13] CHOH,[4,7] CO;[9] R=CH_3, C_2H_5, *i*-C_3H_7, *t*-C_4H_9]. These findings have now prompted us to investigate the conformational analysis of a few alcohols, the diastereomeric pairs of 1-*p*-tolyl-2-phenyl-1-propanol [(*RS*/*SR*)-**3** and (*RR*/*SS*)-**3**], 1-*p*-tolyl-2-phenylethanol (**4**), and a ketone, 1-*p*-tolyl-2-phenyl-1-propanone (**5**), which have the structural resemblance to **1**. It is quite important to explore the generality of the phenomenon (favored *gauche* interactions) in order to know the nature of the interactions, which provide the molecular shapes of these compounds. In this paper we wish to report the results for the conformational assignments of the compounds (**3**—**5**) accomplished with the aid of NMR spectroscopy and comments concerning the interactions involved in the conformational equilibria.

Experimental

(RS/SR)- *and* (RR/SS)-*1*-p-*Tolyl-2-phenyl-1-propanols (3).* 2-Phenylpropionaldehyde (50 g, 0.37 mol) was treated with a Grignard reagent derived from 70 g (0.41 mol) of *p*-bromotoluene and 10 g (0.41 mol) of magnesium in dry ether. After the usual work-up, the crude product was purified by fractional distillation to yield a diastereoisomeric mixture of **3** (73 g, 87% yield); bp 138—139 °C/1—2 Torr (1 Torr≈133.322 Pa). The diastereomeric ratio, (*RS*/*SR*)-**3** : (*RR*/*SS*)-**3**, of the products evaluated by NMR was about 6 : 1. The separation of the diastereoisomers was carried out using a procedure similar to that described for 1,2-diphenylpropanols by Cram and Erhafez.[2] Thus the above mixture (15.2 g, 67 mmol) was treated with *p*-nitrobenzoyl chloride (12.5 g, 67 mmol) in 25 cm^3 of dry pyridine at 90—95 °C for 2 h. Five recrystallizations of the resulting mixture of esters from ethyl acetate yielded the *p*-nitrobenzoyl ester of (*RS*/*SR*)-**3** (9.3 g, 37%); mp 98 °C. The hydrolysis of the above ester (5.3 g, 14 mmol) was carried out in a mixture of 10 cm^3 of water and 10 cm^3 of methanol, with 0.8 g of potassium hydroxide and 0.6 g of sodium hydroxide, to yield 2.9 g of (*RS*/*SR*)-**3**. This was purified by column chromatography on silica gel using ether–hexane (1 : 3) as the eluent. Yield 2.4 g (76%); bp 138 °C/1—2 Torr. Found: C, 84.55; H, 7.98%. Calcd for $C_{16}H_{18}O$: C, 84.92; H, 8.02%.

1-*p*-Tolyl-2-phenyl-1-propanone (**5**) (9.9 g, 44 mmol) was treated with 1.5 g of lithium alminium hydride to yield a mixture of the diastereoisomeric alcohols (9.1 g, 91%); bp 135 °C/1 Torr. The diastereomeric ratio, (*RS*/*SR*)-**3** : (*RR*/*SS*)-**3**, was evaluated to be *ca.* 1 : 4 by NMR. The above mixture (2.5 g, 11 mmol) was treated with 1.7 g (11 mmol) of phthalic anhydride in 2 cm^3 of dry pyridine at 100 °C for 2 h to produce the phthalic acid monoesters of **3**. Four recrystallizations of the ester from ethyl acetate–hexane yielded the ester of (*RR*/*SS*)-**3** (1.9 g, 46%); mp 131—132 °C. The free alcohol (1.0 g) was obtained by hydrolyzing the ester (1.75 g, 4.7 mmol) in 6 cm^3 of methanol–water (1 : 1) using a mixture of potassium hydroxide (0.5 g) and sodium hydroxide (0.5 g). The subsequent column chromatography on silica gel, eluting with ether–hexane (1 : 3), afforded analytically pure (*RR*/*SS*)-**3** (0.95 g, 90%). Found: C, 84.91; H, 8.05%. Calcd for $C_{16}H_{18}O$: C, 84.92; H, 8.02%.

1-p-Tolyl-2-phenylethanol (4). This compound was

prepared by the reaction of phenylacetaldehyde (18 g) with *p*-tolylmagnesium bromide (derived from 27 g of *p*-bromotoluene and 3.9 g of magnesium) in dry ether. After the usual work-up, column chromatography of the crude product on silica gel (ether : hexane=1 : 3), followed by the recrystallization from hexane, yielded analytically pure **4** (23.5 g, 74%); mp 68—69 °C (lit,[3] 68—69 °C).

1-p-Tolyl-2-phenyl-1-propanone (5). The diastereomeric mixture of 1-*p*-tolyl-2-phenyl-1-propanols(**3**) (10.4 g, 46 mmol) was oxidized with 50 mmol of Jones reagent in 200 cm^3 of acetone. The usual work-up, followed by the fractional distillation of the crude product gave analytically pure **5** (7.6 g, 74%); bp 125 °C/1 Torr. Found C, 85.13; H, 7.14%. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19%.

NMR Measurements. The ^1H and ^{13}C NMR spectra were measured for solutions in $CDCl_3$ and/or C_6D_6 (*ca.* 0.3 mol/dm^3) on a JEOL FX-90Q spectrometer. The chemical shifts are given in ppm downfield from internal tetramethylsilane (TMS). The assignments for the carbon resonances were aided by the comparisons of the lanthanoid-induced shifts (LIS).

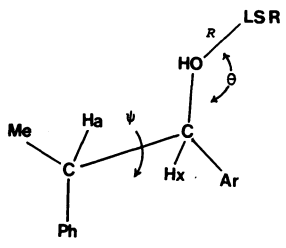
Lanthanoid-induced Shifts (LIS) Measurements. The LIS were determined, for $CDCl_3$ and C_6D_6 solutions, as described in the preceding paper[1] using $Yb(fod)_3$ or $Eu(fod)_3$ as the lanthanoid shift-reagents (LSR). Table 1 lists the relative LIS's for protons and carbons in (*RS/SR*)-**3**, (*RR/SS*)-**3**, **4**, and **5**. The vicinal coupling constants, $^3J_{H_aH_x}$, have been found to be insensitive to the addition of the LSR. Perturbation to the conformational equilibria by coordination is therefore unimportant for **3** and **4**.

Computer-simulation of LIS. The computer simulation of the LIS was carried out according to the procedure described in the previous papers.[4,10] Thus, the distribution of the LSR and the conformation of the molecule (with regard to the central C–C bond) were varied, step by step, in the search for an acceptable fit of the computed LIS's [assuming the McConnell–Robertson's relationship: $LIS_i^{calcd}=K(3\cos^2\chi_i-1)r_i^{-3}$] with the observed values. For the methyl and aromatic protons, and for C(2) and C(3), the contribution of the individual nuclei was calculated and then averaged. The Hamilton reliability factor, $AF=[\sum_i(LIS_i^{obsd}-LIS_i^{calcd})^2/\sum_i(LIS_i^{obsd})^2]^{1/2}$, was used in order to assess the agreement between the computed LIS's and the experimental ones. The calculated shifts were normalized to the average experimental LIS in the computational process.

Results

Figure 1 plots the agreement factor (*AF*) against the O–C(8)–C(7)–C_6H_5 dihedral angle (ϕ) for (*RS/SR*)-**3**. The values of *R* (LSR–O distance), θ (LSR–O–C angle), and *A* (index for the LSR-distribution)[4] are fixed at 0.32 nm, 130°, and 0.8, respectively (see Scheme 2).

An interesting feature of these profiles is the appearance



Scheme 2. A typical model for the (*RS/SR*)-3-LSR complex (Ph: C_6H_5, Ar: $C_6H_4CH_3$-*p*, Me: CH_3).

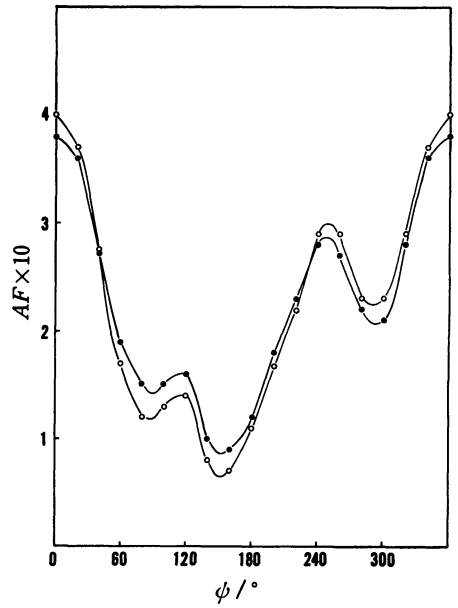


Fig. 1. Plots of *AF vs.* the OH/Ph dihedral angle (ϕ) for (*RS/SR*)-**3**. ●—●: H_a, Me_1, H_x, H_{o1}, H_{o2}, C_1, and C_{16} were used as the monitor nuclei. ○—○: Computed with five proton LIS's.

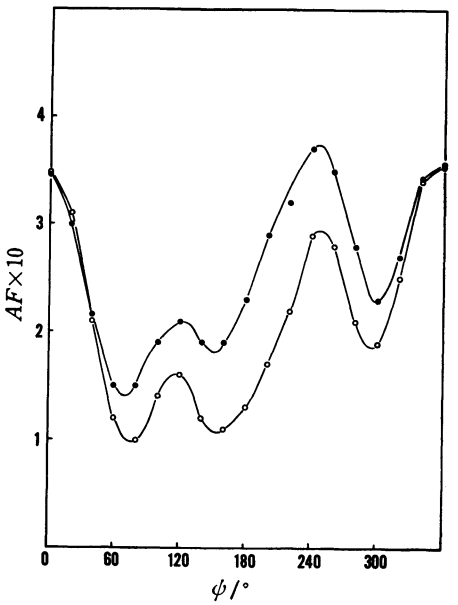


Fig. 2. Plots of *AF vs.* the OH/Ph dihedral angle (ϕ) for (*RR/SS*)-**3**. ●—●: H_a, Me_1, H_x, H_{o1}, H_{o2}, C_1, C_{12}, and C_{16} were used as the monitor nuclei. ○—○: Computed with five proton LIS's.

of three minima at around the staggered geometries (ϕ 80—100°, 140—160°, and 280—300°) of the molecule. Meantime, these results do not differ significantly from those obtained for the sulfoxide analogue, (*RS/SR*)-**1**.[1] For reasons described in previous papers,[1,4,10] we believe that the values of ϕ and *AF* at the minima reflect, although in an indirect manner, the approximate geometries and the contribution of the possible rotamers.[5] Thus, it is suggested that a rotamer in which the tolyl group (Ar) lies about *anti* to the methyl group (Me) and *gauche* to the phenyl group (Ph) (**a** rotamer;

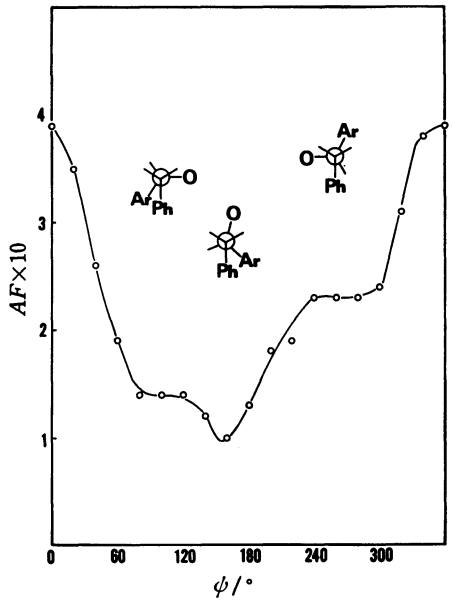


Fig. 3. A plot of *AF vs.* the OH/Ph dihedral angle (ψ) for **4**. The monitor nuclei are H_a, H_x, H_{o1}, H_{o2}, C_1, C_4, C_9, and C_{12}.

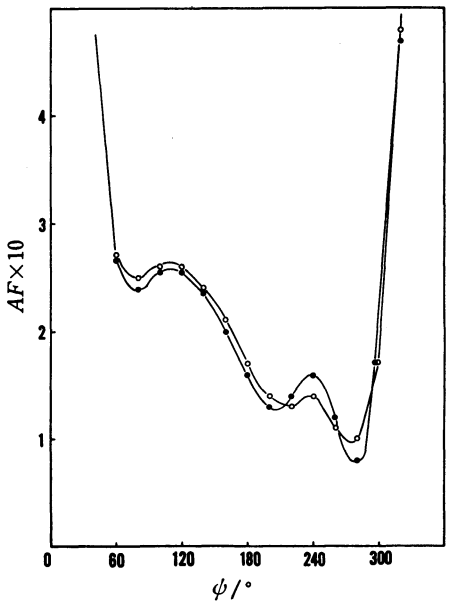


Fig. 4. Plots of *AF vs.* the C=O/Ph dihedral angle(ψ) for **5**. The monitor nuclei are H_a, Me_1, H_{o1}, H_{o2}, C_1, C_4, C_9, C_{12}, and C_{16}. ●—●: R=0.34 nm; ○—○: R= 0.32 nm.

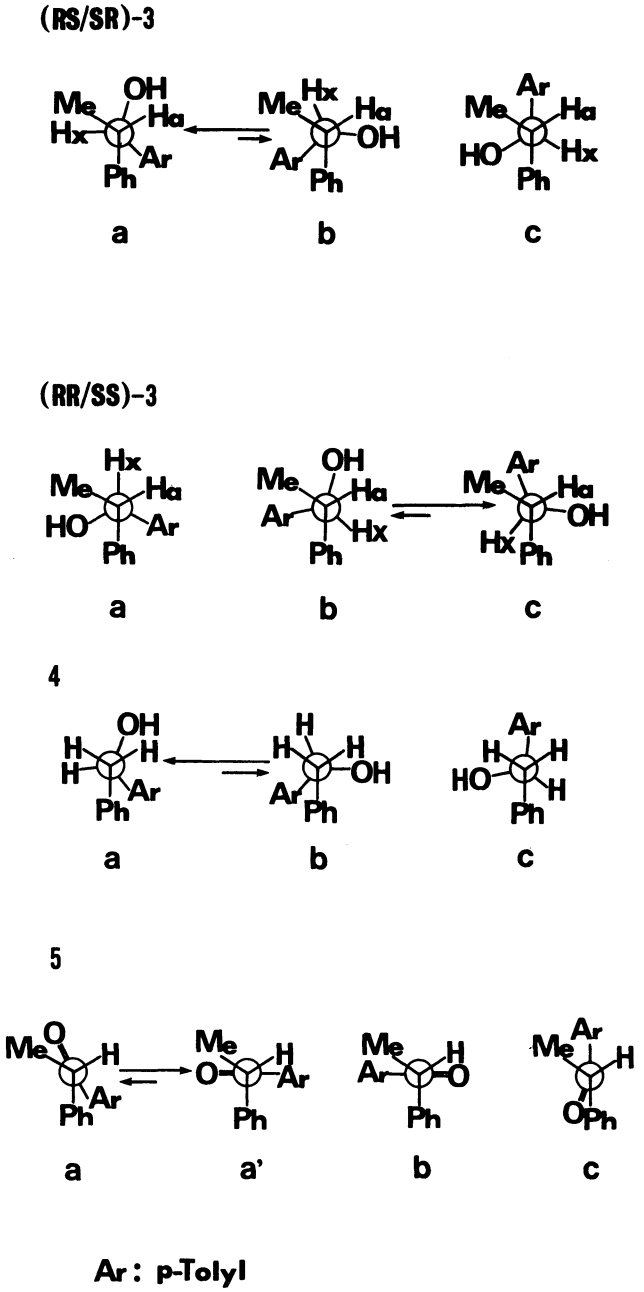


Fig. 5. Plausible conformations and the rotameric equilibria suggested by the LIS-simulation for (*RS*/*SR*)-**3**, (*RR*/*SS*)-**3**, **4**, and **5**.

see Fig. 5) is most preferred in the conformational equilibrium of this compound. The second most stable one is suggested to be the **b** rotamer in which Ar is flanked by Me and Ph.

Figure 2 represents the AF/ψ profiles[6] for (*RR*/*SS*)-**3**. The smallest *AF* is recorded at ψ 60—80° and the second minimum is found at 140—160°; here the most stable rotamer seems to have Ar *anti* to Ph but close to Me (**c** rotamer; see Fig. 5).

In Fig. 3 is given an AF/ψ profile[6] recorded for the benzylic alcohol (**4**). The result is rather similar to those obtained previously for its analogues, in which the tolyl group of **4** is replaced by an alkyl group.[7] Thus, the rotamer having the OH group *anti* to Ph (ψ *ca.* 160°) is suggested to be most preferred.

The profiles obtained for the 1-*p*-tolyl-2-phenyl-1-propanone (**5**) are shown in Fig. 4[8] (R=0.34 nm, θ= 140°, p=0.4). The smallest *AF* values are recorded at ψ [O(=C)/Ph dihedral angle] *ca.* 280° and then 200—220°; the results are analogues to its alkyl derivative, in which the tolyl group in **5** is replaced by an isopropyl group.[9]

Discussion

Figure 5 summarizes the results obtained by the LIS

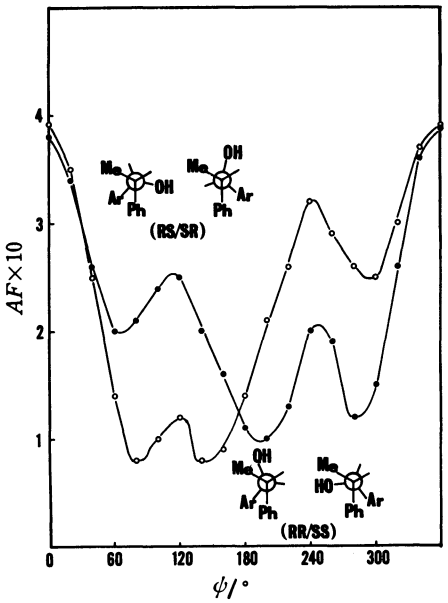


Fig. 6. Plots of *AF vs.* the OH/Ph dihedral angle (ϕ) for (*RS/SR*)-**3** (○—○) and (*RR/SS*)-**3** (●—●). The LIS's were obtained with the use of Eu(fod)$_3$ in C_6D_6 for five protons (H_a, Me_1, H_x, H_{o1}, and H_{o2}).

method for the four compounds, (*RS/SR*)-**3**, (*RR/SS*)-**3**, **4**, and **5**.

We do not wish to mean that the molecular geometries illustrated in Fig. 5 correspond exactly to the shapes of the stable rotameres, since the model (on which the computation is based) is rather primitive and a number of approximations were introduced in the simulation process. The values of *AF*, either, do not necessarily reflect the correct order of the stability (above all, if the difference is small) of the possible rotamers. We may conclude from above results, however, that the folded rotamers are generally preponderant in the conformational equilibria of these compounds. Thus, in the cases of (*RS/SR*)-**3**, the benzylic alcohol (**4**), and the ketone (**5**), the most populated rotamers are suggested to have their tolyl group *gauche* to Ph [rotamers **a** and **b** for (*RS/SR*)-**3** and **4**; rotamers **a** and **a'** for **5**]. The results are consistent with those obtained for the sulfoxide analogues,[1,10] (*RS/SR*)-**1**[1] and the alkyl analogues (**2**).[4,7,9] Meanwhile, in the conformational equilibrium of **5**, the conformer in which the tolyl group is *anti* to Ph (rotamer **c**; C=O is eclipsed to Ph) is least favorable (Fig. 4). The absence of this rotamer has been reported also for other carbonyl compounds.[9] In this respect, it is noteworthy that, in all of the conformations suggested to be preferred (see Figs. 1—4, Figs. 8 and 9 in Ref. 4, Fig. 4 in Ref. 9, and Fig. 3 in Ref. 7), the C=O and OH groups have never been found to lie eclipsed with the phenyl group; *AF*'s are always largest at ϕ *ca.* 0°.

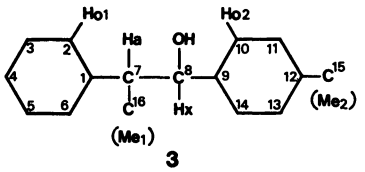
The compound (*RR/SS*)-**3** represents a somewhat different case; here the most stable rotamer seems to have the tolyl group *anti* to the phenyl group but close to the methyl group (**c** rotamer). The second most populated one seems to be the **b** rotamer whereby the tolyl group is flanked by the methyl group and the phenyl group. The result differs from those obtained for the sulfoxide analogue,[1] (*RR/SS*)-**1**.[11] In order to confirm the above suggestions the NMR parameters listed in Tables 2 and 3 were examined in detail.

Chemical Shifts. In harmony with the suggested predominance of the *gauche* Tolyl/Ph conformations, appreciable upfield shifts are observed for the aromatic protons of (*RS/SR*)-**3**. The *ortho* protons (H_{o1} and H_{o2}) give rise to peaks at considerably higher magnetic field (δ 7.07—7.09) as compared to those in reference compounds (δ 7.18—7.23 for alkyl homologues: **2**, X= CHOH).[4] The high-field shifts are not significant in

Table 1. The lanthanoid-induced shifts[a] of 1-*p*-tolyl-2-phenyl-1-propanols(**3**), 1-*p*-tolyl-2-phenylethanol(**4**), and 1-*p*-tolyl-2-phenyl-1-propanone(**5**)

	Me_1	Me_2	H_a	H_x	H_{o1}	H_{o2}	C_1	C_2	C_3	C_4	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{15}	C_{16}
(*RS/SR*)-**3**	22.6	2.6	42.5	64.5	20.5	27.2	28.7	21.4	11.9	10.7	48.9	100	45.3	28.7	13.5	10.7	3.7	30.9
	(37.6)	(5.5)	(73.6)	(100)	(37.3)	(54.5)[b]												
(*RR/SS*)-**3**	23.3	2.9	40.1	65.0	24.1	30.0	37.1	27.6	15.6	13.3	49.1	100	50.1	28.6	11.7	8.5	3.4	29.7
	(42.0)	(3.9)	(54.5)	(100)	(35.4)	(54.0)												
4	—	2.8	36.9	61.5	16.7	26.7	26.7	20.3	10.8	9.5	48.2	100	45.1	28.2	12.8	9.2	4.1	—
5	24.6	1.7	26.6	—	20.2	22.1	24.6	16.2	8.7	6.2	44.8	100	40.6	23.0	9.8	8.4	1.7	30.8

a) Relative values. b) The data in parentheses are obtained in C_6D_6 with the use of Eu(fod)$_3$.



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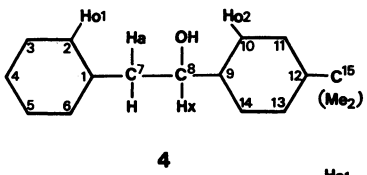

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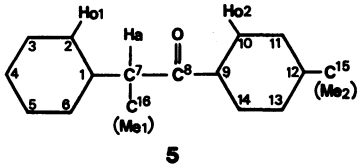

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TABLE 2. PROTON NMR PARAMETERS[a] OF 1-*p*-TOLYL-2-PHENYL-1-PROPANOLS(**3**), 1-*p*-TOLYL-2-PHENYLETHANOL(**4**), AND 1-*p*-TOLYL-2-PHENYL-1-PROPANONE(**5**)

Compound	Solvent	Me_1	Me_2	H_a	H_x	H_{o1}[b]	H_{o2}	OH[c]	$^3J_{H_aH_x}$
(*RS/SR*)-**3**	$CDCl_3$	1.29	2.29	3.07	4.75	7.09	7.07	1.79	5.8[d]
	C_6D_6	1.32	2.07	2.97	4.52	7.16	7.20		6.1
	ASIS[e]	−0.03	+0.22	+0.10	+0.23	−0.07	−0.13		
(*RR/SS*)-**3**	$CDCl_3$	1.05	2.34	2.98	4.60	7.22	7.24	1.79	8.8
	C_6D_6	1.03	2.13	2.92	4.46	7.14	7.19		7.8
	ASIS	+0.02	+0.21	+0.06	+0.14	+0.04	+0.06		
4	$CDCl_3$	—	2.33	2.97[f]	4.83	7.10	7.13	1.89	
	C_6D_6	—	2.14	2.89	4.62				
	ASIS		+0.19	+0.08	+0.21				
5	$CDCl_3$	1.52	2.32	4.66	—	7.24	7.24	—	

a) The chemical shifts are reported in ppm downfield from internal TMS. b) The chemical shifts of aromatic protons were determined by extraporating the linear LIS plots to the intercept at zero of the $Ln(fod)_3$ concentration. c) Extraporated to infinite dilution. d) Reported in Hz; insensitive to the addition of the LSR. e) ASIS = $\delta(CDCl_3) - \delta(C_6D_6)$. f) Equivalent for the diastereotopic protons.

TABLE 3. ^{13}C CHEMICAL SHIFTS[a] OF 1-*p*-TOTLY-2-PHENYL-1-PROPANOLS(**3**), 1-*p*-TOLYL-2-PHENYLETHANOL(**4**), AND 1-*p*-TOLYL-2-PHENYL-1-PROPANONE(**5**)

	C_1	C_2	C_3	C_4	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{15}	C_{16}
(*RS/SR*)-**3**	143.7	128.1	128.1	126.4	47.2	78.5	139.9	126.2	128.9	136.8	21.1	15.1
(*RR/SS*)-**3**	143.6	128.0	128.0	127.0	48.1	79.5	139.6	126.9	129.0	137.4	21.2	18.4
4	138.2	129.5	128.5	126.6	46.0	75.2	140.9	125.9	129.1	137.2	21.2	
5	141.6	127.6	128.8	126.8	47.7	199.8	133.9	129.0	128.8	143.5	21.5	19.4

a) Reported in ppm downfield from internal TMS in $CDCl_3$.

the case of (*RR/SS*)-alcohol. This is not unexpected since the aromatic groups are remote from each other in the most preferred rotamer of this compound. Noteworthy in this regard, is the chemical shift of the methyl protons. The signal attributed to Me (δ 1.05) is remarkably shifted upward in the (*RR/SS*)-isomer as compared with that in (*RS/SR*)-**3** (δ 1.29). This is consistent with the suggestion that in (*RR/SS*)-**3** Me is close to the tolyl group in both of the preferred rotamers (**c** and **b**).

Vicinal Coupling Constants. The spin-coupling constant regarding the vicinal protons ($^3J_{H_aH_x}$) is smaller in (*RS/SR*)-**3** than in (*RR/SS*)-**3**. This may be an indication that the H_a/H_x torsional angle (see Fig. 5) in the most important contributor [rotamer **a** for (*RS/SR*), rotamer **c** for (*RR/SS*)] is closer to 180° in (*RR/SS*)-alcohol than in (*RS/SR*)-isomer, or the proportion of the most stable rotamer is larger in (*RR/SS*)-alcohol than in (*RS/SR*)-alcohol.

Conformational Change in C_6D_6. It is noted that $^3J_{H_aH_x}$ of (*RS/SR*)-**3** does not differ significantly in $CDCl_3$ and in C_6D_6 (Table 2), however, for (*RR/SS*)-**3** it becomes appreciably smaller by replacing the solvent from $CDCl_3$ (8.8 Hz) to C_6D_6 (7.8 Hz). We therefore determined the LIS in C_6D_6 for the diastereoisomeric alcohols and carried out the simulation with the use of these data (Table 1). For (*RS/SR*)-isomer, the profiles are similar to each other in these two solvents. A remarkable difference is found, on the other hand, in the case of (*RR/SS*)-alcohol (Figs. 2 and 6). In C_6D_6 solution, the **b** and **a** rotamers seem to become the most important contributors. The results are compatible with the coupling data. We, however, reserve further discussion on this matter, until more exact knowledge about the conformational equilibria becomes available.

Aromatic Solvent-induced Shifts (ASIS).[46] The ASIS data are listed in Table 2. The results are consistent with the suggested equilibria of these alcohols, but here we only cite an interesting observation that ASIS's for the methyl and aromatic protons are negative in (*RS/SR*)-**3**; at present we have no clear explanation for this phenomenon.

^{13}C NMR Data. The peak attributed to the methyl carbon [C(16)] appears at considerably higher magnetic field (δ 15.1) in (*RS/SR*)-**3** than in the (*RR/SS*)-alcohol (δ 18.4) (Table 3). This is well understood in terms of the *γ-gauche* effect.[1,12] In the most stable rotamer of (*RS/SR*)-**3** (**a** rotamer) OH is *gauche* to Me, but in (*RR/SS*)-**3** this is remote from Me in the most preferred rotamer (**c** rotamer).

In summary, inspection of these conformational analyses reveals that the molecules, (*RS/SR*)-**3**, **4**, and **5**, tend to adopt the folded conformations in solution. In addition, we felt it probable that the phenomenon is general to other kind of molecules, in view of the common preference of the *gauche* rotamers, at least in these simplest systems studied thus far [$C_6H_5CH(R^1)$–X–R^2 : R^1=H, CH_3, or C_2H_5; R^2=alkyl or aryl group; X=CH_2,[13] CHOH,[4,7] CO,[9] S,[14] SO,[1,10] or SO_2,[14]]. The generality of the favored *gauche* alkyl/phenyl conformation (CH/π interaction)[15] was argued previously.[9,16] The scope was therefore examined for the phenomenon in systems, where aromatic groups are incorporated in each end of the molecules.

Table 4 is a summary of a literature survey on compounds relevant to this problem. X-ray studies of 1,2-

TABLE 4. TYPICAL COMPOUNDS WHICH EXHIBIT THE PREFERENTIAL FOLDED CONFORMATION

Compound	Method	Favored conformation	Ref.
$PhCH_2CH_2Ph$(**6**)	X-ray	anti	17
	EFF, CNDO/2	folded	22
	EFF	folded	23
	EFF/EHMO	anti	25
$ArCH_2CH_2Ar$(**6′**)	dipole moment	anti	26
	IR/Raman, Kerr Const.	anti	27
$XC_6H_4CH_2SO_2C_6H_4Y$(**7**)			
(X = MeO, Y=Cl)	EFF	folded	18
	X-ray	anti	18
(X = Me_2N, Y = NO_2)	EFF	folded	18
	X-ray	folded	18
$ArCH_2SO_2Ar$(**7′**)	UV, NMR-2	folded	21
$ArCH_2SOAr$	NMR-2	folded	21b
PhCH(Me)SOPh(**1**)	X-ray	anti	19
PhCH(Me)SOAr(**1**)	NMR-2,4,5	folded	1, 20
PhCH(Me)SAr	indirect evidence	folded	14
PhCH(R)SO_2Ph, R = Me, Et	NMR-4	folded	20
PhCH(Me)CH_2Ph(**8**)	EFF	folded	23
	NMR-1	anti	23, 24
	EFF/EHMO	anti	25
ArCH(Me)CH(Me)Ar(**9**)	IR/Raman, Kerr const.	anti	27
$ArCH_2CH_2OSO_2C_6H_4CH_3$(**10**)	NMR-2	folded	28
$ArCH_2NHPh$(**11**)	UV	folded	29
$Ar(CH_2)_nOCOC_6H_2(NO_2)_3$(**12**)	UV	folded	30
$[ArSO_2CH(Ph)NH]_2CO$(**13**)	NMR-2	folded	31a
	X-ray	folded	31b
$ArSO_2CH_2N(Me)CO_2Ar$(**14**)	NMR-2, UV	folded	32a
	X-ray, EFF	folded	32b
Fl$(CH_2)_3$COR(**15**)			
R = aromatic amino acid residues (Phe, Tyr, Trp)	FL	folded	33
Fl = 3- or 10-flavinyl			
NAD(**16**)	NMR-2	folded	34
	NMR-2	folded	35
	NMR-3	folded	36
Ade$(CH_2)_3$Nic(**17**)			
Ade = 9-adenyl	UV	folded	37
Nic = 1-(3-carbamoyl-1-pyridyl)			
Ade$(CH_2)_3Nic^+$	X-ray	anti	38
$AdeH^+(CH_2)_3Nic^+$	X-ray	folded	39
Ade$(CH_2)_3$iPAde(**18**)			
iPAde = 6-(3-methyl-2-butenyl)adenin-9-yl	UV, FL	folded	40
M(ATP)(Trp)(**19**)			
M = Mn, Cu, Zn	UV, NMR-2	folded	41a
M(ATP)(phen)(**19′**)			
M = Mg, Ca, Zn	NMR-2	folded	41b
phen=1,10-phenanthroline			
NH_2–Ala–Gly–Cys–Lys–Asn–Phe–Phe–Trp–Lys–Thr–Phe–Thr–Ser–Cys–COOH(**20**)			
	CD	folded	42
PhCH(Me)CH(OH)$C_6H_4CH_3$(**3**)	NMR-2,4,5	folded	this work
$PhCH_2CH(OH)C_6H_4CH_3$(**4**)	NMR-5	folded	this work
PhCH(Me)$COC_6H_4CH_3$(**5**)	NMR-5	folded	this work

Methods: NMR-1 = vicinal coupling constant: NMR-2 = ^1H chemical shift; NMR-3 = T_1 measurement (^{13}C); NMR-4 = *γ-gauche* effect; NMR-5 = LIS-simulation; UV = observation of charge-transfer band; CD = circular dichroism; FL = fluorometry; EFF = empirical force-field calculation; EFF/EHMO = EFF/extended Hückel MO hybrid method.

diphenylethane (**6**),[17] *p*-methoxybenzyl *p*-chlorophenyl sulfone (**7**),[18] and (*RS*/*SR*)-**1**[19] demonstrated that these molecules adopt the extended conformations (*anti* aromatic groups) in the crystal fields. In solution, however, **7**,[18] **1**,[1,20] and their analogues[14,20,21] have been shown to be present in folded (*gauche* aromatic groups) conformations. For solution (or gas phase) conformation of **6** and its homologue, 1,2-diphenylpropane(**8**), the results obtained earlier are rather contradictory. Thus, force-field and semi-empirical MO calculations showed that **6**[22] and **8**[23] are more stable in *gauche* Ph/Ph conformations. On the other hand, NMR spin-coupling data of **8**[23,24] (as well as the EFF/EHMO results on **6** and **8**[25] were reported to be incompatible with this conclution. We do not know the reason for the above disagreement, but it may be pointed out that an argument based only on coupling constants often leads to an ambiguous conclusion. Huang *et al.* studied the conformations of substituted 1,2-diphenylethanes(**6'**)[26] and 2,3-diphenylbutane derivatives (**9**),[27] and reported that these molecules prefer the *anti* Ar/Ar conformations (an appreciable proton resides in the *gauche* conformation, however). The conformations of 2-arylethyl *p*-toluenesulfonate (**10**),[28] (*N*-substituted benzyl)anilines (**11**),[29] arylalkyl 2,4,6-trinitrobenzoates (**12**),[30] *N*,*N'*-bis(α-tosylbenzyl)-urea(**13**),[31] *p*-dimethylaminophenyl *N*-methyl-*N*-(*p*-nitrophenylsulfonylmethyl)carbamate(**14**),[32] certain flavinyl peptides (**15**),[33] nicotinamide-adenine dinucleotides (**16**),[34-36] and its analogues (**17**),[37-39] 9-[3-(adenin-9-yl) propyl]-6-(3-methyl-2-butenylamino)-purine (**18**),[40] several mixed-ligand metal complexes (**19**),[41] and somatostatin (**20**)[42] (a cyclic tetradecapeptide) were also studied and they have been shown to exist preferentially in folded forms, whereby two aromatic groups in the molecules are approached to each other.

The reason of the discrepancy cited as above for the conformations of **6** (or **6'**) and **8** remains to be clarified. We believe, however, that the folding tendency of groups (Ar/Ar, Alkyl/Ar,[9,16] and Alkyl/Alkyl[43]) is general to a wide variety of compounds. It may be a rule rather than an exception. In other words, one must seek an explanation if one finds an extended conformation.

As to the origin of the folded conformations, it may be the dispersion force,[13,28,43b,43d] CH/π interaction,[15,44] CH/n interaction,[9,44] and/or other interactions which are not yet disclosed. A folded conformation may, of course, be brought about by other type (such as the hydrogen bonding,[45] dipole/quadrupole,[46] quadrupole/quadrupole, *gauche*-vicinal H/H[47]) of interactions. In any event, the geometry of a molecule is determined as a result of a compromise of various (attractive as well as repulsive) effects. In view of this, it is surprising that the important contribution of weak, attractive interactions has hitherto been underestimated in organic chemistry.[48]

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