The Conformation of a Diastereoisomeric Pair of 2,2-Dimethyl-4-phenyl-3-pentanols[1)]

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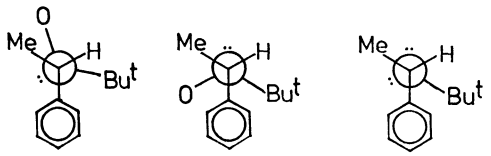
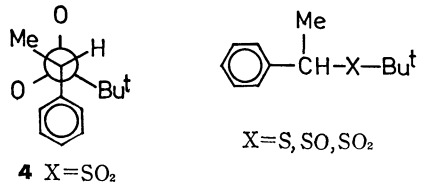
The conformations of a diastereoisomeric pair of 2,2-dimethyl-4-phenyl-3-pentanols were studied by means of ^{1}H-NMR, ^{13}C-NMR, IR, GC, and MS analyses. All of the results point to an unambiguous conclusion that these molecules are present dominantly in conformers where the *t*-butyl and the phenyl group lie close to each other. The generality of the phenomenon (favored *gauche* interaction) as well as the nature of the interactions involved were discussed in light of the conformational problems of the structurally related molecules. The presence of an attractive interaction (CH/π interaction) is suggested between an alkyl and a phenyl group, the possible importance of which in some dynamic phenomena (*e.g.*, selectivities in certain reactions) has then been discussed on this basis.

Evidence has been accumulated that an alkyl group orients itself close to a phenyl group in some molecular environments. The *t*-butyl group in (*SR*/*RS*)[4)] (**1**) and (*SS*/*RR*)-1-phenylethyl *t*-butyl sulfoxides (**2**) as well as in the corresponding sulfide (**3**) and sulfone (**4**), for example, has been shown to be oriented *gauche* with respect to the phenyl group (Fig. 1). Thus,



1 X=SO **2** X=SO **3** X=S



4 X=SO$_2$ X=S, SO, SO$_2$

Fig. 1.

X-ray crystallographic works on these sulfoxides (*p*-Br derivatives) have demonstrated that the dihedral angle defined by C(Bu^t)–S–C–C(Ph) is *ca.* 84° and 65° in **1** and **2**[5)] respectively. Conclusions regarding the conformations of **3** and **4** have been drawn from indirect evidence (for **3**)[6)] and an unpublished X-ray work (for **4**).[7)] The above findings led us to NMR,[5,8)] ORD/CD[5)] and dipole-moment studies[9)] of the diastereoisomeric sulfoxides; the conformations adopted by **1** and **2** in the crystal fields have been shown to be maintained in solutions. In an attempt to explore the generality of the phenomenon, we also extended this work to a conformational study of some structurally related alcohols, (*RS*/*SR*)- and (*SS*/*RR*)-2,2-dimethyl-4-phenyl-3-pentanols.

Experimental

Preparation of Alcohols. The treatment of 2-phenylpropionaldehyde with *t*-butylmagnesium chloride gave 2,2-dimethyl-4-phenyl-3-pentanol, with an (*RS*/*SR*) configuration (**5**, Fig. 2).[4,10)] The reaction mixture was shown to be almost diastereoisomerically pure.[11)] The oxidation of **5** to a ketone, followed by $LiAlH_4$ reduction, gave (*SS*/*RR*)-alcohol (**6**).

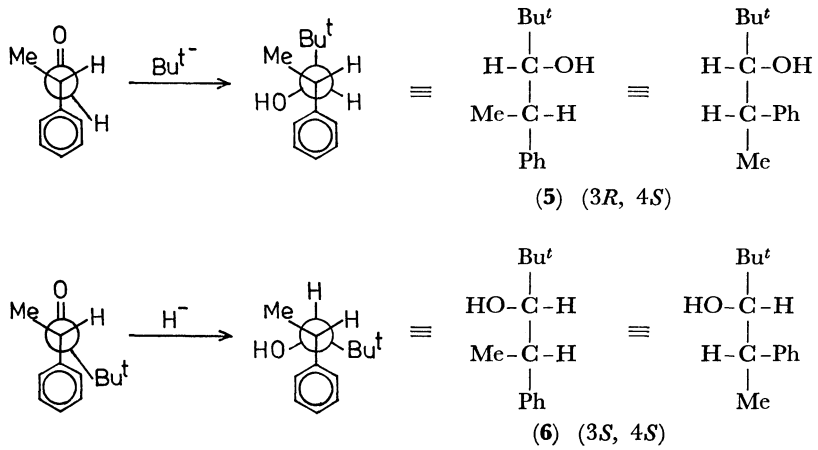


Fig. 2. Procedure for the preparation of alcohols **5** and **6**. Racemic mixtures were used but one of the enantiomers is illustrated for the sake of brevity.

This was again shown to be produced with an almost total exclusion of the other isomer.[10,11] The samples prepared as above and purified chromatographically gave correct analytical data (see Tables 1, 2, and 4 for the spectral data). The configuration assignment of the alcohols has been made by Felkin and his group;[10-12] it is consistent with our own conclusion.

NMR Measurements. The NMR spectra were determined for 0.2 mol/l solutions on a JEOL MH-100 spectrometer (for ^1H) and a JEOL FX-100 spectrometer (for ^{13}C). The chemical shifts are given relative to tetramethylsilane as the internal reference and are accurate to ± 0.01 ppm for the ^1H data and ± 0.04 ppm for the ^{13}C data. The coupling constants are accurate to ± 0.02 Hz. The assignments of the ^{13}C resonances were made by the use of the gated decoupling technique.

IR Measurements. The infrared spectra were obtained at 20 °C for dilute solutions (5.6—8.0 mmol/l) in carbon tetrachloride with a Perkin-Elmer model 112G or a JASCO DS-402G spectrometer. The error in the measurements is estimated to be less than 2.5 cm^{-1}.

GC. A Hewlett-Packard 5830A gas chromatograph equipped with a 6-foot column was packed with Diasolid ZS. The temperature was maintained at 150 °C. The flow rate of the He carrier gas was 35 ml/min. The retention times were 1.61 and 1.46 min respectively for **5** and **6**.

MS. A Hitachi RMU-6MG mass spectrometer was used. The samples were introduced gas-chromatographically. The temperature at the ion source, the ionizing potential, and the accelerating voltage were 230 °C, 20 eV, and 3.2 kV respectively.

Results

NMR Results. Tables 1 and 2 list the proton and carbon magnetic resonance parameters respectively for **5** and **6**.

Vicinal H/H Coupling: An inspection of the Newman projections in which the "bulkiest" groups (Bu^t and Ph) are arranged *anti* (Fig. 3) would lead us to a prediction that the vicinal coupling constant, $^3J_{HH}$, is larger in the (*SS*/*RR*) isomer (**6**) than in the (*RS*/*SR*) alcohol (**5**). This stems from a simple consideration of the Karplus relationship,[13] in which $^3J_{HH}$ is largest (*ca.* 10—12 Hz) when the relevant protons are oriented *anti* or eclipsed. The experimental values, however, were found to be smaller than 4 Hz for both compounds. This promptly rules out the conformation depicted in Fig. 3 for **6**; a much larger $^3J_{HH}$ value is expected for this conformation (H/H *anti*). Possible valence angle deformations involving the respective atoms could render the vicinal coupling constant a poor guide with regard to the conformational problem. In this

TABLE 1. PROTON NMR PARAMETERS FOR (*RS*/*SR*)- AND (*SS*/*RR*)-2,2-DIMETHYL-4-PHENYL-3-PENTANOL

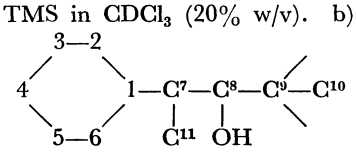
	Bu^t	Me	H_a	H_x	H_o	H_m	OH
			(*RS*/*SR*) (**5**)				
δ[a]	0.90	1.25	2.94	3.33	7.17	7.17	1.48
LIS(obsd)[b]	0.33	0.44	0.48	1.00	0.25	0.03	
(calcd)	0.33	0.44	0.53	1.00	0.19	0.07	
ASIS[c]	+0.04	0.00	+0.07	+0.07	—	—	
J_{HaHx}		3.7 Hz (CCl_4), 3.7 Hz (benzene)					
			(*SS*/*RR*) (**6**)				
δ	0.79	1.32	2.95	3.28	7.22	7.22	(1.3)[d]
LIS(obsd)	0.31	0.37	0.37	1.00	0.38	0.08	
(calcd)	0.28	0.43	0.42	1.00	0.38	0.05	
ASIS	+0.02	+0.05	+0.11	+0.07			
J_{HaHx}		3.9 Hz (CCl_4), 3.7 Hz (benzene)					

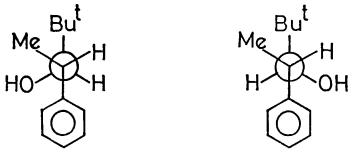
a) Ppm downfield from internal TMS in CCl_4. b) Relative chemical shifts induced by the addition of $Eu(fod)_3$ in CCl_4 solutions. c) δ(benzene)$-\delta(CCl_4)$. d) Not observable, but suggested to be present about here by decoupling experiments (see text).

TABLE 2. CARBON NMR PARAMETERS FOR (*RS*/*SR*)- AND (*SS*/*RR*)-2,2-DIMETHYL-4-PHENYL-3-PENTANOL

(*RS*/*SR*) (**5**)									
	1	2, 6	3, 5	4	7	8	9	10	11
δ[a]	147.99	127.36	128.34	125.88	41.13	82.92	36.06	26.82	16.53
$^1J_{CH}$/Hz	—	154.3	159.2	162.1	125.0	140.6	—	125.0	127.0
(*SS*/*RR*) (**6**)									
δ	144.12	128.84	128.22	126.31	41.71	83.35	35.87	26.70	22.42
$^1J_{CH}$	—	156.2	159.2	159.2	126.0	139.6	—	125.0	127.0
Δ[b]	+3.87	−1.48	+0.12	−0.43	−0.58	−0.43	+0.19	+0.12	−5.89

a) Ppm downfield from internal TMS in $CDCl_3$ (20% w/v). b) $\Delta=\delta(RS/SR)-\delta(SS/RR)$.



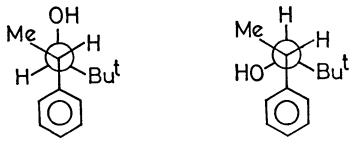


(5) (6)

Fig. 3.

regard, it should be noted that the one-bond coupling constants, $^1J_{CH}$, are quite normal for relevant sp^3-hybridized linkages[14] (for C^7–H and C^8–H, see Table 2). It follows, therefore, that there are no appreciable distortions about the bond angles and bond lengths involving these nuclei. It was also noted that there was little effect in $^3J_{HH}$ with the change in the solvent or the addition of a lanthanoide-shift reagent (LSR). This demonstrates that the conformational equilibria of these alcohols are not much perturbed by the change in the solvent polarity or by complexation.

Lanthanoide Shift Reagent-induced Shift (LIS): One of the most remarkable features to be seen in Table 1 is that the LIS for H_a is appreciably larger in **5** than in **6**, whereas the reverse is true for the *ortho* and *meta*-protons on the phenyl ring. To explain this, we must consider that the hydroxyl oxygen (the substrate-LSR complexation site) is closer to H_a and remoter from the phenyl group in **5** than in **6**. This, along with the coupling data, rules out the possibility that the conformations of these alcohols are like those shown in Fig. 3 (Bu^t/Ph *anti*). To be consistent with the LIS data, we must presume that such conformations as illustrated in Fig. 4 are predominant in these solutions. Note that in both conformations the *t*-butyl group orients itself *gauche* to the phenyl group. For the (*RS*/*SR*)-isomer (**5**), however, a completely staggered conformation is incompatible with the coupling data.

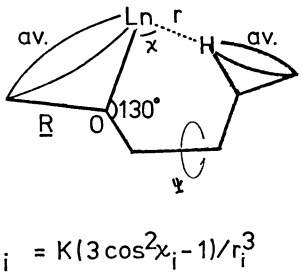


(5) (6)

Fig. 4.

We, therefore, carried out computer simulations of the LIS for these compounds. Thus, a program was written in which the LIS for each proton could be calculated[8] according to the McConnell and Robertson equation.[15] The necessary parameters were assumed as usual, and the LIS data listed in Table 1 were used. For the protons of Me, Bu^t, H_o, and H_m, the contributions of various rotational forms were averaged. The lanthanoide(Ln)–O–C angle was taken to be 130°. The procedure is illustrated in Fig. 5. A Gaussian weight factor (w) for the rotamer population was defined as in Eq. 1,[16] where A is the distribution coefficient and θ is a torsional angle for the rotation of Ln around the C–O bond. For steric reasons,

$$w(\theta) = \frac{A}{\sqrt{\pi}} \exp\left[-A^2(\theta-\theta_0)^2\right] \quad (1)$$



$$\Delta\nu_i = K(3\cos^2\chi_i - 1)/r_i^3$$

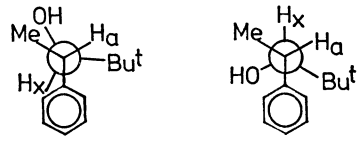
Fig. 5. Procedure for calculating the pseudocontact shifts.

θ_0 was taken so that the position of LSR was farthest from the center of the phenyl ring. The agreement factor (AF) was defined as in Eq. 2:

$$AF(\%) = 100(\sum_i |\mathrm{LIS}_{\mathrm{obsd},i} - \mathrm{LIS}_{\mathrm{calcd},i}|)/\sum_i \mathrm{LIS}_{\mathrm{obsd},i} \quad (2)$$

while the Ln–O distance (R) and the O–C–C–C(Ph) dihedral angle (ϕ) were allowed to vary in order to enable us to obtain the best fit with the experimental values.

The AF values of 5 and 6% were the best fits where R=0.30 nm, ϕ=210°, and A=0.2 for **5** and R=0.30 nm, ϕ=285°, and A=0.6 for **6**. From these data, the H_a–C–C–H_x dihedral angles were estimated to be around 150° and 45° for **5** and **6** respectively.



(5) (6)

Fig. 6. Computer-simulated conformations for **5** and **6**.

This is illustrated in Fig. 6. On the basis of the Karplus relationship (Eq. 3):

$$^3J_{HH} = 8.5\cos^2\theta - 0.28 \quad (0°—90°)$$
$$= 9.5\cos^2\theta - 0.28 \quad (90°—180°) \quad (3)$$

the H_a/H_x dihedral angles, 45°, 50°, 150°, and 135°, give $^3J_{HH}$ values of *ca.* 4.0, 3.2, 6.8, and 4.5 Hz respectively. The computational results are, therefore, not so incompatible with the coupling data in view of the fact that they merely reflect the weighted mean of the possible rotamers. This conclusion is consistent with the solvent effect induced by benzene (ASIS) as well; a larger ASIS was observed for H_a in **6** than in **5** (Table 1). This is expected since H_a in **6** is oriented more apart from the hydroxyl oxygen than in **5**. The trend observed for the LSR distribution index (A) is also reasonable in view of steric considerations. On the basis of the simulated conformations (Fig. 6), the phenyl group in **6** can be said to hinder more effectively the approach of LSR and, hence, give rise to a larger A (0.6 *vs.* 0.2). Also noteworthy are the differences observed in the shielding constants for the *t*-butyl and hydroxyl protons of the isomers. The signals appropriate to the *t*-butyl and OH protons in **6** are appreciably shifted toward the high-field region compared to those in **5** (0.79 *vs.* 0.90 ppm and

1.3 *vs.* 1.48 ppm in CCl_4 respectively). This can be ascribed to the anisotropic shielding effect of the phenyl group. According to the suggested conformations, the *t*-butyl and the hydroxyl group in **6** lie closer to the phenyl ring than do those in **5**; therefore, they suffer from a more profound ring-current effect.

^{13}C-Chemical Shift: In Table 2 are included the differences [$\Delta=\delta(RS/SR)-\delta(SS/RR)$] in the carbon resonances between these isomers. Table 3 lists the corresponding data for some structurally related sulfoxide diastereoisomers, **1** and **2**. The most remarkable differences are those (Δ) observed for the quaternary ring carbon (C^1) and for the methyl carbon (C^{11}) shifts. The peak assignable to C^1 appears at a magnetic field lower by 3.9 ppm for **5** than for **6**. The methyl carbon of **5**, in contrast, gives rise to a signal which is 5.9 ppm higher than that of **6**. Similar trends are also noted for the sulfoxide pairs.

The above results can be explained in terms of the γ-effect or the so-called steric compression shift.[17] On the basis of the suggested conformations (Fig. 6), the hydroxyl group in **5** lies closer to the methyl group than in **6**. It is, therefore, reasonable to expect a more pronounced γ-effect for the methyl carbon in **5**. For the quaternary ring carbon C^1, on the other hand, it is anticipated that such an effect is more profound in the (*SS/RR*) alcohol (**6**) than in the (*RS/SR*) one (**5**). Thus, both OH and Bu^t lie closer to the aromatic carbon in **6** than in **5**. The same trend observed for the sulfoxide pairs ($\Delta=2.7$ and -1.8 ppm respectively for C^1 and C^{11}, where R=H; see Table 3) can be understood on a similar basis. The S–O oxygen atom has been established to be closer to the methyl group in **1** than in **2**.[5] The reverse is true for the spatial relationships of O and Bu^t with respect to the phenyl group. The chemical-shift differences between isomers (Δ) are somewhat smaller for sulfoxides than for the case of alcohol. This is also reasonable in view of the longer bond lengths (S–C *vs.* C–C and S–O *vs.* C–O) for sulfoxides relative to alcohols. The interatomic distances of the respective nuclei are longer for the sulfur compounds; hence, the γ-effects are smaller.

Intramolecular OH/π Interaction. IR Spectra: The above findings led us to an expectation that, whereas an intramolecular OH/π bonding can be operative in the (*SS/RR*)-isomer (OH/Ph *gauche*), this interaction will be absent for the (*RS/SR*)-isomer (**5**), which has a hydroxyl group apart from the phenyl ring. In order to clarify this point, we have examined the IR spectra of these compounds, together with the lower homologues in which the *t*-butyl group is replaced by the methyl, ethyl, and isopropyl groups.[10] Table 4 summarizes the results.

As is shown by a typical example of the IR traces of **5** and **6** in Fig. 7, these alcohols possess characteristic doublet O–H stretching bands, one at 3630—3645 cm^{-1} and the other at 3600—3610 cm^{-1}. It goes without saying that the former is to be assigned to the free OH group.[18] The trend for the position of the high-frequency band to move still to the higher-frequency side as the substituents go from the methyl through ethyl to isopropyl and *t*-butyl seems to demonstrate the effect of steric congestion by the alkyl groups.[18,19] Thus, the conformation in which the torsion angle between the OH and alkyl groups is small ($\leq 60°$) is suggested for the free OH species.

In the *threo* (see footnote a in Table 4 for these

Table 3. Carbon NMR parameters for (*SR/RS*)- and (*SS/RR*)-1-phenylethyl *t*-butyl sulfoxides $p(R)C_6H_4CHMeSOC_4H_9$

	1[a]	2,6	3,5	4	7	8	9	10	11
(*SR/RS*) (**1**)									
R=H	140.0[b]	128.1	129.0	127.8	56.9		55.1	23.7	17.8
R=Br	139.2	132.2	129.8	121.7	56.1		55.4	23.7	17.5
(*SS/RR*) (**2**)									
R=H	137.3	129.1	128.4	127.9	54.8		55.1	23.6	19.6
R=Br	136.4	131.6	130.8	122.2	54.4		55.1	23.6	19.5
Δ[c]									
R=H	+2.7	−1.0	+0.6	−0.1	+2.1		0.0	+0.1	−1.8
R=Br	+2.8	+0.6	−1.0	−0.5	+1.7		+0.3	+0.1	−2.0

a) For numbering of the carbon atoms, see Table 2. b) Ppm downfield from internal TMS in $CDCl_3$. c) $\Delta=\delta(SR/RS)-\delta(SS/RR)$.

Table 4. IR spectral data for the diastereoisomeric pairs of alcohols RCHOHCHPhMe

	Me	Et	Pr^i	Bu^t
erythro[a]	3611.8[b] (0.8_6)[c]	3609.5 (1.8_5)	3614.4 (2.4_8)	3612 (1.0)
	3637.0 (1)	3640.2 (1)	3645.8 (1)	3645 (1)
threo[d]	3595.4 (11)	3601.0 (4.8)	3606.6 (5.5)	3600 (1.9)
	3629.0 (1)	3637.0 (1)	3648.2 (1)	3646 (1)

a) (*RS/SR*) for R=Bu^t, but (*SS/RR*) for R=Pr^i, Et, or Me. According to the sequence rule, the configurationally related alcohols do not necessarily have the same symbols (Bu^t>CHMePh; but Pr^i, Et, Me<CHMePh). b) Wave number in cm^{-1}. c) Relative intensity. d) (*SS/RR*) for R=Bu^t, (*RS/SR*) for the lower homologues.

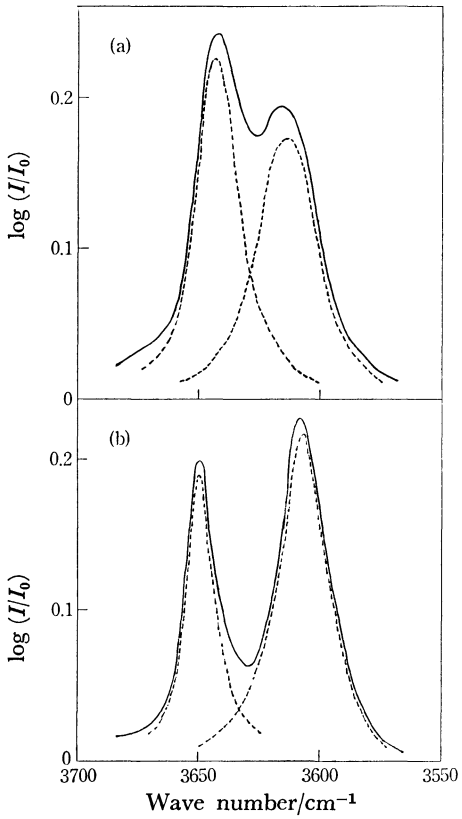


Fig. 7. Parts of the IR-traces for (a) (*RS*/*SR*)-(**5**) and (b) (*SS*/*RR*)-2,2-dimethyl-4-phenyl-3-pentanol (**6**). The dissection of the doublet bands was made by assuming the Lorentzian curve.

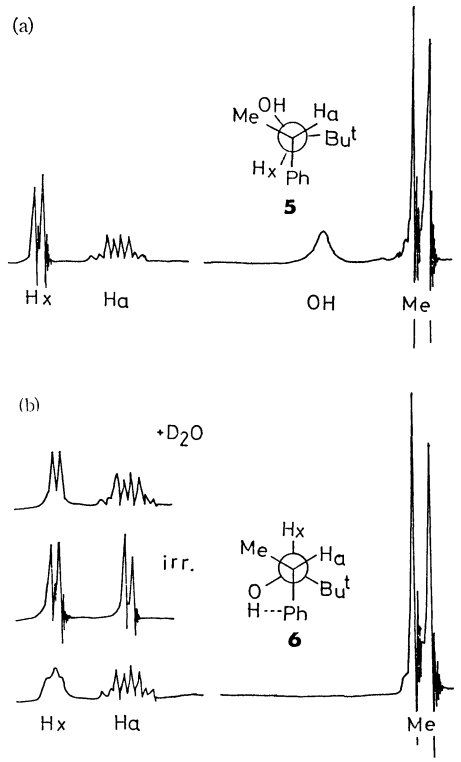


Fig. 8. Proton NMR spectra of **5** and **6** obtained for CCl_4 solutions. See text for inserts.

notations) series, the lower-frequency band is always stronger than the higher-frequency band.[11] It is also suggested by the wave number, as well as by the intensity of the lower-wave-number bands, that the OH/π bonding is strongest in the methyl and gets weaker as the substituent goes to the ethyl and isopropyl.[20] In other words, the OH and the phenyl groups come closer as Group R becomes smaller.

In the *erythro* series, the low-frequency bands are at *ca.* 3610 cm^{-1}. There are two possibilities for the origin of these bands: a weak OH/π bonding, or just a second free OH due to the presence of a OH rotamer in which the hydrogen atom bisects the hydrogen and carbon atoms. If the former is the case, we have to assume the contribution of a conformer with Bu^t/Ph *trans* (see Fig. 3) for **5**. We must reserve our conclusion on this matter until the effects of ring substituents on these low-frequency bands have been studied by performing a standard operational test for the OH/π interaction.[21] (The ν_{O-H} absorptions of these alcohols has already been reported by Sicher *et al.*[11] The present work conforms mostly to their method, but differs in some details because of differences in the resolution of the spectra and the method of the dissection of the doublet bands.)

NMR, GC, and MS Analyses: It has been shown by the above results that a major portion of the hydroxyl group in **6** interacts with the phenyl group, whereas in **5** it is almost free from intramolecular OH/π interaction. This conclusion is supported by an inspection of the NMR spectra. Parts of the proton NMR spectra are given in Fig. 8. The signal appropriate to H_x in **6** appears as a broad peak in both the solvents examined. In contrast, H_x in **5** gives rise to a sharp doublet (spin-coupled only with H_a). This is ascribed to the presence of a further coupling with the hydroxyl proton by H_x in **6**. The broad H_x signal collapsed to a doublet on decoupling (irradiation at *ca.* 130 Hz from TMS, where the broad signal of OH proton was assumed to be present under these conditions) or when the solution was treated with deuterium oxide. Also, the alcoholic hydrogen of **6** could hardly be observed because of the line broadening, while OH in **5** gives rise to a singlet. In the (*RS*/*SR*) isomer the non-bonded alcoholic hydrogen rapidly (at the NMR time scale) exchanges with that in the other molecules, thus giving rise to an observable peak. In the (*SS*/*RR*)-alcohol, on the other hand, the exchange rate is slowed down by the complexation of the hydroxyl group with the π-system, thus resulting in the disappearance of the OH signal.

Further support for the contribution of the intramolecular OH/π interaction in **6** (and its absence in the case of **5**) comes from comparisons of the chromatographic behavior[11] and the mass-fragmentation patterns.[12] Thus, the gas-chromatographic retention time is appreciably shorter for **6** than for **5**.[11] The relative intensity of the molecular ion peak *vs.* the dehydrated ion peak (M^+/M^+-H_2O) is larger for **6** (2.0) than for **5** (0.6). These results can be explained[12] in terms of the presence of OH/π bonding for **6**.

In summary, all of the results point to an unequivocal conclusion that, in the molecules presently studied,

the *t*-butyl group lies *gauche* to the phenyl group.

Discussion

Generality of the gauche *Conformation.* The conformations of **5** and **6** are indeed the consequences of the balance of a number of effects. The interactions involving the hydroxyl group, among others, should be taken into consideration. This seems to be of relatively minor importance in this particular case, however, since, in the (*RS*/*SR*) isomer (**5**), the conformer which lacks the OH/π interaction is found to be preferred. We wish here to emphasize that, in the cases studied thus far (**1**—**6**), the *t*-butyl group is always found to be close to the phenyl group, irrespective of the nature of the X group in the following general structure (Fig. 9) and irrespective of the conditions studied. Moreover, our preliminary data suggest that the above situation (alkyl/Ph *gauche*) holds also in the lower alkyl homologues.[6,22] It, therefore, follows that, in these compounds, an alkyl group has a general tendency to be closer to the phenyl group (or apart from Me) if these groups are present in the molecule.

	1	2	3	4	5	6
X=	SO	SO	S	SO_2	CHOH	CHOH

Fig. 9.

The conformations of molecules have frequently been interpreted in terms of the repulsive forces arising from interaction between nonbonded groups.[23] Such approaches assume that bringing "bulky" groups into proximity leads to unfavorable interactions; the nature of which is generally ascribed to the van der Waals repulsion. However, evidence has been accumulated that this approach does not apply in a number of cases. Thus, the two large groups in a rotamer are very often found to be *gauche* or to eclipse one another, not only in sp^3-sp^3 single-bond systems, but also in most sp^2-sp^3 as well as in certain double-bond systems. To cite only a few cases, it is established that 1,2-difluoroethane and propyl halides prefer a *gauche* rather than an *anti* conformation. Propionaldehyde is known to exist dominantly in the conformation where the methyl group is eclipsed with the C=O double bond. Enthalpy differences in favor of a *cis* over a *trans* isomer are well documented for 1-halopropenes, 1,2-difluoroethylenes, *etc.*[24]

The most impressive of all, however, are probably the cases where such groups as *t*-butyl or trimethylsilyl groups are involved. The examples include *meso*-3,4-dichloro-2,2,5,5-tetramethylhexane (**7**),[25] tetra-*t*-butyldiphosphine (**8**),[26] 1,1,2,2-tetra-*t*-butylethane (**9**),[27] 1,1,2,2-tetrakis(trimethylsilyl)ethane (**10**),[27] and 1,3,5-trineopentylbenzene (**11**)[28] systems (Fig. 10). In all these cases, the bulkiest groups are found to be close to each other in the preferred conformations. It seems, therefore, that this situation (favored *gauche*

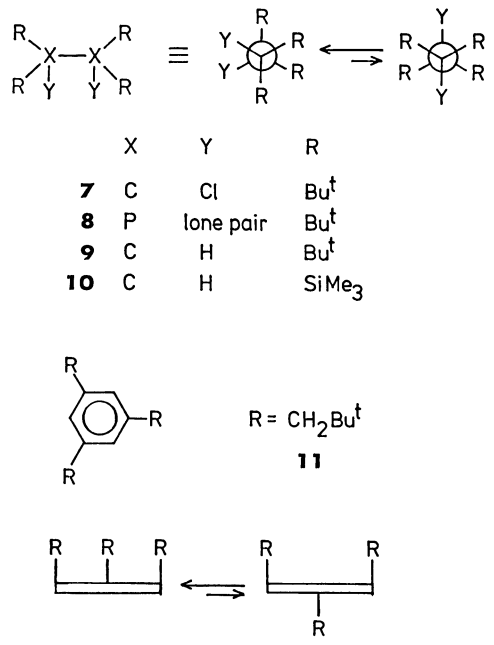


Fig. 10.

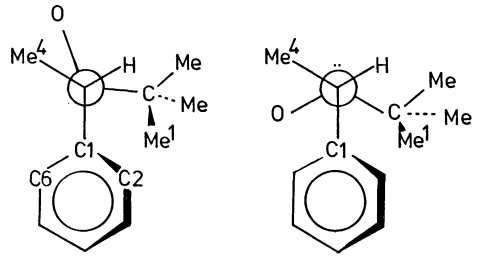
interaction) is a rule rather than an exception.

A number of approaches have been made to account for these "anomalies." The importance of attractive forces between nonbonded groups or atoms was suggested recently, while other workers favor interpretations in terms of repulsive steric effects or a conjugative stabilization (or destabilization) transmitted through bonds.[29] In particular, Carter and his group[28] advanced a concept of attractive steric effects on the basis of their findings regarding the conformational preference of the neopentyl groups in symmetrically substituted trineopentylbenzene systems (**11**). Their suggestion finds support in molecular mechanics calculations,[30] where the origin of the attractive forces is ascribed to London dispersion forces.

In the present case, where the interactions of an alkyl group with a phenyl group are concerned, the same approach will probably not apply, however. In the framework of the traditional approach, *i.e.*, the bulk-repulsive concept, the present result might be explained by regarding the "size" of a phenyl group as effectively smaller than that of a methyl group. A phenyl group is, of course, nonspherical and is capable of relieving the "steric constraint" which might occur in the interaction with the *t*-butyl group by a rotation about the C–C(Ph) bond. This possibility was argued in our earlier papers.[5,6] However, we found recently[31] that benzyl *t*-butyl sulfoxide (**12**) also adopts a conformation (in solution) similar to those established for **1**—**6**. This conclusion is based on NMR (LIS-simulation) evidence. Moreover, the stereospecificity and the stereoselectivities in the diastereotopos-differentiating reactions of **12** can be understood only on the basis of the *gauche* conformation.[32] In short, the preferred rotamer of **12** in solution again suggests that the *t*-butyl group is *gauche* with respect to the phenyl group. Note that in **12** the methyl group is absent. It follows that an interaction other than repulsive Me/Bu^t interaction should also be taken

into consideration.

Possibility of Attractive Alkyl···π-System Interaction; CH/π Interaction Hypothesis. A reexamination of the X-ray data on (*SR/RS*) (**1**) and (*SS/RR*)-1-(*p*-bromophenyl)ethyl *t*-butyl sulfoxide (**2**) (Fig. 1, X=SO) has revealed that a methyl group on Bu^t is oriented so as to be in close proximity to the phenyl ring, the C(Me^1)–C^1 distance being *ca.* 0.33 nm in both compounds (Fig. 11).[33] This is much shorter than the sum of the so-called van der Waals radii of the relevant groups (0.37 nm: 0.20 for a methyl and 0.17 nm for the half-thickness of a benzene molecule). To account for these findings, we recently suggested the importance of an attractive force involving an alkyl and an unsaturated group, namely, CH/π interaction.[31,32] A complexation of the benzene π-system has been known to occur with the acidic hydrogen atom of chloroform[35] or phenylacetylene.[36] For the non-acidic hydrogens of simple alkyl moieties in aliphatic molecules, however, the importance of such an interaction has not yet been suggested.[37]



(α*S*,S*R*)-**1** (α*S*,S*S*)-**2**

Fig. 11. Newman projections for the X-ray crystallographic structures of **1** and **2** (*p*-Br derivatives).

The presence of such a weak interaction has been supported by a semi-empirical MO calculation of a methane/benzene model system.[31] Thus, attractive potential curves were obtained by the CNDO/2 method, where the stabilization energy was estimated to be *ca.* 3.5 kJ/mol at the maximum,[38] the approximate distance between a methane hydrogen (carbon) at this position and the benzene plane being 0.20 nm (0.31 nm: 0.20+0.11). This compares well with the X-ray data cited above.

The magnitude of the interaction energy is very small for a single CH/π bonding. However, a CH group does not generally exist in an isolated state. They are present, more frequently, as parts of an atomic cluster, such as a methyl, ethyl or isopropyl group. It seems, therefore, to be reasonable, in some molecular environments, to expect a simultaneous action of multiple interactions. It might well be that the total interaction energy becomes significant.[39]

The recognition of the above fact would be of help in explaining certain well-known but poorly understood phenomena, especially in the dynamic interaction of reacting molecules. To mention briefly a few examples, it has long been recognized that the extent of asymmetric synthesis is uniformly higher for the phenyl keto esters (R=Ph) than for the methyl keto esters (R=Me) in the Prelog reaction system (Fig. 12).[40a] We suggest that the free-energy level at the competing diastereomeric transition states can be

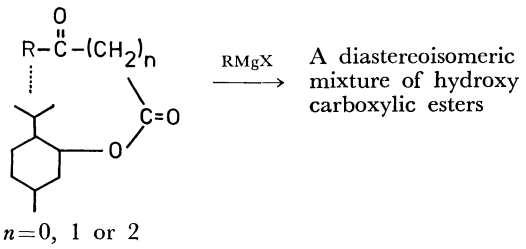


Fig. 12.

affected by an intervention of CH/π complexation. In the case of benzoylformate (R=Ph, n=0), the difference in the activation free energy, $\Delta\Delta G^{\ddagger}$, can be amplified by the interaction of Ph with the chiral aliphatic alcohol moiety (menthol group). Such an effect is absent in the case of pyruvate (R=Me, n=0), where we have a non-π system as R. Similar relationships hold also for the β-keto (n=1) and γ-keto ester (n=2) series.

A similar argument likely applies to the asymmetric reduction of ketones with optically active Grignard reagents (Fig. 13). The data listed in Table 5 are extracted from the works of Mosher and his group.[40b] A significant increase in the optical yield (%e.e.) has been reported when a phenyl group is incorporated in both the substrate and the chiral-reagent part (compare Tables 5a and 5b). In terms of the traditional

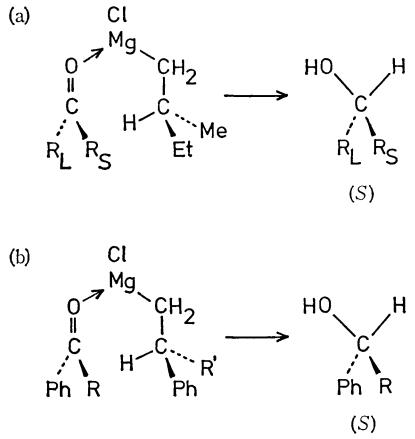


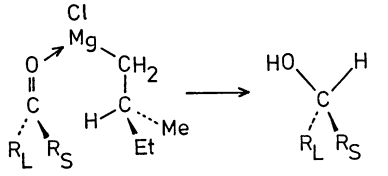
Fig. 13.

bulk-repulsive concept, the optical yield would be anticipated to decrease as the "bulk" of the substituent increases. Quite an inverse trend is observed for all cases, however, where we have a phenyl group in either side of the reacting species (Table 5b and column 3 in Table 5a). The results are comprehensible if one assumes the intervention of an attractive alkyl/phenyl interaction.[32,41] An interaction of this type could well be expected to increase with the number of CH groups in the aliphatic moieties, R and/or R'.

In this respect, the most interesting is probably the recent finding of Endo and his group.[42] In the course of an effort to find the factors controlling chemical reactions, they arrived at a model reaction system. This is composed of the oxidative coupling of a pair of thiols (D-SH and A-SH, Fig. 14) to disulfides. The ratio of the unsymmetrical disulfide over a symmetrical one (r=DSSA/DSSD) reflects the probability of the

TABLE 5. ASYMMETRIC REDUCTIONS WITH OPTICALLY ACTIVE GRIGNARD REAGENTS[a)]

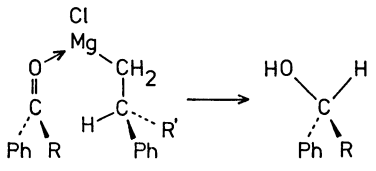
(a)



(S)

$R_S \backslash R_L$	Bu^t	c-C_6H_{11}	Ph[b)]
Me	13	4	4% e.e.
Et	11	9	6
Pr^n	11	9	6
Pr^i	0	2	24

(b)



(S)

R\R′	Me	Et	Pr^i
Me	38	47	—
Et	38	52	66
Bu^t	—	53	—
Pr^i	59	82	80

a) (*S*)-alcohols obtained in excess. *Cf.* Tables 5.6 and 5.7 in Ref. 40. b) See also G. P. Giacomelli, R. Menicagli, and L. Lardicci, *Tetrahedron Lett.*, **1971**, 4135; R. Kretchmer, *J. Org. Chem.*, **37**, 801 (1972).

molecular recognition between the interacting species. The recognition has been found to be most selective when an isopentyl group is introduced as the alkyl substituent (R) in the A-SH molecule (r=21.2, but it gradually decreases on going from i-C_5H_{11} to i-C_6H_{13} and then to i-C_7H_{15} group). Such a remarkable dependence of the selectivity on the structure was not observed for A-SH where a series of straight-chain alkyl groups were used as R. An inspection of the CPK molecular models suggests that the complexes of the reacting species may well be stabilized by the CH/π type interaction; with the aromatic part of the D-SH molecule (dimethylaminophenyl group), the interaction is possible if we have an alkyl group as R in A-SH. This might be expected to be most selective when the R is a branched one and has an appropriate length (Fig. 14b).

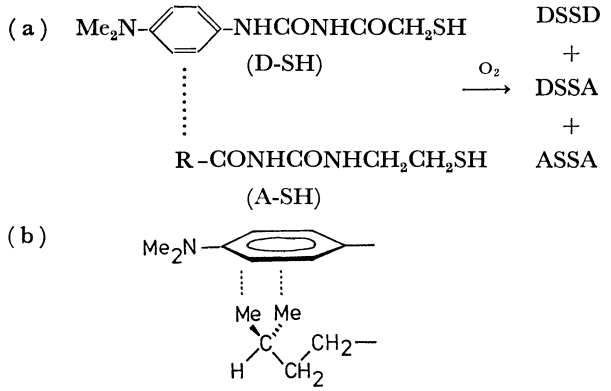


Fig. 14.

We wish to take this opportunity to point out the possibility that a weak interaction of such a kind plays an important role in determining the 3-D structure and the specificity of some globular proteins. These include enzymes, hemoglobins, or immunoglobulins.[43)] As has been emphasized by Watson,[46)] the secondary forces involved in the specific biopolymer interactions should never be too strong. Instead, they should be moderately weak, thus making it possible to assume a rapid recombination of biochemically important molecules (and therefore to be compatible with the cellular existence). Our knowledge about the weak chemical interactions is, however, still very incomplete.[46)] To be a candidate for these forces an interaction must be weak and also have the proper steric requirements. In addition to this, the groups involved in a weak secondary force used in biological devices must be widely distributed in nature. All of the prerequisites are fulfilled by the CH/π interaction—it is weak enough and orientation-dependent. Simple aliphatic groups are so abundant that we can find these moieties in virtually all components of natural sources. As to the abundancy of the groups, we will cite here the case of amino acid: both the aliphatic residues (Ala, Val, Leu, Ile, Met) and the aromatic ones (Phe, Tyr, Trp, His) are commonly found in proteins.

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3) Present address: Institute for Molecular Science, Myodaiji, Okazaki 444.

4) The correct sequence rule symbols for these configurations are (α*S*,S*R*/α*R*,S*S*), (α*S*,S*S*/α*R*,S*R*), (3*R*,4*S*/3*S*,4*R*), and (3*S*,4*S*/3*R*,4*R*) respectively for **1**, **2**, **5**, and **6**. Abbreviated notations are used in the text for the sake of brevity.

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39) It might be that this type of interaction (CH_3/π and CH_3/X, X=O or N) is entropically advantageous in that the chance for the interaction increases upon a clustering of CH groups into certain arrangements. We wish to refer this concept (a multiple as well as a chance effect) to the "isopropyl effect," the implications of which will be discussed elsewhere (M. Nishio and T. Endo, to be published; *cf.* Ref. 34).
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