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CH/π INTERACTION: IMPLICATIONS IN ORGANIC CHEMISTRY†

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CONTENTS

† This paper is dedicated to Professor Sir Derek Barton, the founder of the concept of conformation in organic chemistry, on the occasion of his 70th birthday.

1. INTRODUCTION

For the past few decades, organic chemists have been inclined to consider that a molecule is more stable in an extended conformation (or a conformation having the bulkiest groups remotest to each other) rather than in a folded one.

The reason for this trend in thinking finds its origin in the success of Cram's and Prelog's rules. These rules predicted correctly the predominant diastereoisomer produced by hydride reductions of chiral aldehydes and ketones,[1] and the absolute configurations of chiral alcohols.[2] In order to determine the preferred face of attack, both models assume that the bulkiest of the substituents (L) is locked in the plane of the carbonyl group so that the reagent can select the smaller of the remaining two groups (M and S, in Fig. 1). As a consequence, the conformation with the bulkiest group in the most remote position is assumed to prevail. The original authors made no pretence, however, that the models were accurate descriptions of the real transition state.[3] The tendency of most organic chemists for the 'bulk-repulsive approach' was fortified by the brilliant success of Barton,[4] who explained the stereochemical properties of steroids. Barton's paper introduced the concept of conformation in chemistry and founded conformational analysis, an important field of theoretical organic chemistry.

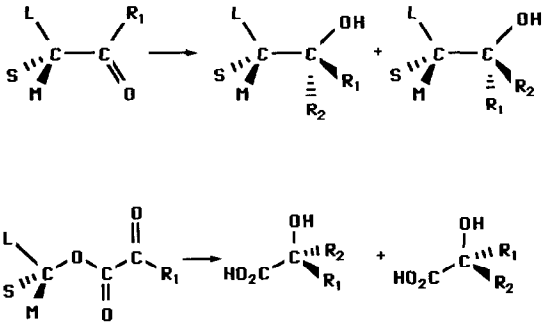


Fig. 1. Cram's and Prelog's rules.

As a result of recent progress in spectroscopic methods and computer techniques, it has become clear that bulkier groups in an organic compound may prefer to approach each other in certain molecular environments. In particular, Carter and his coworkers provided evidence by NMR,[5,6] X-ray,[7] and force–field calculations[8] that 1,3,5-trineopentylbenzene adopts a more favoured conformation with its three *t*-butyl groups on the same face of the aromatic ring. In compounds with a common structure of $C_6H_5CHMe\text{-}X\text{-}Bu^t$, we found that the *t*-butyl group is oriented synclinal to the phenyl and antiperiplanar to the methyl, irrespective of the nature of the group X (Fig. 2).

The generality of the phenomenon was then explored for other molecules. It was found that the *synclinal alkyl/phenyl conformations are common for compounds bearing a smaller alkyl group in* place of *t*-butyl. It appears that the folding tendency of the chain is general for a wide variety of aliphatic molecules. In this report we summarize the results obtained through our recent researches, survey reports scattered in the literature, discuss the interactions involved, and consider the consequences. Evidence will be presented that a weak hydrogen-bond-like interaction, which we have named the CH/π interaction, is important in understanding the conformational behaviours of organic molecules. These include the anomalies observed in conformations and the optical properties of several terpene compounds which have remained unexplained.

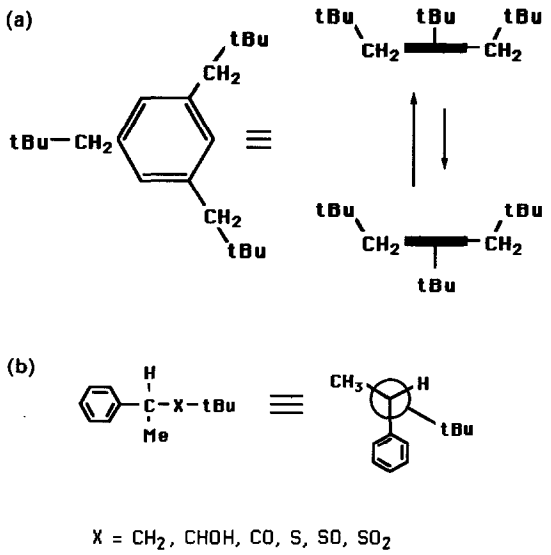


Fig. 2. Preferred conformations of 1,3,5-trineopentylbenzene (a) and Ph–CHMe–X–Bu^t (b).

2. PREFERENCE OF FOLDED CONFORMATIONS IN CERTAIN ACYCLIC MOLECULES

2.1. *Transition states of* 1,2-*asymmetric induction*

In an extension of 1,2-asymmetric induction (Cram's open chain model),[1] we have studied the effect of variation of the group R on the stereochemical outcome in the peroxyacetic acid oxidation of a series of sulphides, PhCH(Me)-S-R[9] (**1**, Fig. 3). The stereoselectivity of the reaction varied from 3.1 for Me, 3.2 for Et, and 3.5 for Pr^i, to 49 for Bu^t. The results are discussed in terms of a reactant-like transition state,[10] where the preponderance of the alkyl (R) and phenyl contiguous conformer was assumed. The variation in the product ratio (*threo* : *erythro*†) was suggested to reflect the difference in the conformational energy of the relevant rotamers[11] (Fig. 3 **1a**, **1b** and **1c**) involved in the transition state.

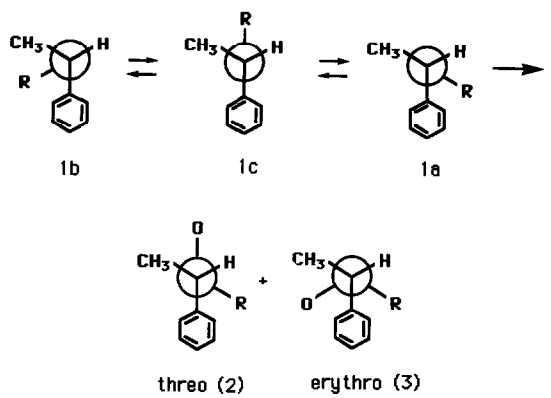


Fig. 3. Oxidation of alkyl 1-phenylethyl sulphides to diastereomeric sulphoxides.

† In order to avoid confusion, *threo*/*erythro* notation is used. The nomenclature by the sequence rule does not correlate the stereochemically corresponding structures. Thus α(*R*)*S*(*S*)/α(*S*)*S*(*R*)-**2**(R = Bu^t) corresponds configurationally to α(*R*)*S*(*R*)/α(*S*)*S*(*S*)-**2**(R = Me, Et, Pr^i).

In early stages of the study, we considered that the conformer in which the alkyl (R) and the phenyl groups are antiperiplanar to each other (rotamer **1c**) was preferred in the reaction mixture (a case of bulk-repulsive approach).[12] The sulphoxide diastereoisomer which was preferentially produced was therefore expected to have the *erythro* (**3**) configuration rather than *threo* (**2**)[12,13] (Fig. 3).

The above presumption was not, however, compatible with the spectroscopic identification of the diastereomeric sulphoxides. The results obtained by LIS (lanthanide-induced NMR chemical shift) measurements suggested the inverse assignment. X-ray crystallographic analyses established that the above configurational assignments were in error.[14,15]

To our great surprise, it was found that both of the diastereoisomeric sulphoxides adopted in their crystal structures synclinal conformations with respect to the bulky *t*-butyl and phenyl groups. The solution conformations of the sulphoxides were then studied extensively by means of NMR,[15] CD,[15] and measurement of dipole moments.[16] All of the results could be explained reasonably if we assumed that the synclinal *t*-butyl/phenyl conformation was maintained in solution, not only for the sulphoxides but also for the sulphides. Molecular force–field calculations supported this.[11] Thus, by analogy, the trends observed in the product ratios of the hydride reductions of the chiral ketones (**4**), reported by Cherest *et al.*[10] could be understood on a similar basis. An alkyl/phenyl synclinal conformer is predominant in the transition states of these reactions[11] (Fig. 4).

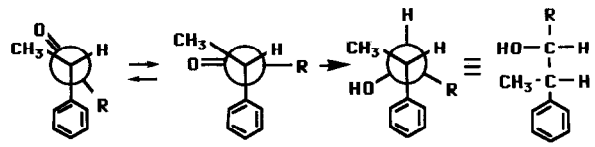


Fig. 4. Hydride reduction of alkyl 1-phenylethyl ketones.

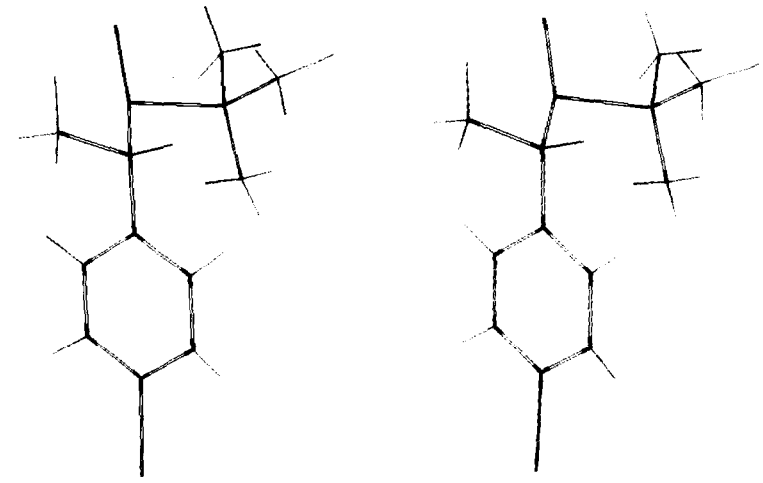
2.2. *Conformations of several sulphoxide diastereoisomers*

2.2.1. *X-ray crystallographic analyses.* Figure 5 illustrates the molecular structures of 1-(*p*-bromophenyl)ethyl *t*-butyl sulphoxide (**5**) with (*SR*)[14] and (*SS*)[15] configurations.† In both of the

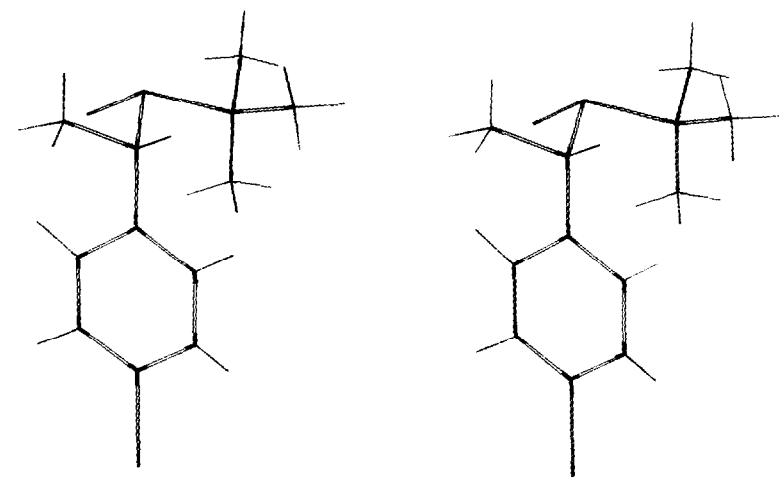
Table 1. Some interatomic distances (d) in (SR)- and (SS)-1-(p-bromophenyl)ethyl t-butyl sulphoxides (5)

Atoms	d/nm	
	(SR)-5	(SS)-5
C(1)-C(Me2)	0.324	0.332
C(2)-C(Me2)	0.368	0.374
C(6)-C(Me2)	0.361	0.361
O-C(Me4)	0.295	0.318

† The correct sequence-rule symbols for these diastereoisomers are $\alpha(S)S(R)$ and $\alpha(S)S(S)$, respectively. However, the abbreviated notations are used throughout the text for brevity.



(a)



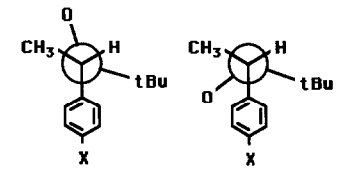
(b)

Fig. 5. X-ray crystallographic structures (stereo view) of *t*-butyl 1-(*p*-bromophenyl)ethyl sulphoxides with (a) (*SR*) and (b) (*SS*) configurations.

diastereoisomers, the *t*-butyl group is found to be positioned synclinal to the phenyl and antiperiplanar to the methyl group. Furthermore the phenyl group rotates about the phenyl connecting bond in order to present its smallest van der Waals dimension to a methyl group (Me-2) of the *t*-butyl group.

Table 1 lists some of the interatomic distances. The distance from Me-2 to C(2) equals that from Me-2 to C(6). Of interest is the fact that Me-2 is in quite close contact with a carbon atom of the phenyl ring (C(1)). It is also noteworthy that the benzylic methyl (Me-4) is close to the sulphoxide oxygen.

Figure 6 shows Newman projections of both isomers. The O–S–C–C(Ph) dihedral angles for (*SR*)-**5** and (*SS*)-**5** are 192° and 310°, respectively.



X = Br (SR)-5 X = Br (SS)-5

X = H (SR)-6 X = H (SS)-6

Fig. 6. Newman projections of the conformations of (*SR*)-**5** and (*SS*)-**5** from X-ray crystallography.

In order to find out whether these compounds adopt a similar conformation in solution, the spectral properties and the dipole moments of the relevant molecules were studied.

2.2.2. *Nuclear magnetic resonance data.* Table 2 lists some of the NMR parameters of these compounds.[9] The data in Table 2 can be consistently interpreted by assuming that the predominant conformers in solution resemble those illustrated in Fig. 6. Thus benzene-induced shifts (ASIS) larger than in the (*RR*)/(*SS*) isomer were observed for both CH and Me signals of the (*RR*)/(*SS*)-isomer whereas greater LISs were recorded for the CH and Me signals in the (*RS*)/(*SR*)-sulphoxide. The peaks attributed to the *ortho* protons (*o*-H) in the aromatic ring of the (*RR*)/(*SS*)-isomer are more sensitive to the addition of the shift reagent.

Table 2. ASIS and LIS of some protons in (RS/SR)- and (RR/SS)-5

	(RS/SR)-5			(RR/SS)-5		
	CH	Me	o-H	CH	Me	o-H
ASIS[a]	+0.31	+0.10	-----	+0.43	+0.27	-----
LIS[b]	-2.15	-2.22	-0.71	-0.91	-1.26	-1.24

a) $\delta(CCl_4)$ - δ(benzene).

b) Shift observed in CCl_4 containing a 0.2 equivalent of $Eu(fod)_3$.

2.2.3. *Optical properties.*[15] An optically active isomer of the *para* non-substituted sulphoxide, (*SR*)-**6** (*threo*), showed a CD curve with a negative Cotton effect. Its diastereoisomeric congener (*RR*)-**6** (*erythro*), on the other hand, displayed a positive Cotton effect at the corresponding wave length in the same solvent (Table 3). The configurations at sulphur of these compounds are the same. These results can be understood if it is assumed that the relative spacial orientation of the sulphoxide chromophore with respect to the strongly perturbing phenyl group is different in these diastereoisomers. This is also what we observed in the crystal conformations of the *p*-bromo derivatives (**5**) [O/Ph antiperiplanar in (*RS*)/(*SR*) and synclinal in (*RR*)/(*SS*)-isomer].

2.2.4. *Dipole moments.*[16] Table 4 lists the dipole moments of the sulphoxide diastereoisomers substituted at the *para*-position of the phenyl ring. The substituent effect in (*RS*)/(*SR*) (*threo*) series is anomalous in that the dipole moment decreases at first and then increases, on replacement of the substituent from H to Br and then to NO_2. The group moment of the substituent increases in this

Table 3. CD characteristics of (SR)- and (RR)-1-phenylethyl t-butyl sulphoxides (6)

Solvent	λ/nm ([θ])	
	(SR)-6	(RR)-6
Ethanol	226 (-78550)	231 (+51800)
Isooctane	239 (-87900)	240 (+21300)
$[\alpha]_D$(ethanol)	-163°	+211°

order. This phenomenon can be understood if the angle between the C–X and S–O bonds is larger than a right angle as was found in the X-ray crystallographic structure of the *p*-bromo derivative of the (*RS*)/(*SR*) isomer. The calculations well reproduced the experimental data (Table 4).

Table 4. Dipole moments of 1-(p-X-phenyl)ethyl t-butyl sulphoxides

X	(RR)/(SS)		(RS)/(SR)	
	μ obsd.	μ calcd.	μ obsd.	μ calcd.
H	3.84	3.75	3.86	3.46
Br	4.23	4.23	3.42	3.28
NO_2	5.69	5.91	4.26	4.10

2.2.5. *Computer simulation of the LIS data.*[17,18] In order to know more about the solution conformations, we carried out a simulation of the LIS of these sulphoxides, together with lower alkyl homologues.

Thus a computer programme was written in which the LIS of each nuclei (^1H and ^{13}C) for an assumed conformation could be calculated.[17] We adopted the approximations usually made in such studies:[19–21] that is, (i) we used the McConnell–Robertson equation (eqn. 1) for an axially symmetric dipolar field (neglecting the non-axial term) where r_i is the length of a vector joining the paramagnetic centre and the ith nucleus (N_i), and χ_i is the angle between this vector and the principal magnetic axis; (ii) we assumed that the conformation of the substrate can be described by a single set of coordinates; and (iii) for the nuclei of the methyl, *t*-butyl, and aromatic groups, we calculated and

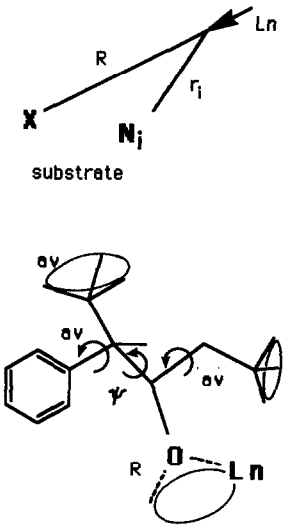


Fig. 7. Procedure for the simulation of LIS.

then averaged the contributions of the individual atoms in a number of conformations. Figure 7 is a brief illustration of this procedure

$$(\mathrm{LIS})_i = K(3\cos^2\chi_i - 1)/r_i^{-3}. \quad (1)$$

Input data were the geometrical parameters of the sulphoxides and the experimental LISs. After several trials, the lanthanide(Ln)–O–S angle was fixed at 120°. The Ln–O distance (R) and the C(phenyl)–C–S–O dihedral angle (ψ) were then varied, step by step, at a given Ln-distribution parameter, in search of a reasonable fit of the computed LISs with the observed ones. The Hamilton reliability factor, AF,† was used to assess the agreement between the calculated and the observed LIS sets. The calculated shifts were normalized to the average experimental LIS in the computational process.

Figure 8 illustrates the plot of the AF against the O/Ph torsional angle obtained for (*RS*)/(*SR*)-

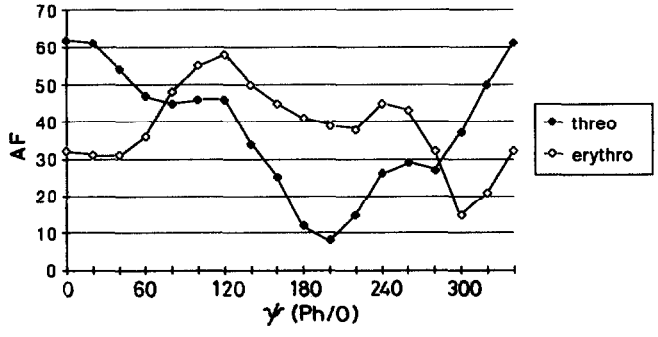


Fig. 8. Plot of AF vs. the O/Ph dihedral angle (ψ) for (*SR*)/(*RS*) and (*RR*)/(*SS*) *t*-butyl 1-phenylethyl sulphoxides. The Ln–S–O angle, Ln-distribution index (A), and Ln–O distance (R) are kept constant at 120°, 0.8, and 0.34 nm, respectively.

† The Hamilton reliability factor is often called agreement factor and defined by the following equation,[29]

$$\mathrm{AF} = [\Sigma(\mathrm{LIS}^{\mathrm{obsd}} - \mathrm{LIS}^{\mathrm{calcd}})^2/\Sigma(\mathrm{LIS}^{\mathrm{obsd}})^2]^{1/2}.$$

6 (*threo*) and (*RR*)/(*SS*)-**6** (*erythro*). Good agreement (minimal AF) was observed at ca. 200° for the (*RS*)/(*SR*) isomer and at ca. 300° for the (*RR*)/(*SS*) one. These torsional angles agree sufficiently well with those determined by X-ray study [(192° and 310°, respectively, for (*RS*)/(*SR*) and (*RR*)/(*SS*)-**5**, Figs 5 and 6]. These results demonstrate that the conformations in the crystal state are the consequence of the intramolecular interaction and that perturbation of the conformational equilibria by the complex formation is unimportant in this case.

It should be noted that the AF values correspond to the reliability maxima (the present model assumes that there is a unique solution for ψ), and by no means indicate the energy minima of the respective rotamers. In this regard, it is noteworthy that the second minimum is seen at ψ ca. 280° for the (*RS*)/(*SR*) sulphoxide and ca. 40° for the (*RR*)/(*SS*) isomer. This suggests that there is an appreciable contribution from the second stable rotamer, the approximate geometry of which corresponds to the above data (Fig. 9a).

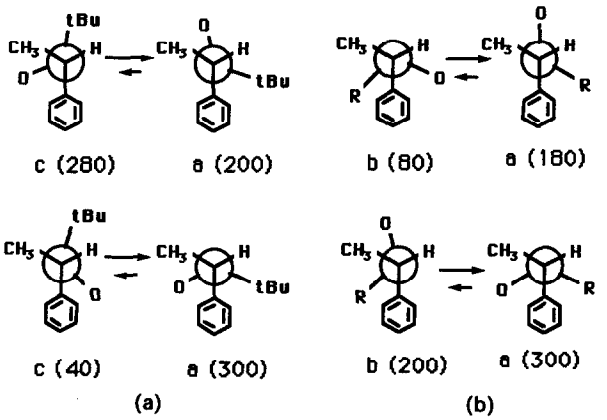


Fig. 9. Possible conformations and the order of the rotameric stability (from LIS) for alkyl 1-phenylethyl sulphoxides.

Essentially the same conclusion was reached for the lower alkyl homologues. Thus inspection of the AF-profiles suggested that the alkyl group is synclinal to the phenyl and antiperiplanar to the methyl group in the most preferred rotamers, irrespective of the nature of R and irrespective of the configuration at sulphur. However, in these cases we also found second minima at ψ ca. 80° and 200°, respectively, for the (*RR*)/(*SS*) (*threo*) and (*RS*)/(*SR*) (*erythro*) sulphoxides. Newman projections in Fig. 9b illustrate the rotamers which correspond to these values: in these conformations (rotamer **b**) the alkyl group is flanked by the phenyl and by the methyl groups.

2.2.6. *γ-Gauche effect.* Support for the above suggestions is provided from consideration of the ^{13}C γ-effect[22–27] (Table 5). The peaks assignable to the benzylic methyl carbon atoms are significantly shifted to higher magnetic fields in sulphoxides.[18] This is attributed to the γ-gauche effect. For *t*-butyl sulphoxides, in view of the differing geometrical disposition of the S–O oxygen with respect to the benzylic methyl group, the γ-effect is expected to be more pronounced for the *threo* isomer (O/Me torsional angle ca. 50° and O/C distance 0.295 nm; see Fig. 6 and Table 1) than for the *erythro* isomer (O/Me torsional angle ca. 70°, O/C distance 0.318 nm).[15] The figures in Table 5 ($\Delta\delta$ −1.8 ppm) support this. This result can also be understood in terms of the involvement of the second stable rotamer in the conformational equilibria of the sulphoxides. Thus the oxygen atom is close to the methyl in rotamer **c** of the *threo* sulphoxide, whereas in rotamer **c** of the *erythro* isomer, the oxygen atom is remote from the methyl group (Section 2.2.5., Fig. 9a). In contrast, the

Table 5. ^{13}C Chemical shifts[a] of 1-phenylethyl alkyl sulphides and sulphoxides C_6H_5CHMe-X-R

R	X	S	SO(thr)	SO(ery)	$\Delta\delta$[b]
Me		22.0	15.6	13.0	+2.6
Et		22.5	16.1	14.1	+2.0
i-Pr		23.0	16.4	----	----
t-Bu		25.3	17.8	19.6	-1.8

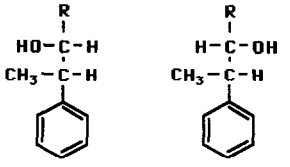
a) For benzylic methyl; ppm downfield from internal TMS in CCl_4.

b) δ(threo) - δ(erythro).

methyl carbon peaks appear at higher magnetic fields for the *erythro*-sulphoxides in lower alkyl homologues (Table 2). This is reasonable, since, in these cases, the sulphoxide oxygen is closer to the methyl in the second stable rotamer of the *erythro* isomer as compared with that of the *threo* one. The situation in the most preferred rotamer is almost the same for both diastereoisomers (see Fig. 9b).

2.3. *Conformations of several alcohols and ketones*

2.3.1. *Conformations of 1-substituted 2-phenyl-1-propanols.*[28,29] In order to explore the generality of the phenomenon, we then studied the conformational equilibria of *erythro* and *threo* 1-alkyl-2-phenylpropanols, MeCH(Ph)CH(OH)R (**7** and **8**, respectively), which are structurally related to the sulphoxides described in the previous section.†



erythro (7) threo (8)

In Fig. 10 are given the AF-profiles plotted against the R/Ph dihedral angle (ϕ) for each of these alcohols.[29] It is noted that these profiles display, in every case, three distinct minima at ϕ around the staggered geometries of the groups. It is likely that the location of ϕ and the goodness of fit at the respective minimum reflect, though in an indirect manner, the probable geometries of the substrates and the relative importance of the rotamers.

† The *erythro*[(*RS*)/(*SR*) when R = Bu^t or (*RR*)/(*SS*) when R = Me, Et, and Pr^i]-alcohols correspond configurationally to the *threo*-sulphoxides and vice versa.[29] See Figs 3 and 4.

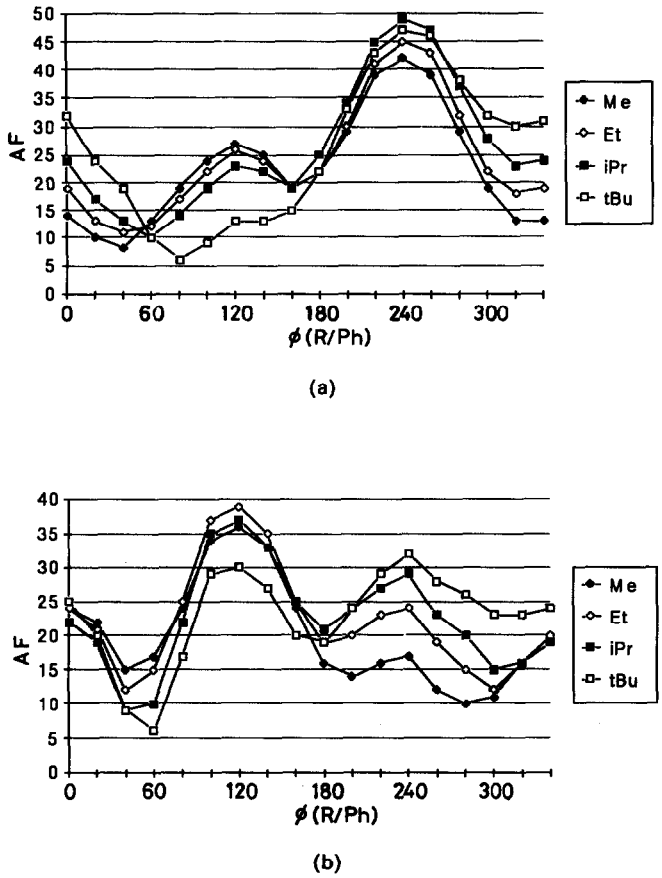


Fig. 10. Plot of AF vs. the R/Ph dihedral angle (ϕ) for (a) *erythro* and (b) *threo* 1-substituted 2-phenylpropanols. The Ln–O–C angle, Ln distribution index (A), and Ln–O distance (R) are kept constant at 130°, 0.8, and 0.30 nm, respectively.

The possibility that complexation perturbs the rotameric equilibria of these alcohols can be excluded since the vicinal coupling constants, $^3J_{HH}$, remained unchanged by the addition of the lanthanide species.

The shapes of the profiles suggest that the alkyl group approaches the phenyl group in the preferred conformation (rotamers **a** and **b**). Rotamer **c** (R/Ph antiperiplanar) seems to be least important, except for the *t*-butyl derivatives. The stability of the rotamer **b** seems to increase progressively on replacement of the alkyl group with a smaller one. Thus in (*RS*)/(*SR*)-3-phenyl-2-butanol (**8**, R = Me) (*threo* configuration), the most favoured conformation is suggested to have the alkyl (Me) group flanked by the benzylic methyl and the phenyl groups (rotamer **b**).

Figure 11 summarizes the results. Note that the relative importance of the rotamers **a**, **b**, and **c** varies in order of the bulkiness of the alkyl substituent, R. Consideration of the $^{13}C\gamma$-effect,[29] the NMR line shapes,[28,29] the vicinal coupling constants,[29] and the IR spectral data[28,30] support the above trends of conformational preference.

2.3.2. *Conformations of* 1-*substituted* 2-*phenylethanols.* In order to see the effect of the presence of a benzylic methyl group on the rotameric equilibria, the conformations of 1-substituted 2-

		ERYTHRO						*THREO*					
													
		a (φ ~ 60°)		c (180°)		b (300°)		a (φ ~ 60°)		c (180°)		b (300°)	
LIS	Me	a	>	b	>	c		b	>	a	~	c	
	Et	a	>	b	≳	c		a	~	b	>	c	
	i-Pr	a	>	c	≳	b		a	>	b	>	c	
	t-Bu	a	>	c	>	b		a	>	c	>	b	
EFF	Me	a	>	c	≳	b		a	≳	c	>	b	
	Et	a	>	c	>	b		a	>	c	>	b	
	i-Pr	a	>	c	>	b		a	>	c	>	b	
	t-Bu	a	>	c	>	b		a	>	c	>	b	

Fig. 11. Possible conformations and the order of the rotameric stability (from LIS) for 1-substituted 2-phenylpropanols. The results from the force-field (EFF) calculations (Table 7) are also given for comparison.

phenylethanols[31] (**9**) were studied by the use of the same method. Possible conformations and the proposed order of the rotameric stability are summarized in Fig. 12.

For the lower alkyl homologues, the rotamers (**a** and **b**) which bear the synclinal alkyl/phenyl groups have been suggested to be more favourable energetically than the antiperiplanar one (rotamer **c**). Benzyl *t*-butyl carbinol was the only exception, where the alkyl/phenyl antiperiplanar rotamer (**c**) has been demonstrated to be most populated.

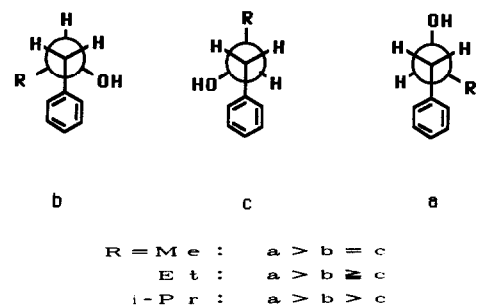


Fig. 12. Possible conformations and the order of the rotameric stability (from LIS) for 1-substituted 2-phenylethanols.

2.3.3. *Conformations of alkyl 1-phenylethyl ketones.* The AF-profiles obtained for this type of compound MeCH(Ph)COR[32] (**10**) are illustrated in Fig. 13. It has been suggested that two types of conformers (**a** and **a'**) are populated in the conformational equilibria of the ketones; the relative importance of the rotamers **a** and **a'** seems to vary in order of the bulkiness of the alkyl substituent. It should be noted that in both of the favoured rotamers, the Me/O torsional angle is ca. 30°.

The results are summarized in Fig. 14. It is impressive that there does not seem to exist any stable rotamer which corresponds to conformation **c** (R/Ph antiperiplanar).

2.4. *Conformations of several alkylbenzenes*

Conformations of *n*-propylbenzenes have been discussed in several papers.[33,34] Hopkins *et al.*[34] observed the presence of two origins in the time-of-flight mass spectra but could not assign them to

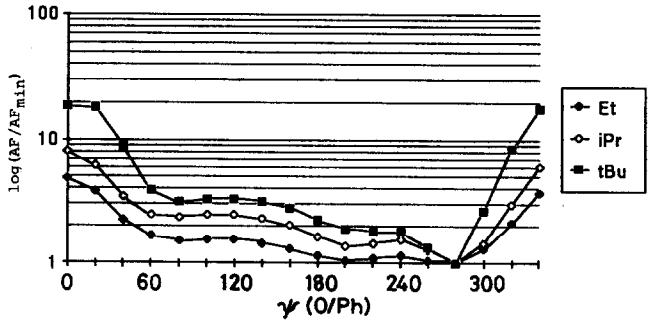
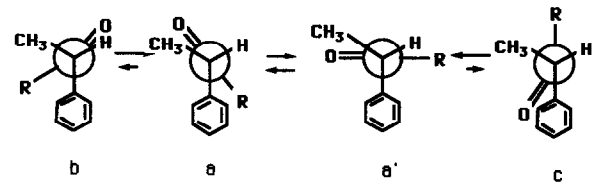


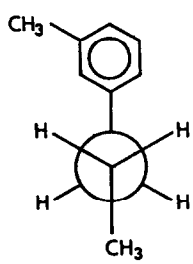
Fig. 13. Plots of the logarithm of relative AF [log (AF/AF_{min})] vs. the O/Ph dihedral angle (ψ) for 2-phenyl-3-pentanone, 2-methyl-4-phenyl-3-pentanone, and 2,2-dimethyl-4-phenyl-3-pentanone. The Ln–O–C angle, Ln distribution index (A), and Ln–O distance (R) are kept constant at 140°, 0.4, and 0.32 nm, respectively.



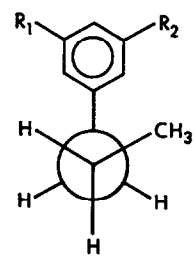
R = H : a > a ' > b ≫ c
Me : a ≳ a ' > b ≫ c
Et : a ' ≳ a > b ≫ c
i-Pr : a ' > a > b ≫ c
t-Bu : a ' ≫ a > b ≫ c
Ph : a ' ≫ a > b ≫ c

Fig. 14. Possible conformations and the order of the rotameric stability (from LIS) for alkyl 1-phenylethyl ketones.

either antiperiplanar, synclinal, or synperiplanar conformer. Seeman and coworkers[33] showed recently by supersonic molecular jet spectroscopy that 3-*n*-propyltoluene exists as *trans* (**11a**), *syn*-gauche (**11b**), and *anti*-gauche (**11c**) conformers. Thus the presence of a CH/π contiguous conformer was proven with an aromatic hydrocarbon carrying an aliphatic side chain.



(11a)



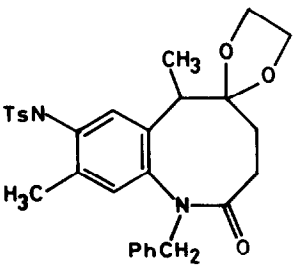
(11b) R_1=H; R_2=Me
(11c) R_1=Me; R_2=H

2.5. *Generality of folded conformations*

A literature survey has been carried out to determine whether the folded conformer in which bulkier groups approach each other is favoured or not. A few examples are presented here but they are not intended to constitute a comprehensive review.

2.5.1. *Alkyl/π-system interactions.* Danyluk studied the conformation in solution of an anti-malarial chloroquine, and found that the three dimensional structure of this compound is very compact with the alkyl side chain curled over the plane of the quinoline ring.[35]

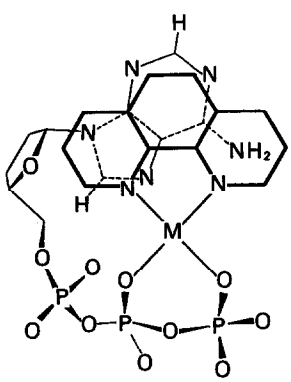
Ban and coworkers found by X-ray that a methyl group in a pair of conformational isomers of an eight-membered lactam (**12**) is oriented very close to a benzene ring in the molecule.[36] Yoshikawa *et al.* suggested that an isopropyl/phenyl group approached conformer is involved in an optical activation process of 3-(*p*-cumyl)-2-methylpropionaldehyde.[37]



(12)

Further, Sigel,[38–40] Okawa,[41–46] Miyoshi[47,48] and their coworkers studied the conformations of a variety of mixed-ligand metal complexes (**14** of Section 3.2.1.), and found that these molecules adopt conformations in which an alkyl group approaches an aromatic group. Kopple,[49,50] Webb,[51] and their coworkers reported the preference of folded conformations for a series of cyclic dipeptides where one of the amino acid-residues is an aromatic one. Preferences of the folded conformation were also reported in the cases of several tripeptides[52] and a nonapeptide (a bradykinin derivative).[53,54] The isobutyl group in a leucine residue of an antibiotic ilamycin (a cyclic hepta-peptide) was reported to position itself above the plane of an aromatic group in the molecule.[55,56] Further, it is known that Leu 17 and Met 105 residues in lysozyme are surrounded by aromatic groups (Leu 17 by Trp 28 and Tyr 20, and Met 105 by Trp 28, 108, 111, and Tyr 23).[57,58]

2.5.2. *Aryl/aryl interactions.* Sigel and his group extensively studied a series of metal complexes (**13**) and reported that these molecules adopt preferentially the conformations whereby the aromatic groups approach each other.[59–65]



(13)

Cyclic tetradecapeptides (somatostatin and derivatives),[66-69] certain flavinyl peptides,[70,71] and nicotinamide–adenine dinucleotide and its analogues[72-79] are reported to be stable in folded conformations in solution.

In an extensive NMR and X-ray study concerning the conformations of acyclic compounds, Engberts and his coworkers established the preference of the folded conformations in a variety of compounds. The examples include benzyl phenyl sulphones and sulphoxides,[80-82] *p*-dimethylaminophenyl-N-(arylsulphonylmethyl)-N-methylcarbamates,[83-85] and N,N′-[bis(α-tosylbenzyl)]urea.[86,87]

Dibenzyl[88] and 1,2-diphenylpropane[89] have been reported to be stable in aromatic/aromatic folded conformations rather than in the extended conformations. 1-Phenylethyl aryl sulphoxides, sulphones, carbinols, ketones and some structurally related benzyl derivatives were also found to be stable in synclinal conformations.[90,91]

The conformations of 2-arylethyl *p*-toluenesulphonates,[92,93] (N-substituted benzyl)anilines,[94,95] arylalkyl 2,4,6-trinitrobenzoates,[96-98] 10-benzylanthrones,[99] cyclic isopropylidene acylals,[100] 3-benzylpiperazine-2,5-diones,[101] and 5-benzyl-3-arylhydantoins[102,103] have been studied. All of them were shown to adopt folded conformations preferentially.

2.5.3. *Alkyl/alkyl interactions.* Evidence has been presented that neopentyl and *t*-butyl groups are more stable in crowded situations, such as in 1,3,5-trineopentylbenzene[5-8] and 1,6-di-*t*-butylcyclooctatetraene.[104]

The synclinal conformations were reported to be more stable than the antiperiplanar conformations in *meso*-3,4-dichloro-2,2,5,5-tetramethylhexane,[105] tetra-*t*-butylphosphine,[106-109] sym-tetra-*t*-butylethane,[110,111] sym-tetra-*t*-butyldisilane,[112,113] sym-tetra(trimethylsilyl)ethane,[110] sym-tetracyclohexylethane,[114] *meso*- and racemic 3,4-dicyclohexyl-2,2,5,5-tetramethylhexane,[114] and racemic 3,4-di(cyclohexen-1-yl)-2,2,5,5-tetramethylhexane.[114]

Table 6. Populations of the conformers of n-octane by molecular mechanics

Conformer[a]	Relative energy kcal mol^{-1}	Abundance %
A A A A A	0.00	17.9
A A A A G^+	0.88	16.2
A A A G^+A	0.92	15.2
A A G^+A A	0.90	7.8
A A G^+G^+A	1.57	5.0
A A A G^+G^+	1.59	5.0
A A G^+A G^+	1.71	4.0
A G^+A A G^+	1.78	3.6
A G^+A A G^-	1.79	3.5

a) A and G refer to antiperiplanar and synclinal conformations, respectively.

Favoured alkyl/alkyl approached conformations are quite general even in saturated aliphatic hydrocarbons. The very straight chain alkanes exist to a large extent in folded conformations in

which two or more of their fragments lie close together. Estimated populations of the conformers of *n*-octane[115] revealed that the all-anti conformer population is less than 20% (Table 6). The rest of the conformers take folded conformations around more than one of the internal C–C bonds. This behaviour may arise from the fact that the folded conformation is entropically favoured. However, dispersive forces help to stabilize the folded conformations measurably, judging from the increased van der Waals stabilization terms obtained by molecular mechanics calculations.

To conclude, the folding tendency of vicinal substituent groups is by no means the exception. It seems to be a rule. In other words, one must seek explanations if one finds an extended conformation. It may be due to extreme steric interaction or to the alignment of molecules in order to realize closest packing in crystals. As to the reason for the folded conformations, there may be a number of attractive interactions besides their advantage in entropy: the most important, we propose, is the dispersive forces or the attractive term of the van der Waals interaction.

2.6. *Preferred conformations from empirical force–field calculations*

Molecular force–field calculations provide an efficient and practical method for the prediction of conformational preferences among the possible rotational isomers of a molecule.[116–121] The force–field method is often called molecular mechanics—this has the advantage of enabling the evaluation of the contribution of various intramolecular forces separately. Since the steric energy of a molecule is calculated as the sum of stretching (E_s), bending (E_b), torsional (E_w), van der Waals (E_{vdw}), dipole–dipole (E_d), and several cross terms, each term can be evaluated independently. Each term consists of the sum of atomic contributions, so the local contribution to the total energy can be estimated by examining the detailed data from a computer. These partial or local energy terms are useful in thinking about the nature of intramolecular interaction but overconfidence in partial and local energy terms can lead to erroneous conclusions in some cases.

A recent version of MM2 by Allinger and coworkers[116,122,123] has parameters for calculations on molecules containing hetero-atoms. This programme is suitable for the production of the conformational distributions of alcohols, ketones, and other functionalized compounds.

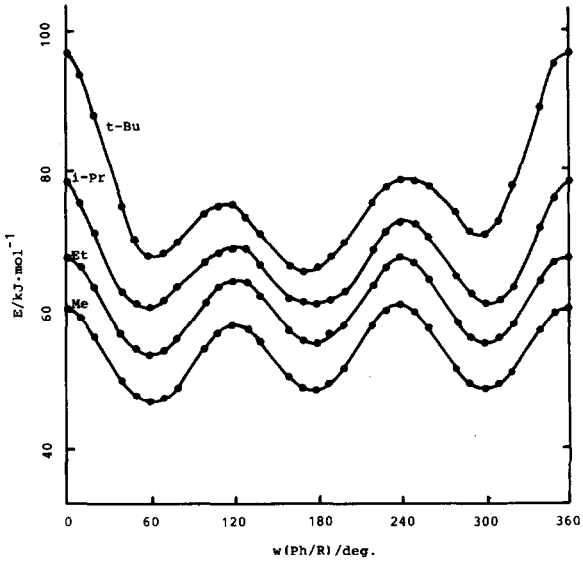


Fig. 15. Total steric energy (E) vs. torsional angle (w) plots for $PhCH_2CHROH$ (R = Me, Et, Pr^i, and Bu^t).

MM1 and MM2 calculations have been reported on several aralkyl derivatives capable of producing intramolecular CH/π interaction. Steric energies of $PhCH_2XR$ and PhCHMeXR, where X is CH_2, CH(OH), C=O, S, or SO, were calculated as a function of the torsion angle around the benzyl carbon–X bond.[124-126] In these calculations, the torsion angle *w* was fixed and all coordinates other than the torsion angle were optimized. Typical results are illustrated in Fig. 15.[125] As the energy minima of the curve correspond to stable rotational isomers, or conformers, the energies and the geometries at the minima were re-calculated without any restriction of the coordinates. According to a rather rough approximation assuming that the population of the conformer obeys Boltzmann's distribution law, the steric energies from the calculation gave the populations of the rotational isomers.

Steric energies and C–X torsion angles of the conformers of $PhCH_2XR$ and PhCHMeXR are given in Table 7. As anticipated, three stable staggered conformations are generated by the calculations. These are one Ph/R antiperiplanar (**c**) and two Ph/R synclinal conformers (**a** and **b**).

In the series of PhCHMeXR, the alkyl group (R) is synclinal to the phenyl group (Ph) and antiperiplanar to the methyl group (Me) in the most stable conformer without exception. The most probable conformers of *threo*- and *erythro*-1-alkyl-2-phenyl-1-propanols were estimated by the LIS experiments as described in the previous section. The calculation succeeded in reproducing the most probable conformer from LIS. However, the LIS experiments demonstrated the fact that a conformer in which R is flanked by Me and Ph is often more stable than an R/Ph antiperiplanar conformer. This result contrasts with prediction from MM2.[125] The disagreement between the calculation and the LIS experiments can be explained at least qualitatively if we assume that an additional attractive interaction exists between phenyl and alkyl groups on the neighbouring atoms.

Table 7. Relative steric energies (ΔE_s) of the stable conformations[a] of $PhCH_2$-X(YZ)-R and PhCHMe-X(YZ)-R

X	Y	Z	R	ΔE_s/kcalmol^{-1}(w/deg) (a)	(c)	(b)
(A) $PhCH_2$-X(YZ)-R						
C	H	H	Me	0.07 (62)	0 (180)	0.07 (298)
			Et	0.07 (62)	0 (180)	0.07 (298)
			i-Pr	0.02 (62)	0 (180)	0.02 (298)
			t-Bu	0.79 (63)	0 (180)	0.79 (297)
C	H	OH	Me	0 (61)	0.41 (178)	0.48 (301)
			Et	0 (60)	0.39 (177)	0.44 (300)
			i-Pr	0 (60)	0.26 (179)	0.29 (299)
			t-Bu	0.33 (62)	0 (171)	1.11 (299)
C	=O		Me	0.13 (58)	0 (180)	0.13 (302)
			Et	0.13 (60)	0 (180)	0.13 (300)
			i-Pr	0 (53)	0.14 (173,187)[a]	0 (307)
			t-Bu	0.18 (80)	0 (180)	0.18 (280)
S	-	O	t-Bu	0 (106)	0.32 (160)	0.85 (294)

continued

Table 7.—*continued*

X	Y	Z	R	ΔE_s/kcalmol^{-1}(w/deg) (a)	(c)	(b)
(B) PhCHMe-X(YZ)-R						
C	H	H	Me	0 (56)	0.64 (173)	1.47 (302)
			Et	0 (57)	0.68 (173)	1.50 (303)
			i-Pr	0 (53)	0.85 (178)	2.67 (306)
			t-Bu	0 (60)	1.99 (172)	3.65 (308)
C	OH	H	Me	0 (58)	0.12 (174)	1.03 (300)
			Et	0 (57)	0.23 (178)	0.77 (301)
			i-Pr	0 (54)	0.36 (180)	1.97 (303)
			t-Bu	0 (61)	0.72 (175)	3.35 (308)
C	H	OH	Me	0 (53)	1.42 (173)	1.54 (307)
			Et	0 (52)	1.40 (172)	1.59 (304)
			i-Pr	0 (48)	1.45 (175)	2.65 (303)
			t-Bu	0 (57)	1.94 (172)	3.31 (308)
C	=O		Me	0 (56)	1.34 (178)	2.44 (314)
			Et	0 (58)	1.47 (178)	2.48 (314)
			i-Pr	0 (51)	1.64 (176)	2.78 (283)
			t-Bu	0 (79)	2.92 (178)	3.95 (309)
S	-	-	Me	0 (59)	0.94 (174)	1.05 (309)
			Et	0 (59)	1.03 (174)	1.09 (309)
			i-Pr	0 (59)	1.16 (180)	1.32 (306)
			t-Bu	0 (63)	1.92 (172)	2.43 (307)
S	-	O	t-Bu	0 (63)	2.52 (139)	3.45 (309)
S	O	-	t-Bu	0 (115)	3.14 (166)	4.84 (308)

a) Conformations **a**, **b**, and **c** are the same as given in Fig. 12 for $PhCH_2$-X(YZ)-R and in Fig. 2 for PhCHMe-X(YZ)-R.

Conclusions from MM calculations on the series of $PhCH_2XR$ are considerably different from those on the PhCHMeXR series. The most stable conformer in this series is dependent both on the bulkiness of the alkyl substituent(s) and on the nature of the X group. Moreover, the energy difference between the antiperiplanar and the synclinal conformers is rather small in most cases. For this reason, both conformers can be expected to coexist in the equilibrium mixture.

The equilibrium may shift delicately towards a particular conformer by the circumstances, such as a change in state, polarity of the solvent, complex formation, etc.[127] Small differences in conformational energies are reflected in the dual behaviour of this sort of compound. Dipole moment measurement on *p*-substituted phenyl *t*-butyl ketones showed them to be antiperiplanar in contrast with the conclusion from LIS.

3. THE PRESENCE AND THE NATURE OF THE CH/π INTERACTION

3.1. *Comparison of LIS data with force–field results*

Comparison of the LIS results (Section 2.3.) with those obtained from force–field calculations (Section 2.6.) suggests that an attractive interaction other than the dispersive force is operating in stabilizing the gauche alkyl/phenyl conformations.

The differences in conformational energies between rotamers **b** and **c** in less bulky alkyl derivatives of benzylic carbinols were found to be small by force–field calculations,[125] whereas in experiments they were found to be appreciable.[31] Secondly, for alkyl 1-phenylethyl carbinols, force–field calculations predicted correctly the most preferred rotamers, but a discrepancy was noted between the experimental and the computational results[21,125] with respect to the relative abundances of the rotamers **b** and **c**. The disagreement is subtle, but distinct. Experimentally, an appreciable fraction of the second stable rotamer (rotamer **b**) was found to appear to contribute in the rotameric mixture of the lower alkyl homologues (R = Me, Et, and Pr^i); in this conformation the alkyl group is flanked by phenyl and methyl groups.[29] The rotamer **c** (R/Ph anti) has been suggested to be less populated than the rotamer **b**. This, however, was not reproduced by the calculations. The force–field calculation predicted the order of the stabilities of the rotamers to be, in every case, **a** > **c** > **b** (Table 7 and Fig. 11).

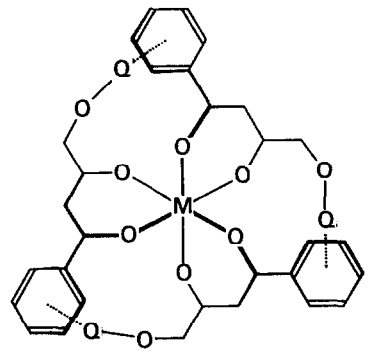
The attractive interactions included in the force–field calculation are van der Waals attractive terms and terms due to attraction between two suitably oriented dipoles. In order to reconcile the above disagreement, therefore, one must ask whether an extra attractive interaction other than the dispersive and dipole–dipole forces is operative between an alkyl and a phenyl group, or can this be attributed to other reasons.

Discrepancies might arise from experimental errors or directed deviation inherent in the method of LIS simulation. Otherwise, they might be ascribed to the contribution of one or another of the following factors:[125] (1) solvent effect in the observed system; (2) underestimate of van der Waals attractive terms in the force–field calculations; (3) excess polarizability effect of the π-electron system; or (4) electrostatic interactions by quadrupole and other higher multipoles. The dipole moments are similar among the rotamers of the alcohols, and the discrepancy could not be correlated with the dipolar nature of the rotamers. The underestimate of van der Waals attractive terms seems improbable, since Allinger's MM2 programme and the parameters used therein have been tested with a large number of compounds and are believed to be highly reliable. Dipole/quadrupole and other higher multipole interactions are usually unimportant.

3.2. *Other circumstantial evidence*

3.2.1. *Stereoselectivity in the formation of metal complexes.* In a series of studies concerning non-covalent interligand interactions in metal complexes,[44] Okawa, Kida, and coworkers observed the preferential formation of the cis-Δ isomer of tris-(1-l-menthyloxy-3-benzoylacetonato)-cobalt(III) ([Co(1-moba)$_3$], **14**). They interpreted the stereoselectivity to be a result of the

interligand attractive interaction which occurs between the l-menthyl group and the aromatic ring.[42,44,128,129] The stereoselectivity becomes even greater when the phenyl group in the benzoylacetone moiety is replaced by a naphthyl group.[130] This is reasonable, since the larger the aromatic ring is, the more favourable is the CH/π interaction.



(14)

They also studied the substituent effect on the stereoselectivities in the formation of several metal complexes $[M(l\text{-moba-}X)_3]$ (where $M = Co, Cr, Mn$; $X = H, Br, Me$).[46] The CD amplitude of the product corresponding to the d–d band region increased as the π-electron density of the aromatic ring increased (Table 8). This also is well understood in terms of the CH/π interaction; the attractive interaction of such a sort should become more significant as the electron-donating property of the substituent increases.

Table 8. CD data ($\Delta\varepsilon$) at d-d region of the complexes $[M(l\text{-moba-}X)_3]$

X	M		
	Co	Cr	Mn
Br	-1.78	-0.74	-0.24
H	-6.1	-1.60	-0.33
Me	-10.0	-3.90	-----

3.2.2. *Conformational equilibria of certain fluorenes and triptycenes.* Ōki and coworkers studied the conformational equilibria of a series of 9-(2-alkylphenyl)fluorenes.[131,132] The differences in free energy between the conformational isomers (ΔG^0_{sp-ap}) were reported to be 0.28, 0.71, 0.52, and >2.7 kcal mol^{-1} (in favour of the synperiplanar-isomer) for the methyl, ethyl, isopropyl and *t*-butyl homologues, respectively. This unusual trend in the substituent effect (minimum at isopropyl) suggests that there is a compromise between attractive and repulsive interactions. The attractive interaction may be CH/π in type (Fig. 16). In fact they found later[132] that the proportion of the antiperiplanar-isomer became greater in the *sec*-butyl homologue than in the isopropyl one ($\Delta G^0_{sp-ap} = 0.38$ kcal mol^{-1}).

Table 9. Conformational equilibria of 9-[2-alkyl(R)phenyl]-fluorenes

R	K(sp/ap)	ΔG^0_{sp-ap}(300K)
Me	1.6	0.28
Et	3.3	0.71
i-Pr	2.4	0.52
t-Bu	>100	>2.7

Ōki and coworkers[133] examined also the population ratios (±sc/ap) of substituted 9-benzyl-8,13-dichloro-1-methyltriptycene derivatives by ^{1}H-NMR spectroscopy, showing that the ratio becomes larger as the substituent (X) on the benzyl group becomes more electron-donating and as the substituent (Y) on the benzeno bridge which bears the 1-methyl group becomes more electron-withdrawing (Fig. 16b). The results were interpreted as the indication of CH_3/π interactions.

3.2.3. *Stereoselectivity in an enantioface-differentiating reaction.* In an enantioface-differentiating reduction of phenyl alkyl ketone with a chiral Grignard reagent, Guette and Capillon found that the introduction of a methoxy group into the aromatic moiety of the reagent resulted in an increase in the optical yield.[134] The extent of asymmetric induction decreased, in contrast, on substitution with a trifluoromethyl group.

These results seem to demonstrate that the interaction involved in stabilizing the favoured transition state is CH/π in type. The π-donating property of the phenyl group should increase upon the introduction of an electron-donating group, while the inverse is true for an electron-withdrawing group.

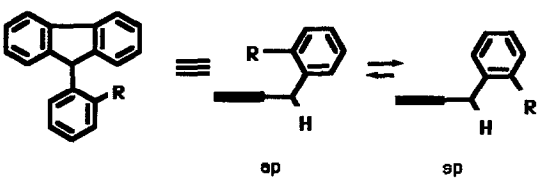


Fig. 16(a). The CH/π interaction in the ap-conformer of 9-(2-alkylphenyl)fluorene.

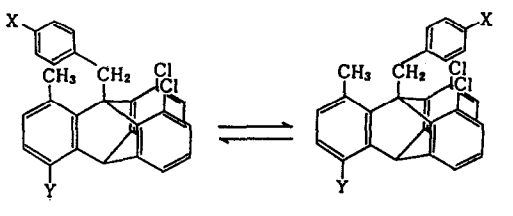


Fig. 16(b). The CH_3/π interaction in the (+)sc-conformers of substituted 9-benzyl-8,13-dichloro-1-methyltriptycenes.

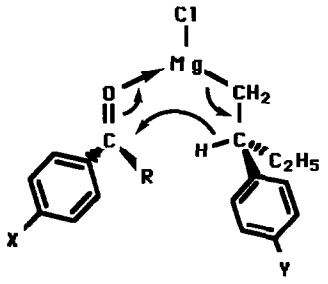


Fig. 17. Asymmetric induction assisted by the CH/π interaction.

Table 10. The optical yields (%ee) of the reduction of alkyl phenyl ketones (RCOPh) with (S)-2-(p-substituted phenyl)-butylmagnesium chloride ($YC_6H_4CHEtCH_2MgCl$)

R Y	H	OCH_3	CF_3
Me	50	57	22
i-Pr	81	84	58

3.2.4. *Aromatic solvent-induced shifts and the intermolecular CH/π interaction.* Since the investigations by Zurcher[135,136] and Williams[137,138] which stimulated a renewed interest in the solvent shifts induced by aromatic solvents, a great number of papers have been published concerning the origin, the theoretical aspects, the steric and electronic effects, and the applications.[139] In the pioneering works by the above authors, the benzene-induced solvent shift was interpreted from the electrostatic point of view and in terms of the repulsive interaction between aromatic π-electrons and carbonyl dipoles of ketosteroids. In every case the polarity of the solute molecule was assumed to be necessary to induce the shift. The solvent-induced shift was named ASIS as the abbreviation of aromatic-solvent-induced shift and applied to many conformational problems, taking advantage of the additivity rules established by Zurcher,[135,136] Williams,[137,138] and Diehl[140] independently.

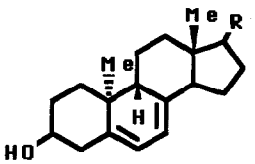
In connection with the CH/π interaction, the nature of the interaction inducing the shift was pursued further. In the early stage of its investigation, a collisional complex was postulated.[141] Later the complex became thought to be tighter and stoichiometric; the geometry of chloroform–benzene complex was estimated, though its lifetime is short. As to the origin of the attractive force between solvent and solute molecules, Schneider proposed a dipole induced-dipole mechanism[142,143] and tried to correlate the ASIS with the dipole moments of the solutes. However, the correlation was only fair and chloroform behaved exceptionally. In order to rationalize the ASIS of some solutes which have rather strong interaction with aromatic solvents, we have to take into account the contribution of hydrogen-bond-like, or delocalizative, interaction in addition to the electrostatic interaction. Enthalpies of the complex formation were shown to increase in the order C_6H_5Cl (-1.5 kcal mol^{-1}) < C_6D_6 (-1.9 kcal mol^{-1}) < $C_6D_5CD_3$ (-2.1 kcal mol^{-1}) < *o*-$C_6D_4(CD_3)_2$ (-2.2 kcal mol^{-1}) < $C_6(CH_3)_6$ (-3.0 kcal mol^{-1}) from our recent investigation.[144] The interaction is likely to have a hydrogen-bond-like character.

3.3. *X-ray data*

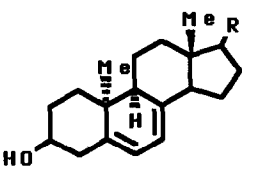
In order to try to find support for the presence of CH/π interaction in crystallographic results, the X-ray data of several compounds were examined. As discussed in Section 2.2.1., the interatomic

distances between the benzylic methyl carbon and a carbon of the phenyl ring in (*RS*)/(*SR*)- and (*RR*)/(*SS*)-1-(*p*-bromophenyl)ethyl *t*-butyl sulphoxides are very short, viz., 0.324 and 0.332 nm, respectively. Riddell *et al.*[145] reported that a 4-axial methyl in 2-(*p*-bromophenyl)-2,4,4,6-tetramethyl-1,3-dioxan is in close contact with a carbon atom of the axial 2-phenyl group (0.32 nm). In an X-ray study of bis(2,4,6-tri-*t*-butylphenyl)phosphinic chloride, Inamoto and coworkers[146] found short interatomic contacts between a methyl carbon in a *t*-butyl group and an sp^2 carbon (0.322 and 0.324 nm). The calculated distance by assuming van der Waals contact between a hydrogen of the *t*-butyl and the sp^2 carbon is ca. 0.37 nm.

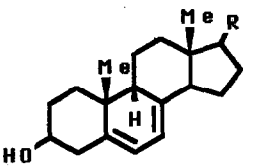
The crystal structures of a number of unsaturated triterpenoids, such as lumisterol (**15**),[147] pyrocalciferol (**16**)[148] and isopyrocalciferol (**17**),[149] were determined by Romers and his associates. The angular methyl groups on C10 and on C13 are known to orient themselves close to the homoannular cisoid diene system (ring B) in these molecules. We therefore reexamined their X-ray data and found that several hydrogen atoms in angular methyl groups were in close contact with one of the sp^2 carbons. The interatomic distances were 0.274 nm (H18/C8) and 0.291 nm (H19/C8) for lumisterol, 0.275 nm (C18/H8), 0.278 nm (H19/C8), 0.297 nm (H19/C6), 0.289 nm (H18/C7), and 0.297 nm (H19/C7) for pyrocalciferol and 0.257 (H18/C8) for isopyrocalciferol. Some of these values are indeed much shorter than the sum of the van der Waals radii of the relevant atoms (0.29–0.31 nm: 0.12–0.14 for H and 0.17 for sp^2 carbon).



lumisterol
(15)



pyrocalciferol
(16)



isopyrocalciferol
(17)

A tricyclic diterpene, levopimaric acid (**18**), has been known to exist in a compact structure, in which the angular methyl approaches close to the cisoid-diene moiety in the molecule. The X-ray data obtained by Karle[150] were reexamined in an effort to determine whether short interatomic contacts are found between relevant atoms (Fig. 18). Close contacts were in fact found between

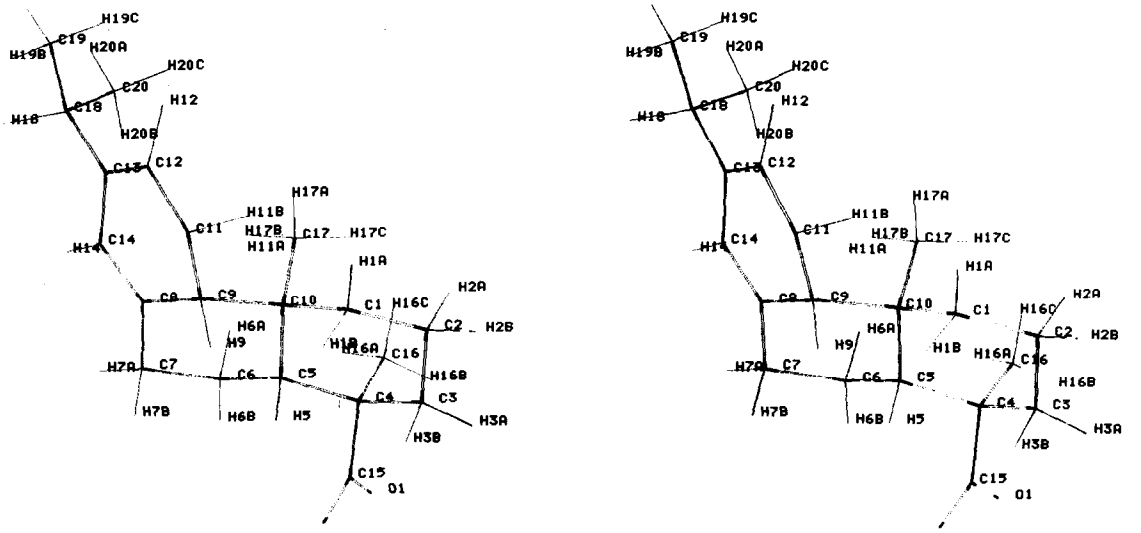
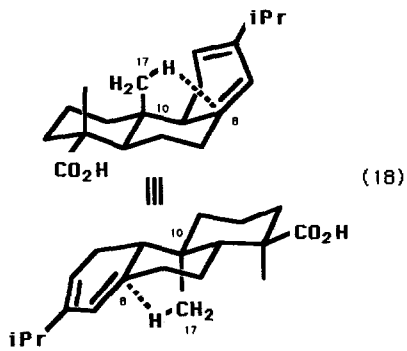


Fig. 18. Molecular structure (stereo view) of levopimaric acid (**18**).

hydrogens in the angular methyl group (**17**) and sp^2 carbons: 0.253 nm (H17B/C8), 0.274 nm (H17B/C14), and 0.296 nm (H17A/C12).



(18)

3.4. *Evidence from infrared studies*

Infrared spectroscopy in the X–H stretching region provides a great deal of information about X–H/Y hydrogen bonding.[151] Thus the hydrogen bonds involving hydroxyl and amino groups as proton donors have been studied most frequently by infrared spectroscopic methods. In the cases of hydrogen bonds involving OH groups, NH groups, and hydrogen halides, formation of hydrogen bonds causes a medium to large low frequency shift of X–H stretching absorption. The low frequency shift is usually called a hydrogen bond shift. It is very often accompanied by a broadening in width and an increase in intensity of the X–H band, and this can be another clue to the detection of the presence of hydrogen bonds. In contrast to the cases of OH/X and NH/X hydrogen bonds, high frequency shifts of C–H stretching absorptions have been reported with several cases of CH hydrogen bonding. For instance, the formyl CH group of *o*-nitrobenzaldehyde has been shown to absorb at 2860 cm^{-1}, which is about 50 cm^{-1} higher than that of unsubstituted benzaldehyde (2807 cm^{-1}).[152] Similar high frequency shifts were observed with methyl 3-formyl-2-, 2-formyl-3-, and 4-formyl-3-thiophenecarboxylates, which absorb at 2896 cm^{-1}, 2904 cm^{-1}, and 2891 cm^{-1}, respectively.[153] The frequencies are more than 50 cm^{-1} higher than the normal thiophenecarboxaldehydes without a neighbouring carbonyl group.

The high frequency shift is plausible if a C–H bond can interact attractively with an electronegative group (X) without weakening itself—in other words, without decreasing its stretching force constant (k_{CH}). The vibrational frequency of a linear (or, when the C–H···X angle is larger than 90°) C–H/X system can be expected to become higher than the frequency of an isolated C–H bond, when k_{CH} remains constant.

With the aim of obtaining evidence for the presence of intramolecular CH/π hydrogen bonding, the infrared spectra of 1-(substituted phenyl)ethyl [1-^{2}H]-isopropyl ketones (**19**) were measured.[154] Deuterium labelling was necessary in order to avoid the interference of other CH absorption bands. [1-^{2}H]-Isopropyl phenylethyl ketone had two CD absorption bands at 2177 cm^{-1} and 2136 cm^{-1} in the carbon tetrachloride solution. The frequency of the higher band was rather higher than those of similar deuterium-labelled ketones such as benzyl [1-^{2}H]-isopropyl ketone (2153 cm^{-1}, one band), [1-^{2}H]-isopropyl methyl ketone (2167 cm^{-1} and 2130 cm^{-1}). Since the effect of steric compression should occur in the CH/π hydrogen bonded conformer of the ketone judging from the CH/C(phenyl) distance (0.265 nm) from molecular force-field calculations, a considerable part of the high frequency shift should arise from the effect of steric compression. However, the attractive interaction between the C–D bond and the aromatic nucleus might also be responsible for the high frequency shift caused by the mechanical reason just described. The infrared C–D absorptions of a series of [1-^{2}H]-isopropyl (*p*-substituted phenyl)ethyl ketones (**19**) are given in Table 11.

Table 11. IR and ^{2}H-NMR data of p-$XC_6H_4CHMeCOCDMe_2$ (in CCl_4)

X	ν_{int}	ν_{free}	$\varepsilon_{int}/\varepsilon_{free}$	δ_D[a]
NO_2	2174	2135	1.10 (0.88)[b]	-5.30
Br	2174	2135	1.29	-5.36
Cl	2175	2136	1.41 (0.75)	-5.36
H	2177	2136	1.59 (0.76)	-5.37
C_2H_5	2176	2136	1.54	-5.37
CH_3	2176	2136	1.59 (0.77)	-5.38
NH_2	2175	2135	1.64	---

a) ^{2}H chemical shifts were given by ppm downfield from external $CDCl_3$ standard.

b) Intensity ratios in $CDCl_3$ are given in parentheses.

Intramolecular hydrogen bonds are usually cleaved when a stronger hydrogen-donating solvent is added. Therefore, the spectra of these ketones were measured in chloroform which is known as a typical C–H hydrogen donor in this sort of hydrogen bonding. The smaller observed ratios of the intensities revealed the fact that the intramolecularly hydrogen bonded species decreased considerably in chloroform, which, in turn, supported the above assignment of the C–D absorption bands and the fact that the CH/π hydrogen bonded conformer absorbs at a frequency higher than the normal in the C–D stretching region.

Accordingly, the band at the higher frequency was assigned to the CD/π hydrogen bonded conformer and the one at the lower frequency to a CD free conformer. The relative formation constant of the hydrogen bond could be estimated from the ratio of the absorption intensities ($\varepsilon_{int}/\varepsilon_{free}$) of the two C–D absorption bands.† The Hammett plot (log $\varepsilon_h/\varepsilon_f$ vs. σ) in Fig. 19 has a negative slope. The negative gradients were usually observed in analogous plots for hydrogen-bonded systems[155] and have been used to prove the hydrogen-bond-like character of the interactions involved. The electron-rich phenyl group carrying an electron donating substituent should favour the formation of a hydrogen bond and vice versa.

3.5. *Molecular orbital calculations*

The very decisive criterion for specific hydrogen-bond-like interaction should be the presence of delocalizative interaction between the 'non-bonded' hydrogen atom of C–H and the carbon atom bearing π-electrons. Thus the molecular orbital or other quantum mechanical approach takes a

† As the intrinsic molar absorptivities of the CD/π hydrogen bonded conformer and that of the free conformer are not necessarily equal, a proportionality constant a which is equal to their ratio was introduced in eqn. 2, in which K is the real formation constant. However, the proportionality constant can be expected to be constant throughout the series, since the substituent was located on the aromatic nucleus far from the C–D bond. For this reason, the substituent effect could be discussed in terms of the ratio of the intensities of the two C–D bands

$$K = a(\varepsilon_{int}/\varepsilon_{free}). \quad (2)$$

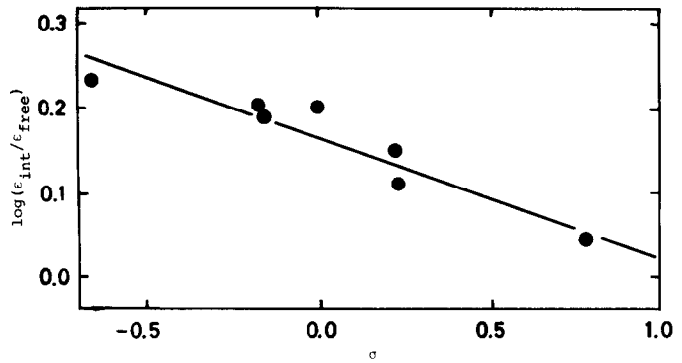
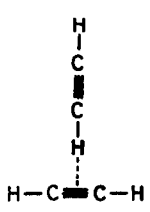


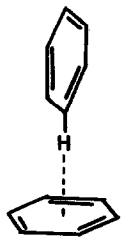
Fig. 19. Substituent effect on the ratios of the free and the CH/π interacted CD stretching bands of $XC_6H_4CHMeCOCDMe_2$. The log ($\varepsilon_{int}/\varepsilon_{free}$) vs. σ plot.

decisive part in discriminating whether the observed attractive CH/π interaction is worth being called a CH/π hydrogen bond or not.

Interaction between a so-called acidic C–H group and an aromatic compound was first introduced in order to interpret several phenomena relating to solvent–solute interactions and more evidently in order to interpret the aromatic-solvent-induced shift of the ^{1}H-NMR spectra of some organic compounds.[135–143] Ever since compounds carrying acidic C–H groups were shown to interact with the π-bases, several model calculations have been carried out with binary systems consisting of chloroform, hydrogen cyanide, acetylene, etc., as the acidic C–H component and of ethylene, acetylene, benzene, etc., as the π component with the aim of characterizing the interaction involved. Thus *ab initio* calculations on acetylene[156] and benzene[157] dimers showed that the 'T-shaped' geometries (**20** and **21**) are the most stable. Kodama and coworkers[158] reported the interaction energy for the most stable methane–benzene system to be -3.5 kJ mol^{-1} by CNDO/2 calculations. Recently more elaborate and sophisticated calculations were reported on CH_4–C_2H_4(ethylene) and CH_4–C_2H_2(acetylene) binary systems by Takagi and coworkers.[159] The report includes an *ab initio* calculation using a 4-31G basis set on the CH_4–C_2H_4 supermolecular system (**22**) in which one of the C–H bonds of methane is fixed on the perpendicular of the molecular plane of C_2H_4 passing through the center of the C=C bond with optimization of an intermolecular distance R_{CC}. The results were analysed by employing Kitaura and Morokuma's method[160] and the charge–transfer from ethylene to methane was shown to contribute largely to stabilizing the supermolecule (Table 12).



(20)



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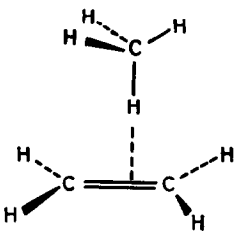


(22)

As to the intramolecular interaction, *ab initio* 4-31G calculations on the several conformers of 1-phenyl-2-propanol have been reported.[161] The population analysis gave positive bond populations

Table 12. Calculated energy components[a] (in kJ mol^{-1}) and optimized intermolecular distances (R_{CC}) for the CH_4(A)-C_2H_n(B; n = 2, 4, 6) systems

B	R_{CC}/nm	E	ES	CT_{B-A}	DISP
H-C≡C-H	0.44	-2.75	-0.56	-2.16	-0.80
$H_2C=CH_2$	0.44	-3.67	-0.60	-3.00	-0.99
CH_3-CH_3	0.50	-1.01	-0.33	-0.34[b]	-0.79

a) E; stabilization energy in reference to isolated A and B, ES; coulombic energy, CT_{B-A}; charge transfer energy due to electron migration from B to A, and DISP; dispersion energy.

b) $CT_{B-A} + CT_{A-B}$.

between non-bonded H in methyl and aromatic C atoms (0.48×10^{-2} and 0.74×10^{-2} for conformers **a** and **b**, respectively). The bond populations are about half as large as the case of well characterized OH/π interaction (Table 13). This suggests the participation of the delocalizative, or charge-transfer, force between CH_3 and the π-electrons of the aromatic ring in the CH/π approached conformers **a** and **b**.

Table 13. Relative energies (Δ E) and populations of several conformations of 1-phenyl-2-propanol

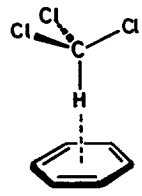
Conformation[a]	a	c	c_{H-bond}	b
Δ E/kcal mol^{-1}	-0.64	0.00	-2.20	+0.38
Population				
$C(Ph)_{mean}$	6.167	6.159	6.171	6.161
OH··· Ph (x 10^2)	-0.03	-0.02	+1.62	-0.02
CH_3··· Ph (x 10^2)	+0.48	-0.03	-0.03	+0.74

a) Conformations **a**, **b**, and **c** are the same as given in Fig. 12. c_{H-bond} refers to the intramolecularly OH/π hydrogen bonded conformation **c**.

3.6. *Nature of the CH/π interaction*

A typical example of intermolecular CH/π interaction is found in the benzene-induced upfield shift of the ^{1}H-NMR signal of chloroform in benzene solutions as discussed in Section 3.2.4. From

the NMR spectroscopy and other evidence, the chloroform molecule can be supposed to form a 1 : 1 complex with benzene in which the chloroform molecule is located just above the plane of the aromatic ring directing its CH bond towards the π-electron cloud of the ring (**23**). Analogous to the case of OH/π interaction, hydrogen-bond-like interaction is believed to be the driving force of the complex formation.



(**23**)

When a single hydrogen atom is forming bonds to two distinct atoms, one of them is almost the same as the usual covalent bond, while the other is much weaker and is called the hydrogen bond.[162] If we accept the concept of delocalizing molecular bonds, the CH/π interaction is literally a hydrogen bond since the hydrogen atom of the C–H covalent bond forms another weak bond with a benzene molecule. From a different viewpoint, the CH/π interaction can be interpreted as a non-bonded interaction strengthened by the participation of strongly polarizable π-electrons on the aromatic ring and by the polar C–H bond whose carbon atom is linked to three electronegative chlorine atoms. However, the term 'hydrogen bond' has a rather ambiguous definition, and the typical OH/O hydrogen bond is assumed to gain the energy of its formation by the combined contribution of electrostatic, delocalizative, dispersive, and repulsive van der Waals energies.[163] All of these terms should contribute to the energy of CH/π interaction though the relative importance among these terms might be quite different from the case of the OH/O hydrogen bond. Thus the nature of CH/π interaction will be discussed in analogy with the hydrogen bond.

(a) Electrostatic contribution to CH/π hydrogen bonding. As to the contribution of electrostatic interaction, the magnitude can easily be estimated by examining the dipole–dipole interaction energies from molecular force–field calculations: the geometry and the charge distribution of the molecule can be calculated very accurately by these calculations. As anticipated, purely electrostatic contributions to both the OH/π and CH/π hydrogen bonds are considerably less than that of the OH/O hydrogen bond (6 kcal mol^{-1}). In the case of the chloroform/benzene complex, the repulsion between the electronegative chlorine atoms and π-electrons of benzene can be decreased by taking the CH/π contiguous arrangement (**23**). However, the net CH/π dipolar interaction is estimated to be extremely small. Since the CH/π interaction occurs between non-polar hydrocarbon moieties, the contribution of the attractive dipole–dipole interaction term is generally small, though some favourable contribution due to the highly polarizable aromatic π-system can be expected.

(b) Delocalization contribution to CH/π hydrogen bonding. As can be straightforwardly deduced from the fact that the CH/π hydrogen bond is classified as an interaction between a soft acid C–H and soft base π-system, the delocalization effect should play a more important role in forming the weak bond than in the case of the OH/O hydrogen bond. From this point of view, molecular orbital calculations of various levels of approximation have been applied to several CH/π interacted systems.[159,161] As described in the previous section (Section 3.5.), the calculation on the whole renders support to the contribution of the delocalizative force, evaluating the stabilization energy of the interacted system, giving considerably large positive bond populations between non-bonded CH and π-systems, or showing the contribution of charge transfer from π-base to CH.

Table 14. Classification of the interactions involved in CH/π and related weak bonds

Type of weak "bond"	Type of interaction			
	delocalizative	electrostatic	dispersive	repulsive v. d. W.
O-H (hard acid) ... O (hard base)	variable	strong	not important	similar
O-H (hard acid) ... π (soft base)	important	weak	important	
C-H (soft acid) ... O (hard base)	not important	important	not important	
C-H (soft acid) ... π (soft base)	important	not important	important	

(c) Dispersion contribution to CH/π hydrogen bonding. Methods for the estimation of attractive and repulsive van der Waals interaction have been advanced hand in hand with the development of molecular force–field calculations. The molecular force–field (MM1) originally proposed by Allinger and coworkers[164] employed somewhat too 'hard' potential functions for the evaluation of the van der Waals interaction. After the controversy with Schleyer and Osawa,[165] the force–field parameters concerning the evaluation of E_{vdw} was modified in a more recent version MM2 (1978).[115] Several force–fields and equations for this purpose have since been proposed by Schleyer,[117] Bartell,[118] and other investigators.[120,121] Previously the most commonly used expression for the van der Waals interaction was the Lennard–Jones expression. However, this has now been replaced by that by Hill[166] in most popular computer programmes for molecular force–field calculations. The attraction terms in these expressions are identical and include r^{-6} factor coming from the fact that the dispersion force originates from the interaction between two dipole-induced dipoles. In molecular force–field calculations, the intramolecular van der Waals interaction is calculated practically by summing up the interatomic terms of attractive and repulsive van der Waals energies. Thus the approximate contribution by dispersive (attractive van der Waals) energy can easily be estimated by examining the results of MM calculations.

For example, the most stable Ph/Bu^t synclinal conformer of *t*-butyl 1-phenylethyl ketone gains local stabilization energy of 3.35 kJ mol^{-1} by Ph/Bu^t non-bonded interaction.[125] The local non-bonded interaction energy was calculated as the sum of the van der Waals terms (E_{vdw}) between the atoms comprising the phenyl group and the atoms comprising the *t*-butyl group. The local non-bonded interaction energies from MM2 calculations are given in Table 15.

Table 15. Local E_b and E_{vdw} terms (in kJ mol^{-1}) affecting most significantly the conformational stability of t-butyl 1-phenylethyl ketone

Conformer	**10a**	**10c**	ΔE ($=E_{10c}-E_{10a}$)
Torsional Angle	79°	178°	
Bending (E_b) term			
C_{Bz}-C_{CO}-Bu	0.852	1.592	
C_{Ph}-C_{Bz}-CO	0.000	0.132	
C_{Me}-C_{Bz}-CO	0.154	1.471	
Total	1.006	3.195	2.19
Non-bond interaction (E_{vdw}) term			
Ph/Bu^t	-3.35	-1.34	
Me/Bu^t	-0.67	+1.05	
Total	-4.02	-0.29	3.73

As mentioned previously,[125] the molecular force–field calculations have succeeded in reproducing the conformations of most of the CH/π interacting systems. This implies that dispersive or attractive

van der Waals forces contribute most predominantly to the so-called CH/π interaction. However, the substituent effects on several seemingly CH/π interacted systems[46,134,144,154] reveal that the electron-rich π-system is more favourable than the electron deficient one in forming the CH/π interacted complex both intra- and inter-molecularly. The effect is best interpreted by assuming a delocalizative contribution to the CH/π interaction. In conclusion, the CH/π interaction is a sort of weak hydrogen bonding in which the dispersion contribution is relatively large.

4. IMPLICATIONS IN ORGANIC CHEMISTRY

4.1. *Chemical consequences of the CH/π interaction*

As discussed in the preceding two sections, the nature of the CH/π interaction is ascribed to a kind of weak hydrogen bond, or through-space hyperconjugation, between a CH group and a π-system.

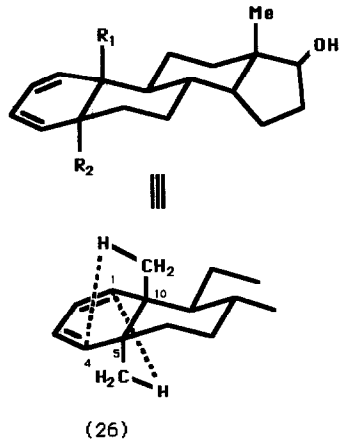
The concept of the CH/π interaction, in itself, is not an original idea of the present authors. The interactions of two acetylene molecules[156] and chloroform with benzene[167,168] have been known for a long time. Our suggestion is that this type of interaction not only is possible with activated CH groups, but also is important with normal non-acidic CH groups such as those in alkyl groups. It would be pertinent, in this regard, to mention the ubiquitous nature of the groups involved in the CH/π interaction. (1) The CH groups are present in virtually all types of organic compounds. (2) The π-containing groups are also abundant in nature; examples are: C=C, C=O and C=N double bonds (either isolated or conjugated) and aromatic groups such as nucleic acid bases, porphyrines, and the side-chain groups of aromatic amino acid residues (Phe, Tyr, Trp, His) etc. Although the energy of the CH/π interaction is very small, CH groups have a possibility of participating simultaneously in interactions with multiple atoms. In addition, this type of interaction is entropically advantageous in that the probability of interaction increases upon arrangement of the CH group into certain symmetric structures such as methyl or isopropyl groups, etc.

Recognition of such a weak general force will be of help in elucidating several interesting molecular phenomena, the origins of which remain poorly understood. These include intramolecular as well as intermolecular interactions.[32] In the following sections are presented a few examples from the stereochemistry of terpenes and related compounds.

4.2. *Conformations and chiroptical properties of* 1,3-*cyclohexadienes*

4.2.1. *The axial homoallylic effect.* In order to explain the chiroptical properties of compounds with a conjugated double bond, Moscowitz and coworkers presented an empirical rule.[169-171] This is called the diene helicity rule and states that the sense and the amount of skewness of the chromophore in a 1,3-cisoid diene determines the sign of the Cotton effect (CE) and the rotational strength of the compounds. According to this rule, a left-handed helix (M helicity) produces a negative CE at the long wavelength (π–π^*) transition, whereas the right-handed helix (P helicity) corresponds to a positive CE. This was shown for the representative cases of levopimaric acid (**18**, M chirality, $\Delta\varepsilon$ −12.2) and 2,4-cholestadiene (**31**, P chirality, $\Delta\varepsilon$ +12.4).[170] This investigation was followed by a theoretical study.[172]

Fig. 20. Right-handed and left-handed helicity.



R1 = R2 = H (24)

R1 = CH3, R2 = H (25)

R1 = R2 = CH3 (26)

(26)

Later, Burgstahler and coworkers presented evidence that the contribution of an axial alkyl substituent allylic to the double bond outweighs the effect of the skewness of the diene chromophore.[173] To illustrate this, they showed that the introduction of an axial methyl group on C(10) of 5α-estra-1,3-dien-17β-ol (**24**) inverted the sign of the CE of the non-substituted steroid (Δε from +3.8 for **24** to −2.8 for **25**). Further, the introduction of a second methyl group on C(5) of 5α-androsta-1,3-dien-17β-ol (**25**) intensifies the CD amplitude [5α-methylandrosta-1,3-dien-17β-ol (**26**), −11.1]. The helical sense (left-handed) and the amount of twist remain practically unchanged throughout the substitution steps.

This is known as the concept of axial allylic chirality contribution.[173,174] The chiroptical properties of cisoid 1,3-dienes have since been explained against this background. Thus the long wavelength CE of 1,3-cyclohexadienes has been considered to be controlled dominantly by the chirality contributions of the allylic axial substituents or bonds according to their size or polarizability. A number of approaches (theoretical as well as empirical) have since been made,[175–179] in order to find the origin of the phenomenon, but none of them appears to be very successful.

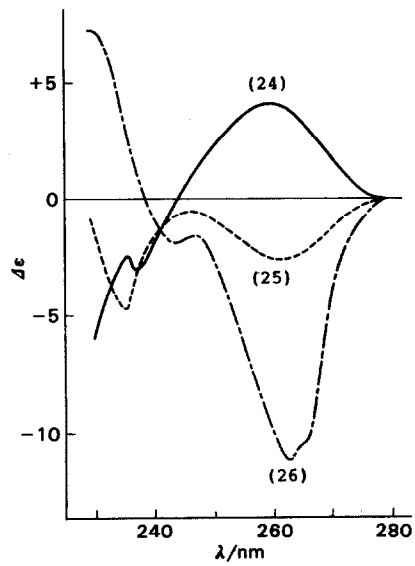


Fig. 21. The CD spectra of **24–26**.[173]

The above phenomenon can be accommodated in terms of the CH/π interaction.[32] It seems reasonable to suggest that the so-called axial allylic effect operates primarily through the dissymmetric perturbation of the π or π*-orbital of the diene chromophore by virtue of the CH groups, which are oriented suitably for this interaction to take place. This situation is illustrated in Fig. 22. If an axial alkyl group is present at the allylic position to an sp^2 carbon in a cyclohexadiene, it is, at the same time and inevitably, homoallylic to another sp^2 carbon which is positioned at the other terminal of the diene system.[180]

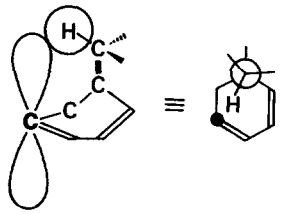
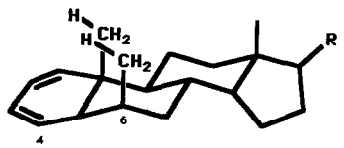


Fig. 22. Schematic illustration of the participation of the CH/π interaction in the enhancement of the rotational strength.

In this disposition, a hydrogen atom in the alkyl group can interact, in a through-space manner, with the π or π* orbital on the sp^2 carbon which is separated by four bonds from it. Inspection of Dreiding models suggests that the hydrogen atom is oriented above the molecular plane of the diene system, and thus is capable of forming a five-membered hydrogen-bond-like interaction with an sp^2 carbon; the interatomic distance at relevant nuclei is ca. 0.25 nm. Therefore, the important and essential condition for the enhancement of CD amplitude is not that the alkyl group is allylic to a double bond system, but that it is homoallylic to it.

Turning again to the example presented by Burgstahler,[173] we see that a CH hydrogen in the 10β-methyl group of compound **26** can participate in a five-membered hydrogen-bond with C(4) which is four-bonds apart from it, but not with C(1) to which the methyl group is allylic. Similarly, the 5α-methyl group can interact with C(1) from the rear side of the molecular plane, but not with C(4). In view of this, the so-called allylic chirality contribution may, more appropriately, be termed the homoallylic chirality rule. Gawronski and Kielczewski[181] have already reported an important contribution of groups homoallylic to a double bond in a series of *exo*-methylene steroids. Burgstahler and associates[182] compared the CD spectrum of 6β-methyl-5α-cholesta-1,3-diene (**27**) with its 6α-isomer and found that the CE magnitude of the 6β-methyl (axially homoallylic to the diene system) isomer was much larger ($\Delta\varepsilon$ −5.5) than that of the equatorial congener ($\Delta\varepsilon$ −1.4). They found also that,[182] in compound **28**, the presence of a methyl group at the homoallylic position exerted a significant influence on its CD spectrum. The two axial methyl groups are situated at positions capable of participating in five-membered hydrogen-bonds, if the cyclohexane ring is frozen in a chair conformation. The weak CD band with a positive Cotton effect ($\Delta\varepsilon$ +0.8 at 20°C) in fact showed an inversion of sign and an increase in its amplitude on cooling ($\Delta\varepsilon$ −3.5 at −169°C).



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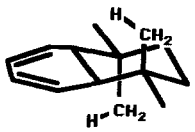

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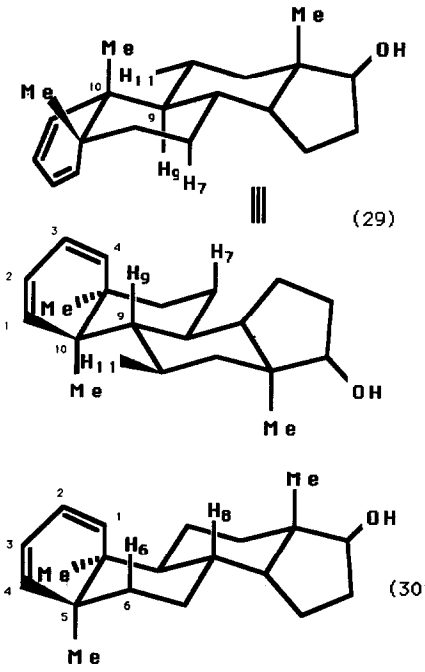


The CD amplitude of diene **29** ($\Delta\varepsilon$ +27.6) has been reported[173] to be larger than that of compound **30** ($\Delta\varepsilon$ +14.7). They attributed this to the difference in polarizability of the groups positioned axially allylic with respect to the diene system. It was argued that, in compound **29**, the C(9)–C(10) bond is tertiary, whereas the C(5)–C(6) bond in compound **30** is secondary, thus resulting in a larger allylic contribution in the former case. In terms of the CH/π interaction, the explanation is more straightforward (Fig. 23). In compound **29**, the number of CH groups which can interact simultaneously in a through-space manner with the diene system is three (7, 9 and 11α-H), whereas in compound **30** it is only two (6β and 8β-H); other situations (e.g., the skew sense and the contribution from the axial methyls) are similar for both compounds. Note that in **29** an extra CH (11α-H) is present, which is capable of participating in CH/π interaction with C(1). This interaction is absent in **30**.

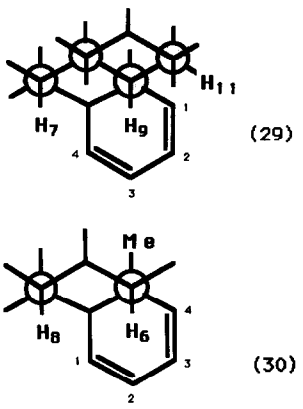
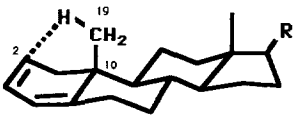


Fig. 23. Newman projections of **29** and **30**.

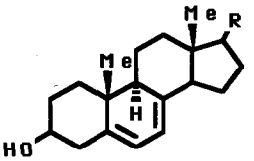
4.2.2. *Folded conformations of levopimaric acid and α-phellandrene.* Levopimaric acid (**18**), a tricyclic diterpene, has been known to exist in a folded conformation in the solid state.[150,183] ORD and NMR studies demonstrated that this compound also favours the folded conformation in solution.[170] This is in contrast to the extended conformation deduced for the configurationally related cholesta-2,4-diene (**31**). To account for this, the possibility of a specific attractive interaction in **18** was once postulated by Burgstahler.[170] However, this was later superseded by an explanation based principally on repulsive interactions (relief of 1,3-diaxial repulsion or 4,4-dimethyl effect, etc).[183–185]



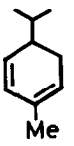
(31)

In levopimaric acid, which has M-helicity, the 10 axial methyl group (C(17)) is homoallylic to C(8), and can interact with the diene system. This is compatible with the strong negative CD absorption of this compound and explains why levopimaric acid adopts the folded conformation. The folded conformation of **18**, at least in part, is a consequence of attractive interaction. In fact, the distances between hydrogens in 10β-methyl to sp^2 carbons have been found to be very short by X-ray crystallography[150] (see Section 3.3.).

In cholesta-2,4-diene (**31**), which has P-helicity, the 10 axial methyl group (C(19)) is homoallylic to C(2), and can engage in a five-membered CH/π interaction with this carbon. This explains why **31** has the extended conformation and a strong positive CD absorption. In this respect, it is noteworthy that tetracyclic triterpenes such as ergosterol (**32**, $\Delta\varepsilon$ −11.4), lumisterol (**15**, $\Delta\varepsilon$ +14), pyrocalciferol (**16**, $\Delta\varepsilon$ +31), and isopyrocalciferol (**17**, $\Delta\varepsilon$ +25) are reported to have large CD at a wavelength corresponding to the π–π^* transition.[169,178] All of these compounds have angular methyls (C(18) and/or C(19)) ideally positioned for the homoallylic axial effect to play a role. Interatomic distances of the relevant atoms (H(18) or H(19) vs. C(8)) have in fact been found to be very short (see Section 3.3.).



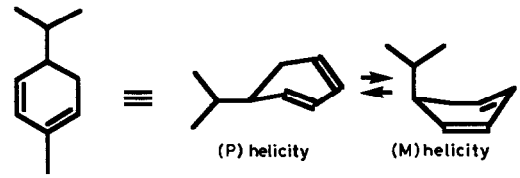
ergosterol
(32)

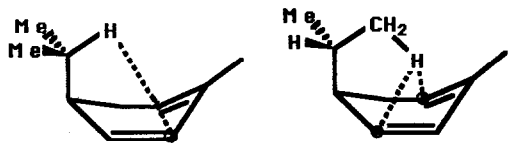


(33)

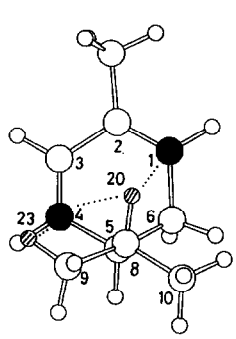
A cyclic monoterpene compound, α-phellandrene (**33**), has been shown to be a mixture of quasi-equatorial and quasi-axial conformers.[169] A substantial proportion of the quasi-axial form exists at room temperature, and it is known that the rotational strength of the quasi-axial conformer

(M-helicity: negative CD) is much larger than that of the quasi-equatorial one (P-helicity), as evidenced by low-temperature CD measurements.[186–189] This may also be due to the CH/π interaction. The axial isopropyl methine as well as the CHs in methyls can interact with an sp^2 carbon in the diene system by forming a five- or six-membered weak hydrogen-bond.



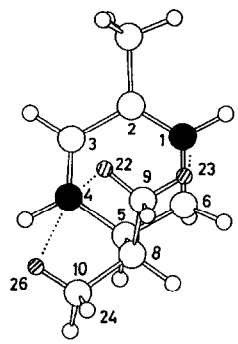


Ab initio calculations[190] (4-31G//STO-3G) on the three optimized conformations of **33** gave positive bond populations between the non-bonded H and the olefinic C atoms which occupy geometrically advantageous positions for CH/π interaction (Fig. 24). Further examination of the MO functions showed that the relevant H and C orbitals are always in phase both in HOMO and LUMO in most cases in Fig. 24. This is strong evidence for the participation of delocalization forces between these pairs of atoms.



5-iso-Pr axial, C(6)-H(20) +sc

	d	p
C(4)-H(23)	2.61A	1.18×10^2
C(4)-H(20)	2.79A	7.11×10^3
C(1)-H(20)	2.86A	1.18×10^2



5-iso-Pr axial, C(6)-H(20) -sc

	d	p
C(4)-H(26)	2.86A	5.51×10^3
C(4)-H(22)	2.86A	1.13×10^2
C(1)-H(23)	2.80A	8.80×10^3

Fig. 24. Five-membered and six-membered CH/π interactions in α-phellandrene.

Lightner and coworkers[189,191] have studied the conformational equilibria of a series of 5-substituted cyclohexa-1,3-dienes. They report that the quasi-equatorial conformers are only slightly more stable than the quasi-axial ones; ΔG_{ax-eq} is ca. 0.05, 0.25, and 0.4 kcal mol^{-1} for methyl, isopropyl (α-phellandrene), and *t*-butyl derivatives, respectively. Lack of 1,3-diaxial repulsion (in contrast to

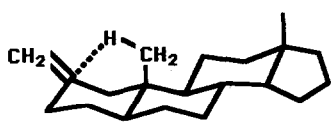
the parent cyclohexane system) may play a part in stabilizing the quasi-axial conformer with respect to the quasi-equatorial one. It seems reasonable, however, to look for other kinds of interactions which are attractive in nature. Thus, in the 5-methyl group there are three hydrogens which can participate (not necessarily simultaneously) in a five-membered interaction with C(1), whereas in the isopropyl group there is only one. The *t*-butyl group has no hydrogen of this type. On the other hand, the number of methyl groups increases in the order from methyl to *t*-butyl. One of the hydrogens in a methyl (in isopropyl and *t*-butyl) group may also form an intramolecular weak hydrogen-bond with the use of the same or another sp^2 carbon in the diene system.

4.2.3. *Chiroptical properties of olefinic compounds.* The concept would have implications in other π-systems. A possible example reported by Fetizon and Hanna,[192] and by Hudec and Kirk,[193] is cited here. As has been pointed out by Gawronski and Kielczewski,[181] the axial homoallylic methyl group in *exo*-methylene steroids exerts significant effects on their CD spectra (Table 16).[192,193]

Table 16. CD Spectra of several exo-methylene steroids

Compound	Δε	λ/nm
1-methylene-5α-androstane	-2.2	199
2-methylene-5α-androstane (**34**)	+10.5	197
3-methylene-5α-androstane	+6.4	193
4-methylene-5α-estrane	-4.1	199
4-methylene-5α-androstane	-10.5	200
6-methylene-5α-estrane	-0.3	205
6-methylene-5α-androstane	+4.2	197
6-methylene-5α-cholestane	+5.6	200
6-methylene-5β-spirostane-3β-ol	+9.0	198
deoxyonocerine (**35**)	-14.5	202
16-methylene-5α-androstane	-7.9	193
17-methylene-5α-androstane	+3.8	193

Dreiding models of these steroids suggest that a five- or six-membered interaction is possible in cases where a significant enhancement of CD is observed. This is illustrated for representative cases of 2-methyleneandrostane (**34**) and an 8-methylene compound, deoxyonocerin (**35**). Such an interaction does not easily occur in 1- and 17-methylene steroids.



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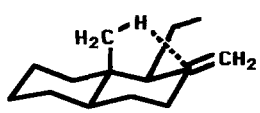


(35)

In conclusion, we suggest that the axial homoallylic effect represents a symbolic expression of a more general rule. The essential and sufficient factor for the enhancement of the Cotton effect amplitude is the presence of CH groups which can interact in a through-space manner with the π-orbital of the chromophore. The CH group (more generally XH, X = C, O, N, etc.) may be located more remote than the homoallylic position if the groups are oriented suitably for the orbital interaction to occur. Therefore, the conditions to be considered are, (1) the number and the nature of the CH groups, (2) the distance (and angle) of the hydrogen atom to the plane of the π-system, (3) the shape of the orbitals at the relevant atoms, and (4) the mobility of the groups involved in the interaction; the probability for the interaction depends on the mobility and the symmetry properties of the groups.

4.3. *Conformations and chiroptical problems of cyclohexanones*

4.3.1. *The alkyl ketone effect.* After the pioneering work of Robins and Walker,[194] axial groups in 2- or 3-substituted cyclohexanones have been known to be thermodynamically stabilized in contrast to those in the parent cyclohexane derivatives. The problem was elucidated later by Klyne[195] and this was termed the alkyl ketone effect. According to Cotterill and Robinson,[196] the alkyl ketone effect is defined as the following quantity:

$$\Delta H_{eq-ax}(\text{alkylcyclohexanone}) - \Delta H_{eq-ax}(\text{methylcyclohexane}).$$

Efforts have since been made to account for the origin of this effect.[196-200] The interpretations were largely made on the basis of a diminution in repulsive interactions in the axial isomers brought about by substituting a methylene moiety with a carbonyl group.

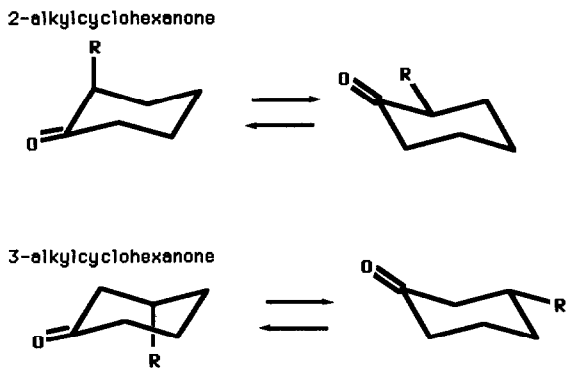
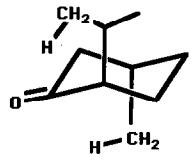


Fig. 25. Conformational equilibria of 2- and 3-alkylcyclohexanones.

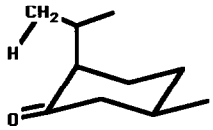
We prefer to explain the above phenomena in terms of interactions which are attractive in nature. The alkyl ketone effects have been estimated[199,200] to be ca. 0.7 and 1.4 kcal mol^{-1} for 2-ethyl- and 2-isopropylcyclohexanones, respectively. This is reasonable, since the number of CH groups which can interact favourably with the sp^2 carbon increases when the 2-substituent is transformed from ethyl to isopropyl. The effect is negligible in the case of 2-methylcyclohexanone. This is understandable since the 2-methyl group has no hydrogens which can interact with the carbonyl group (note that four-membered interaction occurs only with difficulty due to the wrong angle and torsional strain). For 3-methyl and 3-isopropylcyclohexanones the free energy differences were estimated, respectively, to be ca. 1.3[200] and 1.6 kcal mol^{-1}.[199] Accordingly, 3-alkyl ketone effect is smaller in 3-isopropylcyclohexanone than in 3-methylcyclohexanone. This also is reasonable, since there are

three hydrogens in 3-methylcyclohexanone, which can be involved in the five-membered interaction. The isopropyl homologue has only one such hydrogen.†

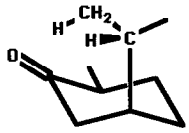
Thus, appreciable contribution from axial conformers has been reported in a number of terpenic ketones. To cite a few cases, importance of the diaxial conformer has been demonstrated in the conformational equilibrium of (−)-menthone (**36**).[203,204] It has been suggested that the axial isopropyl conformation is an important contributor for (+)-isomenthone (**37**).[201,202,204,205] For isocarvomenthone (**38**), the axial isopropyl conformer has been reported to be preferred.[196]



menthone (36)



isomenthone (37)



isocarvomenthone (38)

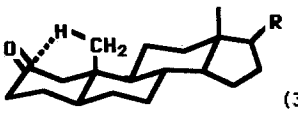
Another interesting feature in the chemistry of 2-alkyl-cyclohexanones is the increase in the magnitude of the Cotton effect observed in compounds bearing an axial isopropyl group. Significant increases in CD amplitudes corresponding to the n–π^* transition have been reported for the diaxial conformer of **36** and the axial-isopropyl conformer of **37** as compared with those in equatorial ones.[202] For 2β-isopropyl-19-nor-5α-androstan-3-one, an increase of about five-fold in CD amplitude has been reported as compared with that of the 2α (equatorial isopropyl) isomer.[206]

4.3.2. *Short wavelength* (190 *nm*) *CD of cyclic ketones.* Effects due to polarizability of nearby atoms or groups are important in considering the chiroptical properties of carbonyl compounds. It has been established that the sign and magnitude of CE at 290 nm is determined principally by the chirality contribution of a group or an array of bonds (e.g., zig-zag arrangement in steroids) to the carbonyl chromophore.[207] Thus the effect of an axial methyl group located at position β to the carbonyl group (equivalent to the homoallylic methyl in the C=C double bond systems) is known to be relatively unimportant as compared with that from an α-axial methyl group in determining the CD amplitude at n–π^* transitions.[207,208]

Kirk[209] has reported that, at a shorter wavelength transition (ca. 190 nm) of various decalones and steroids, a significant effect is brought about by introduction of an axial methyl group to the carbonyl function. Thus, 5α-cholestan-2-one (**39**) gives a large CE (Table 17, $\Delta\varepsilon$ +4.9) dominated by a significant contribution from the β-axial methyl group, while CE in 19-nor compound is negligibly small. A D-homo-5α-androstan-17-one (**40**) also exhibits a significant but negative CE ($\Delta\varepsilon$ −5.0). Another illustration of this effect is provided by comparison of the CE of a 4-oxo-5α-steroid (**41**) with those of the 6-oxo-isomers (**42a–c**).[208] The geometrical disposition of the 10-methyl group with respect to the carbonyl chromophore is quasi-enantiomeric in these compounds. Accordingly, they give rise to 190 nm CD curves which are approximately mirror images of each other, while at 290 nm all these compounds exhibit similar CD bands (with positive CE).

Analogous to the discussion in the preceding section about the chiroptical properties of cyclohexadienes, we suggest that charge-transfer, or delocalization, interactions may well be relevant. Obviously, the same approach does not apply because the relevant CE is concerned with other types of transitions (n–σ^*, n–3s (Rydberg), or others).[209] The above phenomenon is, however, interpreted reasonably if we assume that an orbital interaction takes place in a through-space manner by use of a CH in the β-axial methyl groups (**39–42**).

† Only one of the CH group actually interacts with the π-system of the carbonyl group. However, the number of the CH groups can be expected to contribute to the free energy difference by causing the increase in entropy term, since almost all of the reported alkyl ketone effects have been calculated on the basis of free energy difference.



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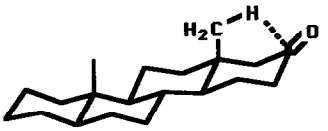

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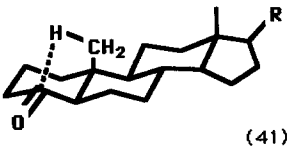
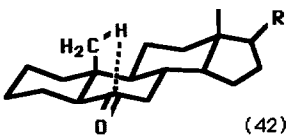


(41)



(42)

Table 17. Short wavelength CD spectra of several cyclic ketones

Compound	$\Delta\varepsilon$	λ/nm
5α-Cholestan-2-one (**39**)	+4.9	194
19-Nor-5α-cholestan-2-one	0.0	
3β-Acetoxy-D-homo-5α-androstan-17-one (**40**)	-5.0	187
5α-Cholestan-4-one (**41**)	-4.2	194
5α-Cholestan-6-one (**42a**)	+5.1	194
5α-Androstan-6-one (**42b**)	+4.8	192
5α-Pregnan-6-one (**42c**)	+5.1	194
5α-Estran-6-one	+1.0	195
5β-Androstan-4-one (**43**)	+16	188
10-Methyl-7-isopropyl-cis-decalone (**44**)	-12.7	185
5β-Spirostan-2-one (**45**)	-8.7	187
1,10-Dimethyl-7-isopropyl-cis-decalone (**46**)	-3.0	185

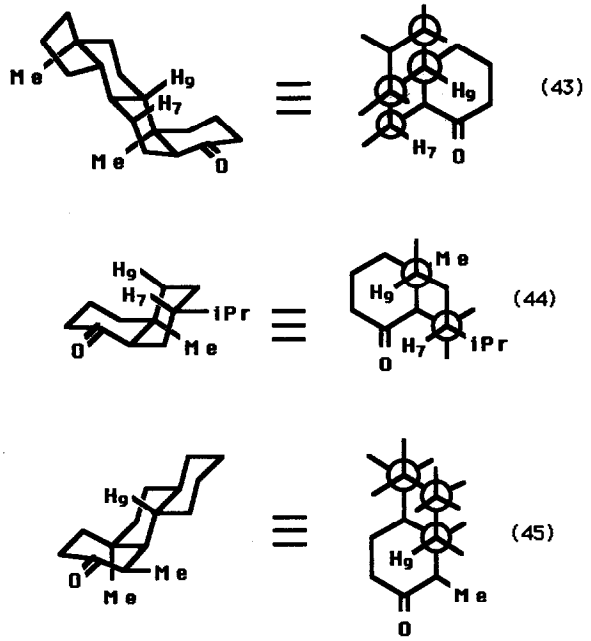


Fig. 26. The CH/C=O interaction in cyclic ketones **43**–**45**.

Exceptionally large CEs have been reported for 5β-androstan-4-one (**43**, Δε +16) and 10-methyl-7-isopropyl-cis-1-decalone (**44**, −12.7). This was argued to be due to the presence of a secondary zig-zag array which is possible in this type of compound.[209] As an alternative interpretation, it may be pointed out that there are two CH bonds (e.g. 7α and 9α-H in **43**) which are positioned suitably for through-space interaction (Fig. 26). 5β-Spirostan-2-one (**45**) shows a smaller CE (Δε −8.7) than those of the two compounds (**43** and **44**). This is understandable because such a CH bond (as H_7 in **43** and **44**) is absent in the molecule (**45**).

Dissymmetric perturbation of the *n*-orbital is thought to be mainly responsible for the 290 nm CE (n–π^* transition) of a ketone. However, this may not be valid in other types of transition such as n–σ^*, π–π^*, or n–3s, as was envisaged in the preceding discussion. We believe that it is difficult to account for the chiroptical problems of these compounds without taking into account through-space orbital interactions involving CH groups.

5. CONCLUSION

Interaction between hydrocarbon moieties is often classified as hydrophobic interaction and is assumed to result from attractive and repulsive van der Waals forces operating between the molecules involved. However, the hydrogen-bond-like character of the interaction can be observed experimentally in some cases, especially in systems containing an acidic CH group and a basic π-moiety. The concept of CH/π interaction is an extension of hydrogen bonding and can be expected to be widely used in the interpretation of the behaviour of organic molecules and their assemblies.

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