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The Conformations of 2-Phenylpropionaldehyde and Some Aliphatic Ketones. The Possible Importance of the CH/π and CH/n Interactions in Determining the Molecular Geometry of a Mobile System

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The conformations have been studied by means of NMR spectroscopy, largely by the computer simulation of the lanthanoid-induced shifts, for a series of aliphatic carbonyl compounds with the following structures: $CH_3CH(C_6H_5)CO$–R; R=H, CH_3, C_2H_5, i-C_3H_7, and t-C_4H_9. It has been suggested that two rotamers are important in the conformational equilibria of these ketones, in which the R–C–C–C_6H_5 dihedral angle is *ca.* 30° and *ca.* 90°. The relative stability of the above two rotamers has been found to depend on the nature of the alkyl group, R. The results have been discussed in light of the possible weak attractive forces, the CH/π and CH/n interactions.

In connection with the interest described in the preceding paper,[1)] we have now studied the conformation of a series of acyclic carbonyl compounds with the following structures:

$$CH_3CH(C_6H_5)CO\text{–}R$$

$$R = H(\mathbf{1}),\ CH_3(\mathbf{2}),\ C_2H_5(\mathbf{3}),\ i\text{-}C_3H_7(\mathbf{4}),\ t\text{-}C_4H_9(\mathbf{5}).$$

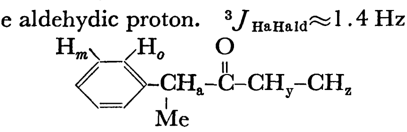
Results

Tables 1 and 2 list the proton and carbon NMR data, respectively, for 2-phenylpropionaldehyde (**1**), 2-phenyl-3-butanone (**2**), 2-phenyl-3-pentanone (**3**), 2-methyl-4-phenyl-3-pentanone (**4**), and 2,2-dimethyl-4-phenyl-3-pentanone (**5**).

TABLE 1. PROTON CHEMICAL SHIFTS[a)] FOR THE $CH_3CH(C_6H_5)CO$–R KETONES

R		H_z	H_y	Me	H_a	H_m	H_o	H_{ald}[b)]
H	(**1**)	—	—	1.40	3.58	7.44	7.32	9.63
Me	(**2**)	—	2.01	1.37	3.70	7.21	7.19	—
Et	(**3**)	0.95	2.35	1.38	3.73	7.20	7.20	—
Pr^i	(**4**)	0.90 1.06	2.66	1.36	3.89	7.20	7.20	—
Bu^t	(**5**)	1.09	—	1.38	4.26	7.26	7.26	—

a) Ppm downfield from internal TMS in $CDCl_3$.
b) The aldehydic proton. $^3J_{H_aH_{ald}} \approx 1.4$ Hz.



The Computer Simulation of the Lanthanoid-induced Shifts. The conformations of these compounds have been studied according to the method described in the preceding paper. For the present purpose of simulating the conformation of a ketone, a modification is necessary for the lanthanoid-distribution parameter. In the case of a carbonyl compound, the LSR can be assumed to be distributed, practically, only in the plane of the C=O double bond and to orient itself toward the lone-pair electrons on the carbonyl oxygen atom; the rationale for this approach has been presented by Montaudo and his co-workers.[2)] Here, we used an index, p, the molar fraction of the Type **a** complex in Fig. 1, for describing the proportions of the diastereoisomeric LSR–ketone complexes. The input data were the atomic coordinates (standard values) and the experimental LIS's (Table 3) for the appropriate nuclei. The lanthanoid (Ln)–O–C angle (ω) was fixed at 140.[2b)] The Ln–O distance (R) and the R–C(8)–C(7)–Ph dihedral angle (ϕ) were then varied, step by step, at a given LSR-distribution parameter (p) in order to search for the most reasonable fit of the computed LIS's with the observed ones. The number of the monitor nuclei were 9.[1)]

Figure 2 plots the agreement factors (AF) against

TABLE 2. CARBON CHEMICAL SHIFTS[a)] FOR THE $CH_3CH(C_6H_5)CO$–R KETONES

R		1	2,6	3,5	4	7	8	9	10	11
H	(**1**)	137.7	128.3	129.0	127.4	52.9	200.8	—	—	14.6
Me	(**2**)	140.6	127.8	129.0	127.1	53.7	208.5	28.3	—	17.2
Et	(**3**)	140.9	127.8	128.8	127.0	52.7	211.2	34.2	8.0	17.5
Pr^i	(**4**)	140.7	127.9	128.8	127.0	51.1	214.4	39.2	18.3 19.2	18.2
Bu^t	(**5**)	141.4	127.6	128.5	126.7	46.4	215.7	45.1	26.6	21.1

a) Ppm downfield from internal TMS in $CDCl_3$.

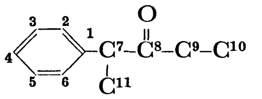


Table 3. The lanthanoid-induced shifts[a] for the $CH_3CH(C_6H_5)CO$-R ketones

R		H_o	H_m	H_a	Me	H_{ald}	H_y	H_z	1	2,6	3,5	4	7	8	9	10	11
H	(**1**)	0.11		0.27	0.22	0.52	—	—	0.22	0.15	0.11	0.08	0.39	1.00	—	—	0.24
Me	(**2**)	0.16		0.27	0.23	—	0.31	—	0.23	0.15	0.1	0.08	0.38	1.00	0.46	—	0.27
Et	(**3**)	0.13	0.06	0.27	0.23	—	0.26	0.20	0.25	0.22	0.19	0.11	0.44	1.00	0.44	0.36	0.31
Pr^i	(**4**)	0.13	0.06	0.26	0.22	—	0.25	0.20 0.16	0.26	0.18	0.1	0.06	0.42	1.00	0.42	0.26 0.25	0.32
Bu^t	(**5**)	0.22	0.03	0.26	0.25	—	—	0.18	0.27	0.20	0.09	0.07	0.46	1.00	0.44	0.24	0.32

a) The chemical shifts induced by the addition of $Yb(fod)_3$ in $CDCl_3$ solutions. The data are normalized to the value for C(8) carbon ($LIS_{rel}=1.00$). See Tables 1 and 2 for the numbering of the nuclei.

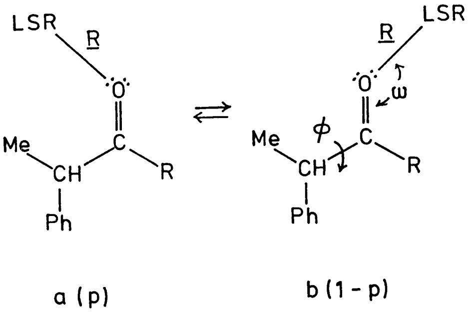


Fig. 1.

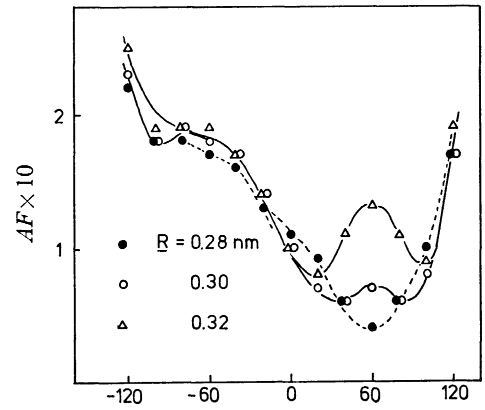


Fig. 2.

the R/Ph dihedral angle (ϕ) for the representative case of Compound **2** (R=Me). Here, the value of p is fixed at 0.4, while the Ln–O distance (R) is varied from 0.28 to 0.32 nm. For R=0.28 nm, the profile shows a single minimum at $\phi=60°$, accompanied by a shoulder at *ca.* $\phi=-80°$. For a longer Ln–O distance, this minimum splits into two shallow minima at $\phi=40°$ and 80° (R=0.30 nm), and then into more distinct minima at $\phi=20°$ and 100° (R=0.32 nm). The agreements have been found to become poorer for R=0.26 and 0.34 nm. A similar trend has also been found to exist for the other ketones and aldehyde. Thus, at a certain Ln–O distance (0.30—0.32 nm) the agreements become reasonably good, and the presence of a second minimum or an inflection becomes most clear. To illustrate this, parts of the AF maps for Compounds **4** and **5** (R=Pr^i and Bu^t) are shown in Table 4. The shape of the AF/ϕ profile has been found to be rather insensitive to the population index in the range of *ca.* p=0.2—0.6 in the case of the **2** ketone. The most satisfactory results have been obtained at around p=0.4, 0.4, 0.3, and 0.2 respectively for **2**, **3**, **4**, and **5**.[3)]

Table 4. Parts of the AF (in %) maps for compounds **4** and **5**

	ϕ/deg							
R/nm	0	20	40	60	80	100	120	140
(a) Compound **4** (p=0.3)								
0.26	25	23	20	18	17	18	23	39
0.28	21	17	14	12	9	9	16	32
0.30	19	15	14	14	10	6	12	28
0.32	19	16	16	17	13	8	11	27
0.34	19	17	19	20	17	11	12	27
(b) Compound **5** (p=0.2)								
0.26	44	42	40	38	37	37	39	58
0.28	27	24	22	21	18	16	18	46
0.30	20	17	16	15	11	6	11	41
0.32	22	19	18	17	14	11	15	40
0.34	26	24	23	22	20	18	21	41

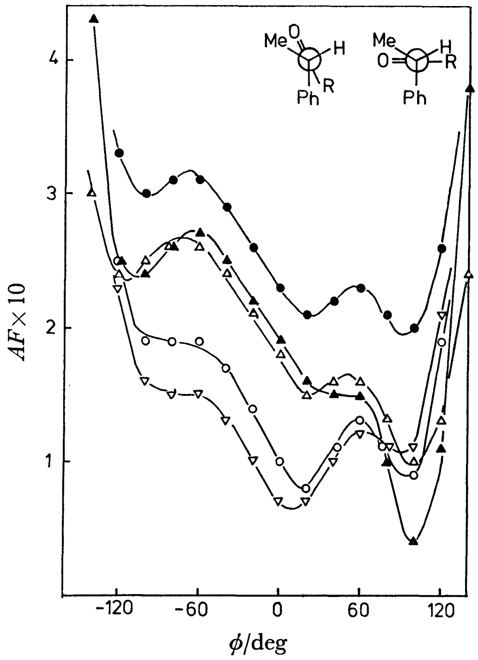


Fig. 3. Plots of AF *vs.* the R/Ph dihedral angle (ϕ) for Compounds **1**—**5**.
The Ln–O distance (R) is kept constant at 0.32 nm. ▽: R=H (**1**), ○: R=Me (**2**), ●: R=Et (**3**), △: R=Pr^i(**4**), ▲: R=Bu^t(**5**).

Figure 3 gives the AF/ϕ plots for all of the compounds presently studied (R is fixed at 0.32 nm). We may note at first that there are three minima (or two minima and an inflection) in these figures. The above finding is consonant with the general understanding that there is a three-fold barrier to rotation about the carbon-carbon bond for aliphatic aldehydes and ketones. The agreements are better in the ϕ=0°—120° range and worst at around ±180°. The most impressive is perhaps the fact that two AF minima are found at *ca.* ϕ=30° and 90° for all of the compounds examined here. The relative importance of these minima appears to be dependent on the nature of the alkyl group, R.[4]

The Relevance of the Present Results to the Conformational Problem of Carbonyl Compounds. A change in the conformational equilibrium may be brought about by the addition of a LSR. This has been found to be negligible in the case of **1**. The vicinal coupling constant between the aldehydic proton and the benzylic proton was found to be *ca.* 1.4 Hz; this was shown to be insensitive to the addition of the lanthanoid species. It is assumed, by analogy, that the rotameric equilibria are not appreciably perturbed by the complex formation for the other compounds in this series, either. This is supported by the fact that the perturbation to the conformational equilibria has been found to be unimportant in the cases of the structurally related sulfoxides[5] and alcohols.[1,6] Except for some particular cases,[2b,7] the conformation of a molecule has been shown not to be influenced by the complexation with a LSR. The internal consistency of the simulated result (*vide infra*) is an additional support for the above assumption.

It has become clear, from earlier studies, that the Ln–O distance (R) at which the best agreement is obtained varies with the nature of the functional group in the substrate molecules. Thus, in the case of the sulfoxides we have noted that the goodness of fit reached its maximum at R=0.34—0.38 nm.[5b,8] The best fit has been recorded at R=0.30—0.32 nm in the case of alcohols.[1,9] This is illustrated in Table 5 for some representative cases. This does not imply that the above values are necessarily the most correct ones for the Ln–O distance. It is likely, however, that these values reflect the complexing abilities of the SO, OH, and C=O groups. Among these groups, the carbonyl oxygen is intermediate as a base, and it is reasonable to expect that the value of R falls between the above two cases. In view of this, the results computed at around R=0.32 nm have been taken to be pertinent to the present problem of the conformational preferences of the ketones. The agreements are, indeed, reasonably good in this range of the Ln–O distance. It is noteworthy that the AF/ϕ plots (for R=0.30—0.32 nm) have two distinct minima, at ϕ=20°—40° and 80°—100°, in all of the cases studied.[10] We believe that this phenomenon is relevant to the present problem of the conformational behavior of these compounds. It is likely that there are two rotamers which correspond approximately

TABLE 5. THE R-DEPENDENCE OF AF[a] FOR $CH_3(Ph)CH$-X-R COMPOUNDS

R	Bu^t	Me	Bu^t	Me	Bu^t(5)	Me (2)	
X[d]	SO	SO	CHOH	CHOH	CO	CO	
p (or A[b])	0.4	0.4	0.4	0.4	0.2	0.4	0.4
Dihedral angle/deg[c]	70	60	80	60	100	20	100
R/nm							
0.24	376	82	31	22	71	21	25
0.26	125	46	19	16	37	14	16
0.28	59	25	10	12	16	9	10
0.30	31	13	6	11	6	7	8
0.32	16	7	7	11	11	8	9
0.34	8	7	10	13	18	11	12
0.36	3	10	13	15	23	13	15
0.38	3	12	15	16	27	15	17
0.40	5	13	17	18	30	16	19
0.42	7	14	19	19	32	18	20

a) $AF\times10^2$. b) Index for the LSR distribution (see text). c) The R–X–C–Ph dihedral angle. d) The X group in $CH_3(Ph)CHX$-R. The Ln–O–C angle was set at 120°, 130°, and 140° respectively for sulfoxides, alcohols, and ketones.

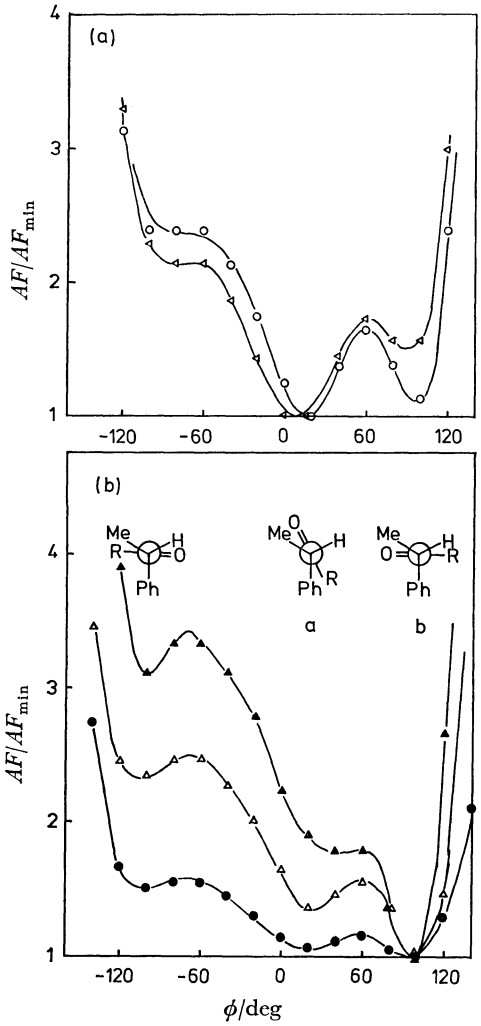


Fig. 4. Plots of the relative AF (AF/AF_{min}) *vs.* the R/Ph dihedral angle (ϕ) for (a) **1** and **2**, and (b) **3**—**5**.
The parameters p and R are kept constant at 0.4 and 0.32 nm, respectively. ◁—◁: R=H (**1**), ○—○: R=Me (**2**), ●—●: R=Et (**3**), △—△: R=Pr^i (**4**), ▲—▲: R=Bu^t (**5**).

to these ϕ-values.[11]

The Preferred Rotamers in the Conformational Equilibria of 1—5. In order to see the effect of the alkyl substitution on the conformational preference, the relative *AF* (AF/AF_{min}) was plotted against the R/Ph torsional angle (ϕ).[12] It is clear from Fig. 4 that the relative *AF* values at $\phi \approx 30°$ and $\phi \approx 90°$ (these correspond to the rotamers **a** and **b** in Fig. 5, respectively) vary regularly with the change in the R group. Judging from the shapes of the curves, the contribution of the rotamer **a** appears to be largest for 2-phenylpropionaldehyde (R=H, **1**). The proportion of the rotamer **a** to the rotamer **b** seems to decrease as the aldehydic hydrogen in **1** is replaced by the methyl, ethyl, isopropyl, and then *t*-butyl groups. The two types of rotamers appear to be equally probable in the cases of **2** and **3**; the rotamer **b** is suggested to prevail in the rotameric mixture of **5**.[13]

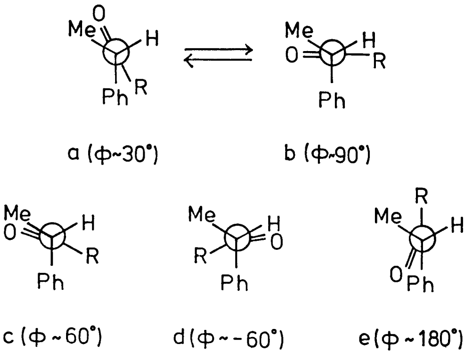


Fig. 5.

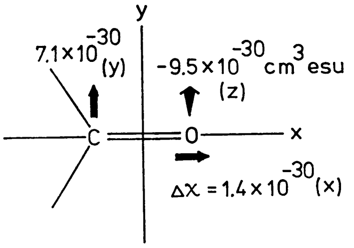


Fig. 6.

Support for the above suggestion regarding the conformational preferences of these compounds is provided by the proton NMR data. The peaks attributed to the benzylic hydrogen (H_a) appear at 3.58 ppm for **1**. They gradually move to a lower magnetic field upon the alkyl sustitution, and finally to a value of 4.26 ppm for the *t*-butyl homologue (**5**). This trend can be well understood in terms of the magnetic anisotropy of the C=O double bond (Fig. 6). Table 6 summarizes the computed data ($\Delta\sigma$ for H_a) for various conformations of a ketone.[15] Thus, in the most preferred conformations, the H_a in **1** positions itself in the shielding region of the carbonyl group, whereas H_a in **5** does not (Fig. 7a). The intermediate data found for the other ketones, **2**, **3**, and **4**, correspond to the suggested change in the conformational equilibria.[17] For the conformation of **1**, another support is provided by the fact that the aromatic protons in this compound are significantly shifted to lower magnetic fields relative to those in other compounds. According to the suggested conformation (Fig. 7b), H_o and H_m in **1** are well positioned in the deshielding region of the carbonyl group. The coupling constant found for the aldehyde is compatible with this conformation.

Table 6.

ψ	ϕ	$\Delta\sigma \times 10^{-30}$/cm^3 esu
150°	90°	−0.40
120°	60°	−0.42
90°	30°	−0.46
60°	0°	−0.81

a) For the meaning of the angles, see Fig.7 (a). $d_{\mathrm{C=O}}$, 0.14 nm; $d_{\mathrm{C-C}}$, 0.152 nm; ∠C–C=O, 120°, ∠C–C–H, 110°.

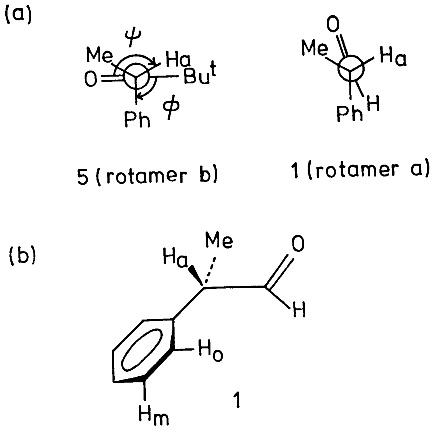
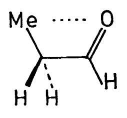


Fig. 7.

The suggestion that these conformations are important for the **1**—**5** ketones is in line with our thesis that an alkyl group prefers to lie close to a phenyl group; this again indicates the necessity to invoke an attractive force between these groups. The above conformation is compatible with the molecular geometries of some carbonyl compounds previously proposed for describing the transition state of the diastereoface-differentiating reactions.[18] We believe that the present results have an obvious implication in this problem.

Discussion

A Possible Role of the Weak CH···O Hydrogen Bond in Determining the Conformational Preferences of Carbonyl Compounds. The above conclusion is consonant with the general understanding that a methyl group interacts favorably with a carbonyl group. Thus, for a number of aldehydes and ketones, it has been established that a methyl group is nearly eclipsed by the carbonyl oxygen in the preferred conformations. The examples include microwave and NMR studies of propionaldehyde (**6**),[19] an electron-diffraction study of isobutyraldehyde (**7**),[20] and NMR studies of substituted acetaldehydes (**8**),[21] ethyl alkyl ketones (**9**),[22] and 2-substituted 3-pentanones (**10**).[23] For the sake of simplicity, and in



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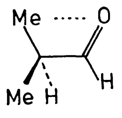

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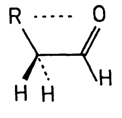

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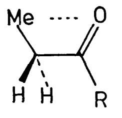

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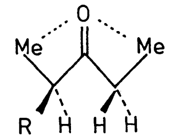

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view of the limitation of the methods as well, the conformations for **6**—**10** are drawn as completely eclipsed. A somewhat twisted conformation, however, is more likely to exist in reality.[21,24] We suggest that such conformations as the above two types (rotamers **a** and **b** in Fig. 5; CH_3/O torsional angle *ca.* ±30°) are both important in the consideration of the conformational problems of these molecules (**1**—**5**). An inspection of the Dreiding models suggests that it would be easier for a hydrogen-bond like interaction involving the CH_3 and O (*vide infra*) to take place with a slightly distorted conformation. By twisting from the completely eclipsed conformation, a molecule comes to be capable of avoiding the energetically unfavorable vicinal H/H interaction (Fig. 8)[25] and simultaneously participating in a CH/O hydrogen bonding.

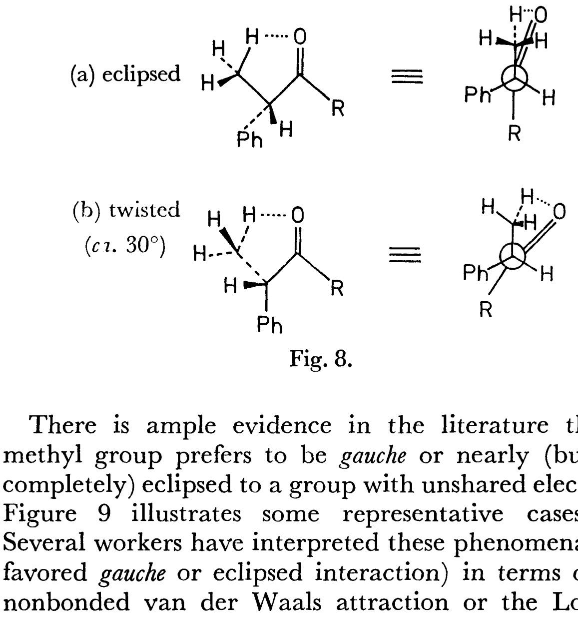


Fig. 8.

There is ample evidence in the literature that a methyl group prefers to be *gauche* or nearly (but not completely) eclipsed to a group with unshared electrons. Figure 9 illustrates some representative cases.[26,27] Several workers have interpreted these phenomena (the favored *gauche* or eclipsed interaction) in terms of the nonbonded van der Waals attraction or the London dispersion force.[28] However, we think it more probable that the favored CH_3/O (more generally CH_3/X, X=O, N, or halogens) interaction traces its origin in a kind of weak hydrogen bond.[6,29] In virtually all cases reported so far, it seems easy for the formation of a 5- or 6-membered intramolecular hydrogen bonding to take place (see **6**—**10**, Figs. 9 and 10). We would refer this hypothetical secondary force to the CH/*n* interaction[29,30] (*n*: unshared electrons).

Supports for the above suggestion have been provided by a number of experimental and theoretical studies.

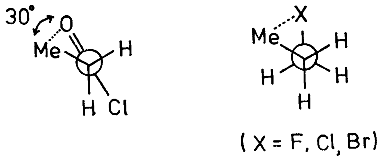


Fig. 9.

In particular, Sutor presented good evidence, from an extensive X-ray study, that there is strong possibility that a CH (CH_2, CH_3) group participates in a weak hydrogen bond with an oxygen atom.[31] Her proposal has since found a number of supports in X-ray[6,32] and NMR[5b,33] studies of a variety of molecules. Some representative examples are illustrated in Fig. 10. The presence of such a weak, hydrogen-bond like interaction has also been suggested by the MO (semi-empirical[34] as well as *ab initio*[35]) calculations of several model systems.

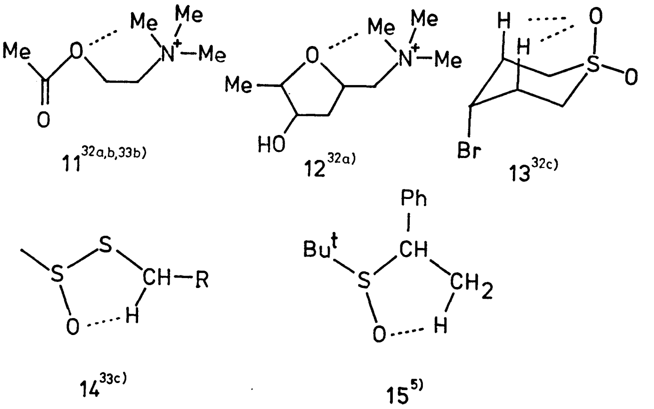


Fig. 10.

Karabatsos and his co-workers studied, by NMR, the conformation of a number of substituted acetaldehydes (**8**).[21] They reported that the relative stability of the rotamer **a** to the rotamer **b** (Fig. 11) decreases as the "size" of the alkyl group (R) increases, and explained this in the framework of the bulk-repulsive concept. We prefer to interpret this differently; this may be a proof for the presence of a CH/O hydrogen bond. It seems likely that it is the "number" of the CH group (which can effectively interact with the carbonyl group) which is more important in determining the relative stabilities of the respective rotamers. The factors responsible for the rotamer stability might thus be the number, the nature (5- or 6-membered, the orientation of the CH bond, the kind of X-group, *etc.*), and the probability of participating in the interaction. In fact, it has been reported that, if one of the substituents in **16** is a methyl group (Fig. 11), the most stable rotamer has always its methyl group which is eclipsed by the carbonyl oxygen.[21] The relative stability of the rotamer **a** in relation to the **b** has been reported to decrease when the methyl group is replaced by another alkyl group. This is reasonable, in our view, since the "number" of the CH groups, which can form a 5-membered H-bond with the carbonyl group,[36] decreases

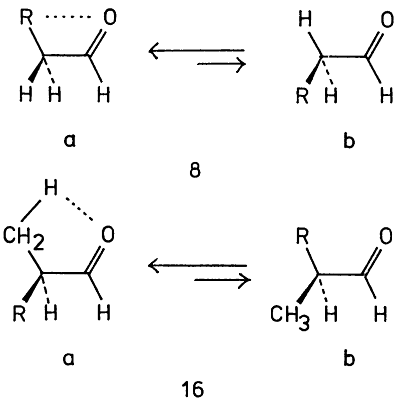


Fig. 11.

on the replacement of the methyl group by another alkyl group.

The Factors Controlling the Relative Stability of the Rotamers ***a*** *and* ***b****; 5- and 6-Membered Intramolecular H-Bond.* With regard to the stability of the rotamer **a** relative to that of the rotamer **b** in Fig. 5, we would invoke the importance of the CH/π interaction. This is a weak attractive force likely to be operative between an alkyl and a π-system,[33a,37,38] the nature of which is ascribed to a kind of weak hydrogen bond. On the basis of experimental and theoretical evidence, the interaction has been suggested to be most effective at a C–H···C(sp^2) interatomic distance of approximately 0.20—0.25 nm.[37,39] An inspection of the Dreiding models (Fig. 12) suggests that such an interaction is likely to occur in the rotamer **a** with the use of a hydrogen (H$_y$) attached to C9 (Type **a** interaction). If the CH/π interaction is operative with the use of the C-1 carbon, the Type **a** interaction is a kind of 5-membered intramolecular H-bond. Another type of interaction is possible with the use of H$_z$ (Fig. 12; Type **b** interaction). This type of interaction forms a 6-membered H-bond and is most likely to occur with the rotamer **b** (Dreiding model). The 5-membered, Type **a** interaction decreases as the alkyl group changes from being a methyl to an ethyl and then to an isopropyl group; in the case of a *t*-butyl group, it is absent. On the other hand, a 6-membered, Type **b** interaction increases in this order.[40]

To explain the present results, one may argue in the framework of the bulk-repulsive concept. It is conceivable that the London dispersion force[41] is responsible, at least in part. We believe, however, that the present finding is better accommodated by considering the effects of the above two types of CH/π interaction involved there. The basic geometries of the respective rotamers are determined by the more dominant CH$_3$/n interaction, which we feel to be somewhat stronger than the CH/π bond. It would be pertinent, in this respect, to cite a recent finding of Inamoto and his group in an X-ray study of a very crowded molecule, bis(2,4,6-tributylphenyl)phosphinic chloride (Fig. 13).[32d] Some of the intramolecular distances found in this compound ($CH_3/C_{aromatic}\approx 0.32$, $CH_3/Cl\approx 0.33$, and $CH_3/O\approx 0.30$ nm) are shorter by 0.04—0.05 nm than the respective van der Waals distances.

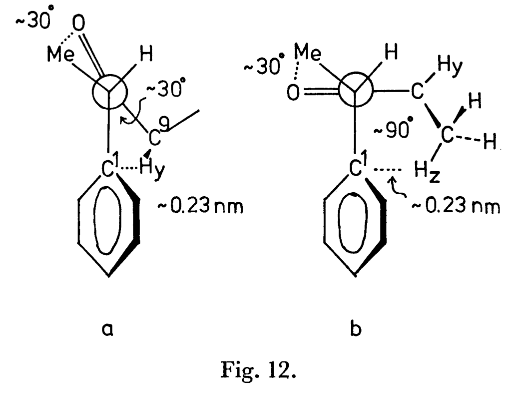


Fig. 12.

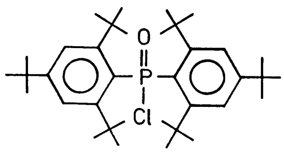
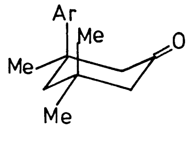


Fig. 13.

Possible Importance of the CH/π Interaction in the Conformational and Selectivity Problems of Various Systems; CH/π Interaction Hypothesis. The stabilization energy for a unit CH/π bonding is very small (*ca.* 3.5 kJ mol^{-1} or less).[6,37] However, we suggest that this type of interaction may contribute to bringing about an appreciable difference between the free-energy levels of a competitive interaction (intramolecular or intermolecular) system. The CH groups (as well as π-system) are generally arranged in a chemical structure with a certain symmetry. The difference in the interaction energies might thus become remarkable, since the "number" and the "chance" for the interaction may be expected to increase in such a case.



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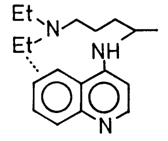

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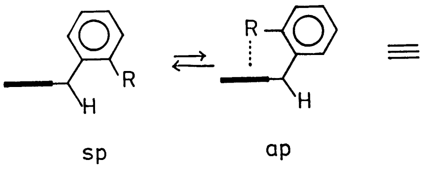

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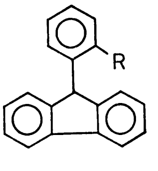


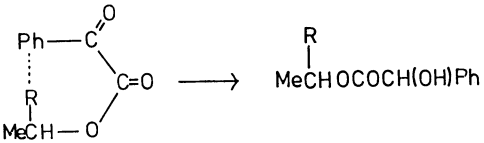
19

Intramolecular Interactions: To cite a few possible cases, Shapiro and his group have reported a remarkable preference for the axial aromatic (as opposed to the methyl) group in **17**.[7a,42] The conformation of an antimalarial substance, chloroquine (**18**), was studied by the LIS method; the side-chain alkyl group in this compound has been shown to be curled over the plane of the quinoline ring.[43] Nakamura, Nakamura, and Ōki recently studied the conformational problem of 9-(2-alkylphenyl)fluorenes (**19**).[44] The free-energy differences between the rotamers have been reported to be 0.3, 0.6, and 0.4 kcal mol^{-1} at 0° (in favor of the sp-rotamer) for the methyl, ethyl, and isopropyl derivatives respectively. The above unusual behavior of the isopropyl homologue might be an indication of the involvement of the CH/π interaction.

$$\underset{(\mathbf{20})}{RCOCOOC_{10}H_{19}} \longrightarrow RCH(OH)COOC_{10}H_{19}$$

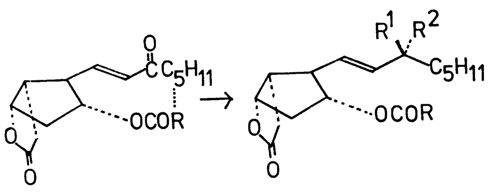
$C_{10}H_{19}$ = menthyl

R	CH_3	C_6H_5
% e.e.	14, 18	22—30



21

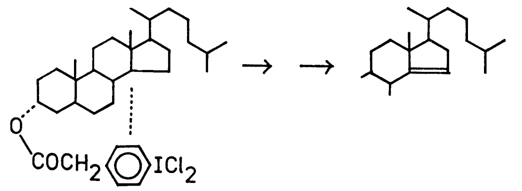
R	n-C_6H_{13}	C_6H_5	α-$C_{10}H_7$
% e.e.	18	3	12



22

23S R^1=OH, R^2=H
23R R^1=H, R^2=OH

R	$(CH_2)_7CH_3$	PhPh(*p*)	PhC_5H_{11}(*p*)	NHPh
S/*R*-ratio	≈55/45	82/18	82/18	89/11



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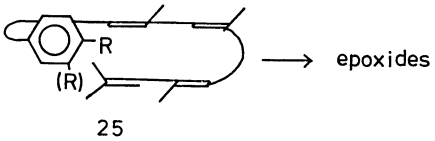

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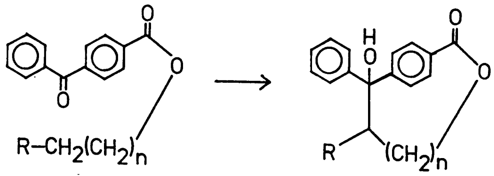
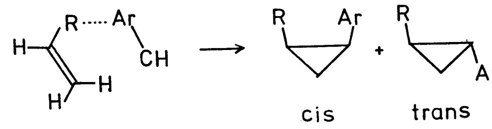


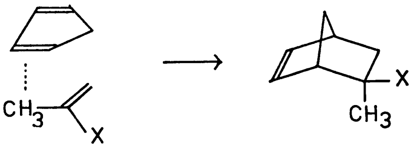
26

Evidence about the conformations of flexible molecules is well reflected in the selectivities in certain reactions (see **20**—**26**). The extent of asymmetric synthesis in a Prelog reaction system (**20**) has been shown to be greater for the benzoyl formate ester (R=Ph) than for the pyruvate ester (R=Me).[45] A similar result has been observed for **21** in the case of a 1-methylheptyl ester (R=*n*-C_6H_{13}) *vs.* a 1-phenylethyl (R=C_6H_5) or 1-(1-naphthyl)ethyl (R=$C_{10}H_7$) ester, the former giving rise to the highest optical yield.[46] Corey and his coworkers have reported that the stereoselective reduction of **22** (a prostaglandin precursor) was better accomplished when they used an ester with an aromatic substituent.[47] The examples from **24** to **26** are extracted from the template-directed functionalizations of Breslow and his group;[48] they have presented good evidence that these molecules are extensively folded in solution. Note that, in all of the reactions cited thus far where remarkable selectivities were observed, the reacting species have an aromatic group on one side, and a long-chain (or branched) alkyl group on the other end of the molecule; an alkyl/alkyl or aromatic/aromatic interaction does not seem to yield a good result in a selective reaction. Therefore, we think it very probable that an attractive interaction of the CH/π type plays an important part in determining the molecular shapes of flexible molecules.



R	Me	Et	Pr^i	Bu^t
cis/*trans*	3.1	2.1	1.4	0.45

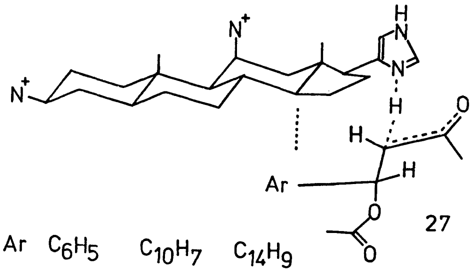
Fig. 14.



(X = CN, COOMe, CHO)

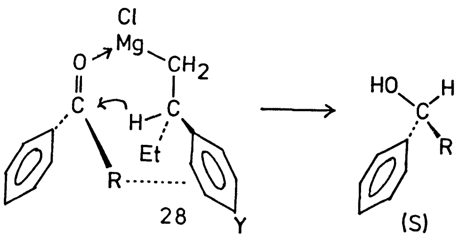
Fig. 15.

Intermolecular Interactions: We feel further that the attractive CH/π interaction plays a more important role in controlling the subtle aspects of the dynamically interacting systems,[49] *e.g.*, the efficacy of molecular recognition[50] and the selectivity problems in certain multimolecular reactions. Thus, Closs and Moss reported a remarkable effect of the alkyl substitution on the stereochemical outcome in a carbene addition to a series of olefins (Fig. 14).[51] A similar result has recently been presented in another case.[52] The *endo*-orienting tendency of the methyl group has been demonstrated for a Diels-Alder reaction (Fig. 15).[53] A steroidal enzyme model has been studied by Guthrie and his group;[54] the enolization of **27** has been shown to be most effectively catalyzed when a large aromatic group is incorporated in the substrate molecule. The rate enhancement has been reported to increase regularly when a phenyl group in **27** is replaced by a naphthyl and then by a phenanthryl group. In an enantioface-differentiat-



27

Ar	C_6H_5	$C_{10}H_7$	$C_{14}H_9$
k_{rel}	9	27	110



28

R\Y	H	OMe	CF_3
C_2H_5	50	57	22 %e.e.
i-C_3H_7	81	84	58

ing reduction of phenyl alkyl ketones with a chiral Grignard reagent (**28**), Guétté and Capillon[55] have found that the introduction of a methoxyl group to the aromatic moiety of **28** results in an increase (slight but distinct) in the optical yield. The extent of the asymmetric synthesis decreases, in contrast, on substitution with an electron-withdrawing group such as CF_3.

In all of the cases cited above, the free-energy level at the transition state (which leads to the favored product) seems to be stabilized by the interaction of an alkyl group with an aromatic system. Certain of the above results were explained in terms of the van der Waals (repulsive as well as attractive) and the so-called hydrophobic interaction.[56] We feel that the substituent dependence of the product ratio (*cis*/*trans*) in the cyclopropane formation (Fig. 14) can better be understood by considering the involvement of the CH/π interaction. The effective "number" of the CH group, which can participate in the stabilization of the activated complex, might thus decrease upon a successive α-methylation ($CH_3 \rightarrow CH_2Me \rightarrow CHMe_2 \rightarrow CMe_3$). In fact, a significant increase in the *cis*/*trans* ratio has been observed upon the replacement of the olefinic hydrogen with a second *cis*-methyl group.[52] The London dispersion force and the hydrophobic interaction[56] perhaps play important parts in the selective enolization of **27**.[54] However, we think it likely that the CH/π interaction plays a role, since the probability of the interaction can be expected to increase with an increase in the surface area of the aromatic ring (phenyl→naphthyl→phenanthryl). At any event, we see no good reason why a compound becomes a good substrate only with an aromatic substituent, if the so-called nonpolar interaction is solely responsible for the observed selectivity.[57] A similar argument may apply to the selectivity problem reported for the reduction of **22** to **23**.[47] Alkyl substituents such as CH_3 and $CH_3(CH_2)_7$ have been reported to be by far less effective than aromatic ones; this is to be anticipated since we have an aliphatic moiety (C_5H_{11}) on the other terminal of the molecule. The results reported for the last example[55] seem to demonstrate that the interaction involved here, in stabilizing the favored 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, such as CH_3 or CH_3O; the inverse is true for CF_3.

Possibilities of Biological Importance: It is tempting to speculate about the possibilities that the interactions of the above kind play an important role also in the biological system.[29,58] These possibilities include the problems of biopolymer folding [59] and the substrate specificities of some globular proteins, such as enzymes and immunoglobulins. As was emphasized by Watson some 15 years ago,[60] the interactions which determine the subtle behavior of the dynamically interacting, complex biomolecules *should be weak* and orientation-dependent. Our knowledge about the important, weak chemical interactions, however, is still far from complete. We suggest that the CH/π (as well as CH/n) interaction is a good candidate for the above important secondary forces in view of its *weakness* and flexibility. Our study is thus being oriented toward an understanding of the nature and the characteristics of these forces, the biological implications of which will form the subject of a future paper.

Experimental

Materials. The 2-phenylpropionaldehyde (**1**) was obtained from a commercial source. The ketones (**2**—**5**) were prepared by treating **1** with appropriate Grignard reagents, followed by the oxidation of the resulting alcohols. The samples were purified chromatographically and gave correct analytical and spectral data.

NMR Measurements. The NMR spectra and the LIS data were determined as has been described in the preceding paper.[1]

We wish to thank Professors Tadashi Endo (Aoyama Gakuin University) and Naoya Nakagawa (University of Electro-communications) for their discussions, Professor Naoki Inamoto (University of Tokyo) for providing information prior to publication, and Dr. Teiichiro Ito (Meiji Seika Kaisha) for his encouragement.

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3) This trend of the Ln-distribution is reasonable in view of the steric consideration.

4) The agreements are very poor for Compound **2** (R=Et). This may be attributed to the absence of *C*3 symmetry for the alkyl group in this molecule. In the above procedure, the contributions from all of the rotamers (regarding the rotation

around the C8–C9 bond) were computed and then averaged. This is a good approximation for compounds with a symmetric group (R=H, Me, or Bu^t), but not for Compounds **3** and **4**. The deletion of the LIS data for H_y, H_z, and/or C10 has, in fact, improved the agreements.

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10) The presence of a single rotamer (ϕ *ca.* 60°; rotamer **c** in Fig. 5) may be suggested for **2** if one considers the results obtained with $R=0.28$ nm to be more appropriate in this case. We, however, feel this to be an artefact which is brought about by the use of an improper Ln–O distance. The above single minimum probably corresponds to the time-averaged geometries of the two rotamers, **a** and **b**, in Fig. 5. It is difficult to believe that the above computational procedure will produce the wrong, artificial conclusion that there is a mixture of two rotamers if, in reality, there is only an unique rotamer prevailing in the solution.

11) The usefulness (as well as the limitations) of the LIS method in studying the conformational problems of carbonyl compounds has been demonstrated by Montaudo *et al.* in the cases of unsaturated ketones and amides.[2]

12) The position and the goodness of fit at the respective *AF*-minimum reflect, although in an indirect manner, the plausible geometry and the relative importance of a substrate–LSR complex.

13) Impressive also is the fact that the rotamer corresponding to ϕ *ca.* −60° (rotamer **d** in Fig. 5) seems to be rather unimportant for all of the compounds studies here. Another notable feature of the above results is the (suggested) nonexistence of the rotamer corresponding to $\phi\approx180°$ (rotamer **e** in Fig. 5); this latter conclusion differs significantly from that of a preliminary force-field calculation of these molecules.[14]

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