Relevance of Weak Hydrogen Bonds in the Conformation of Organic Compounds and Bioconjugates: Evidence from Recent Experimental Data and High-Level *ab Initio* MO Calculations

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1. Introduction

Organic chemists tend to consider the conformation of compounds as a consequence of repulsive steric interactions. In other words, "the steric effect" means "repulsive" in many cases. Thus, folded conformations observed in organic molecules have been often regarded as unusual, while the reason remained undecided. However, accurate determinations by modern spectroscopic methods, recent crystallographic data, and high-level *ab initio* MO calculations have demonstrated that the folded conformation is by no means exceptional. We will show that the *gauche* or folded conformation prevails in organic compounds bearing at least an electronegative or π-group in the molecule. We consider that the above phenomenon finds its origin, in most cases, in nonconventional hydrogen bonds such as the CH/X (X = O, halogen, etc.) and the XH/π (X = O, N, C, etc.) hydrogen bonds.

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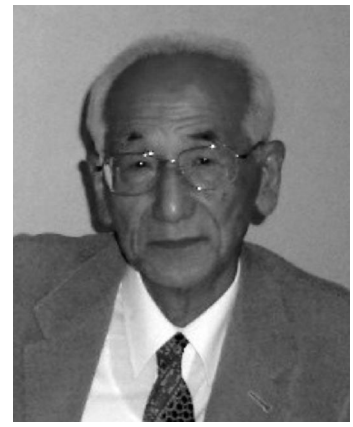
Yuji Kohno obtained his Ph.D. in organic quantum chemistry from Hiroshima University in 1996 under the supervision of Prof. Akira Imamura. He worked at Chugoku Kayaku Co., Ltd (1982−2000), after which he was a research worker for about two years at Hiroshima University. From 2002 to 2004, he was a research fellow at Shock Wave Research Center, Institute of Fluid Science, Tohoku University. He is currently a research worker of Yokohama National University. His research interests include chemical dynamics and kinetics and organic quantum chemistry.

1.1. Conformation of Organic Compounds

The conformation of an organic compound is determined as a compromise of various molecular interactions, attractive as well as repulsive. If two atoms or groups come too close compared with the sum of the van der Waals distances, they repel each other as a result of exchange repulsion. If they are at an appropriate distance, they attract each other by the London dispersion force. Figure 1 illustrates this.

Carter,[1] Streitwieser,[2] and their co-workers provided examples for the attractive steric effect in the conformational equilibrium of 1,3,5-trineopentylbenzene and di-*t*-butyl-cyclooctatetraene (Figure 2). In these cases, the attractive dispersion force outweighs the repulsive van der Waals force.

During the last decades, however, organic chemists have been inclined to explain the conformation of compounds in terms of the repulsive steric interaction between groups.[3] In other words, the steric effect usually means "repulsive". This trend of thinking seems to be due, at least in part, to the success of the Cram rule[4] (Figure 3) and the Prelog rule.[5] According to these rules, the allegedly bulkier groups are



Motohiro Nishio obtained his Ph.D. in physical organic chemistry from the University of Tokyo in 1965. He worked at Meiji Seika Kaisha Ltd (1959−1996), after which he was a visiting professor for 3 years at Chiba University. During that period, he also acted as a visiting scientist (1996−2000) at the Institute of Physical and Chemical Research and Yokohama National University as a Lecturer. In 1999, he established the CHPI Institute in his home address. He published 91 papers, 24 reviews, and 5 books. His research interests include stereochemistry, weak hydrogen bonds in chemistry and structural biology, and rational drug design.

presumed to be in the *anti* relationship (the original authors did not pretend this to be a precise description of the transition states). The brilliant success of Barton in steroid

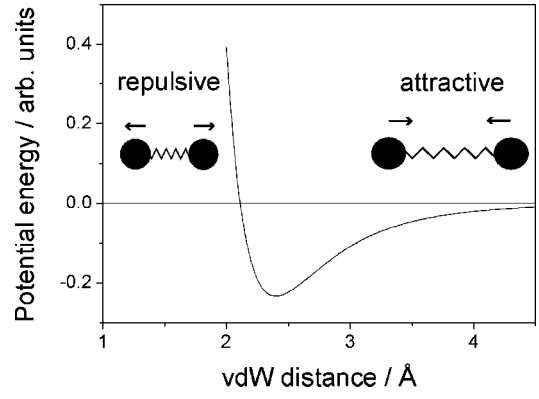


Figure 1. Van der Waals energy plot for the H/H interaction.

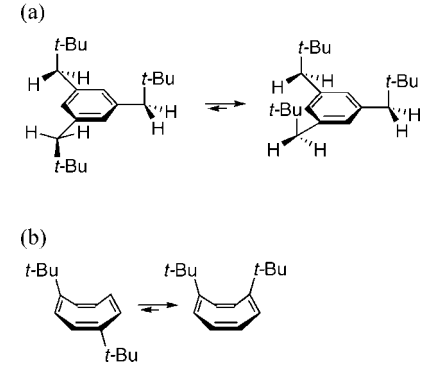


Figure 2. Attractive steric effect as exemplified by the conformational equilibria of (a) 1,3,5-trineopentylbenzene and (b) di-*t*-butyl-cyclooctatetraene.

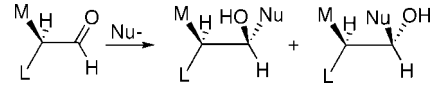


Figure 3. Cram open-chain model (L, largest; M, medium; Nu^-, nucleophile).

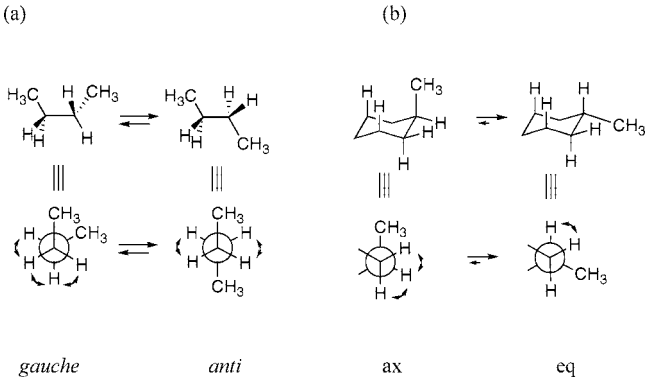


Figure 4. The *anti* conformation is favored in (a) *n*-butane ($\Delta G_{gauche-anti}$ ca. 0.7 kcal mol^{-1}) and (b) methylcyclohexane (ΔG_{ax-eq} ca. 1.8 kcal mol^{-1}). Curved arrows indicate unfavorable vicinal H/H interactions.

chemistry might have intensified the trend of this bulk-repulsive approach. In 1950, Barton explained the thermodynamic and reaction selectivity data of many steroidal compounds, which had remained unexplained to that date,[6] and founded the firm basis of conformational analysis in organic chemistry.

The *anti* conformation is indeed favored in many cases, where "bulky" groups are in the vicinal relationship or in the axial position in a cyclohexane system. Figure 4 illustrates this for *n*-butane and methylcyclohexane.

In 1974, Wertz and Allinger stated that the interaction between vicinal CH groups influences the conformational equilibria of *n*-butane and methylcyclohexane.[7] As a result of the shorter C−H bond length compared with that of the C−CH_3 bond, the repulsive interaction between vicinal CH groups might become more severe than that of CH vs CH_3. In such a geometric disposition, H becomes "more crowded" than CH_3. In support of this hypothesis, in *n*-butane, the allegedly unfavorable H/H interactions are three in the *gauche* but are two in the *anti* conformation (Figure 4a). In methylcyclohexane, there are two H/H interactions in the axial methyl conformer but only one in the equatorial methyl conformer (Figure 4b). According to Allinger, the preference of the equatorial methyl group is not a result of the 1,3-diaxial CH_3/H repulsions but is attributed to the two vicinal H/H interactions in the axial methyl conformer. We do not know, at present, whether this reasoning is correct.

1.2. Folded Conformation

On the other hand, evidence has accumulated that the *gauche* or folded conformation (as opposed to the *anti* or extended conformation) is preferred. In 1958, Morino and Kuchitsu reported that the *gauche* conformer is favored, though slightly, in 1-propyl chloride $CH_3CH_2CH_2$−X (Figure 5, X = Cl).[8] In 1962, Hirota reported a similar result for 1-propyl fluoride (X = F).[9] The reason remained unclear, though the electrostatic attraction was supposed to work between CH_3 and X. We will discuss this point later (section 3.1.3).

In the 1960s, the preference of axial isopropyl group in unsaturated cyclohexane derivatives was reported for terpenic compounds including isomenthone (*cis*-2-isopropyl-5-methylcyclohexanone),[10] isocarvomenthone (*cis*-2-methyl-5-isopropylcyclohexanone),[11] and α-phellandrene [(*R*)-(−)-5-isopropyl-2-methyl-1,3-cyclohexadiene].[12] The reason for the above unusual (in view of the conventional stereochemical considerations) conformations remained unexplained, however. We will discuss on these problems in sections 4.2 and 4.4.

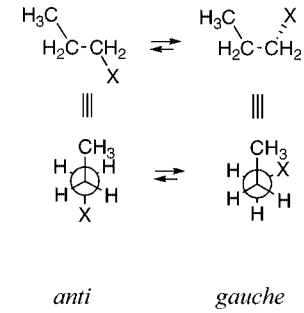
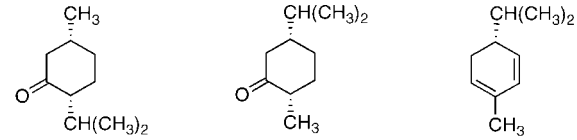


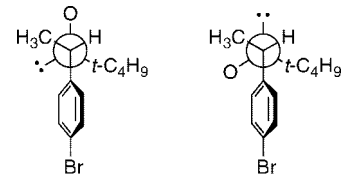
Figure 5. CH_3/X-*gauche* conformation is preferred in $CH_3CH_2CH_2$−X.



isomenthone isocarvomenthone α-phellandrene

In 1961, Burgstahler et al. reported that levopimaric acid exists in the folded conformation in solution, as opposed to the extended conformation, contrary to the anticipation of most organic chemists (Figure 6).[13] In 1971, the crystal conformation of levopimaric acid was found to be similar to that in solution.[14] We will discuss on this point in section 4.5.

A more recent example is the folded conformation reported for a series of simple organic compounds $C_6H_5CHCH_3$−X−R (R = alkyl or aryl). In 1974, we reported that the *t*-butyl group in a sulfoxide diastereoisomer (*p*-Br$C_6H_4CHCH_3SO$-*t*-C_4H_9) is *gauche* to the phenyl group in the solid state.[15] Subsequent spectral[16−18] and dipole moment[19] studies have revealed a similar conformation to maintain in solution.



α(*S*),S(*R*) α(*S*),S(*S*)

The *gauche* R/C_6H_5 relationship has also been shown in the solution conformation of a series of structurally related compounds, including $C_6H_5CHCH_3S$−R, $C_6H_5CHCH_3SO_2$−R,[20] $C_6H_5CHCH_3CH(OH)$−R,[21] $C_6H_5CHCH_3CH_2CO$−R,[22] and $C_6H_5CH_2CH(OH)$−R.[23] These findings led the authors to suggest an attractive force to operate between these groups (Figure 7).

2. Importance of Weak Hydrogen Bonds

Weak attractive forces are important in deciding the conformation of organic compounds and the 3D structure of biomacromolecules. Among molecular interactions, the van der Waals force, electrostatic interactions, and hydrogen

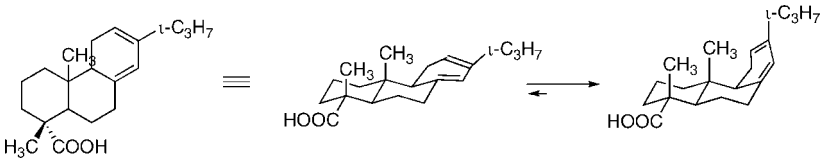


Figure 6. Levopimaric acid exists in the folded conformation.

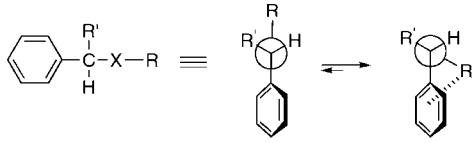


Figure 7. Attractive interaction suggested between R and C_6H_5 (R = alkyl, R′ = H or CH_3).

bonds are the most important. Before discussing the conformational problems of organic compounds, a brief introduction to the hydrogen bond (conventional) and weak (nonconventional) hydrogen bonds seems necessary.

2.1. Hydrogen Bond

In 1960, Pauling stated that the hydrogen bond is formed between X−H and Y, where X and Y are electronegative atoms such as O and N, and that the stabilization comes, largely, from the Coulombic force.[24]

According to Pimentel and McClellan,[25] a hydrogen bond exists between A−H and B when there is evidence of bond formation and that this new bond linking specifically involves the hydrogen atom already bonded to A. Notice that no restriction is made on the chemical nature of the donors and acceptors, nor the energy and the geometry of the participants. The definition of Pimentel has proved to be very useful to the progress of modern chemistry. The hydrogen bond is now recognized to be a much broader phenomenon than envisaged earlier; the energy range of the hydrogen bond covers ca. 0.1 to 60 kcal mol^{-1}.[26]

The energy of hydrogen bonds familiar to most organic chemists and biochemists is ca. 1−7 kcal mol^{-1} per a one unit interaction. In the conventional (normal, ordinary, or classical) hydrogen bond,[27,28] contribution from the Coulomb energy is the most important since this is an interaction between a hard acid (HA) and a hard base (HB) in the context of the Pearson's hard and soft acids and bases (HSAB) principle.[29] The enthalpy of the classical hydrogen bond between OH or NH and O or N is 3−7 kcal mol^{-1}.

2.2. Weak Hydrogen Bonds

In the second half of the last century, evidence has gradually accumulated that hydrogen bonds other than the conventional hydrogen bond are ubiquitous.[30−32] These include CH/*n* hydrogen bonds (*n*, lone pair electrons, as contrasted to π; CH/O, CH/N, etc., 2−4 kcal mol^{-1}) and XH/π hydrogen bonds (X = O, N, etc., 2−4 kcal mol^{-1}).

2.2.1. CH/n Hydrogen Bond

The CH/*n* hydrogen bond is the hydrogen bond between a soft acid (SA; CH) and a HB (O, N, F, Cl). In 1962, Sutor first suggested, on the basis of her own crystallographic data, that the CH/O interaction is a kind of hydrogen bond.[33] In 1982, Taylor and Kennard studied the issue,[34] by using the Cambridge Structural Database (CSD),[35] and proved that the above statement is correct. Extensive database studies by Desiraju[36] and Steiner followed. This is now established as a true hydrogen bond by a number of spectral and crystallographic studies, including database analyses.

2.2.2. XH/π Hydrogen Bonds

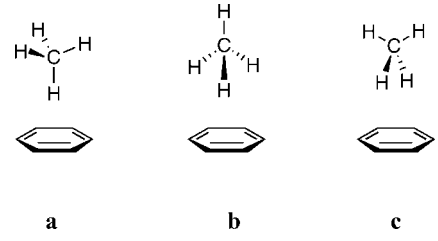
In the 1950s and 1960s, Josien and Sourisseau,[37] Oki and Iwamura,[38] and Yoshida and Osawa[39] studied the OH/π hydrogen bond by infrared spectroscopy. Oki and Mutai[40] and Perutz[41] studied the NH/π hydrogen bond. These types of hydrogen bond occur between a HA and a soft base (SB; π) and are now established as true hydrogen bonds by a number of spectral and crystallographic studies.

2.3. CH/π Hydrogen Bond

More recently, a still weaker molecular force, the CH/π hydrogen bond (a SA/SB combination),[42] has been shown to play significant roles in organic chemistry: conformation,[43−45] crystal packing,[46] host/guest chemistry,[47] reaction selectivity,[48] and biochemical phenomena.[49,50] Contribution from the electrostatic energy is relatively unimportant, except for nontypical ones such as Cl_3CH/π or C≡CH/π. In typical CH/π hydrogen bonds involving sp^3- and sp^2-CH groups as the hydrogen donor, stabilization of the complex (1.5−2.5 kcal mol^{-1}) comes, essentially, from the dispersion force. In 1977, one of the present authors presented a hypothesis that CH/π hydrogen bonds involving aliphatic and aromatic CHs as the hydrogen donor bear implications in a variety of molecular consequences, chemical as well as biochemical.[51]

Evidence for the CH/π hydrogen bond has since been obtained by various experimental methods,[52] including calorimetric determinations,[53] CSD analyses,[54,55] electronic substituent effect on crystal structures,[56] spectroscopic data,[57] conformational equilibrium,[58] enantiomeric selection,[59] selectivity in organic reactions,[60] and coordination chemistry.[61] Support for the hydrogen bond nature of the CH/π hydrogen bond has been provided by the electronic substituent effect on thermodynamic properties.[62]

In 1993, Sakaki, by *ab initio* molecular orbital (MO) calculations at the MP2 level, first suggested that the CH/π hydrogen bond originates, largely, from the dispersion force; contribution from electrostatic forces is of minor importance in typical CH/π hydrogen bonds.[63] In a CH_4/C_6H_6 complex (Figure 8), a binary molecular cluster **a**, which has been shown to be the most stable among three possibilities, adopts



a **b** **c**

Figure 8. Binary molecular clusters CH_4/C_6H_6 at various relative orientations.

Table 1. Energy Components of CH/π and Related Weak Hydrogen Bonds (in kcal mol^{-1})

acid/base	example	total[a]	ES[b]	ER[c]	corr[d]	corr/total	ES/total
CH/π[69]	CH_4/C_6H_6	−1.45	−0.25	1.10	−2.30	1.59	0.17
CH/π[69]	C_2H_4/C_6H_6	−2.06	−0.65	1.82	−3.22	1.56	0.32
CH/π[69]	C_2H_2/C_6H_6	−2.83	−2.01	1.44	−2.26	0.80	0.71
CH/π[70]	C_6H_6/C_6H_6	−2.46	−0.55	1.57	−3.48	1.41	0.16
CH/π[70]	CH_2Cl_2/C_6H_6	−4.5	−1.8	2.4	−5.1	1.13	0.40
CH/π[70]	$CHCl_3/C_6H_6$	−5.6	−2.4	4.6	−7.9	1.41	0.43
CH/π[70]	CHF_3/C_6H_6	−4.2	−2.4	1.7	−3.4	0.81	0.57
CH/O[71]	CH_4/H_2O	−0.29	−0.42	0.38	−0.08	0.28	1.45
CH/O[71]	CHF_3/H_2O	−3.70	−7.06	4.14	−0.25	0.07	1.91
OH/π[72]	H_2O/C_6H_6	−3.02	−1.86	1.07	−2.23	0.74	0.62
NH/π[72]	NH_3/C_6H_6	−2.22	−1.01	1.14	−2.36	1.06	0.45

[a] Total energy. [b] Electrostatic energy. [c] Exchange repulsion. [d] Correlation energy.

a C_{3v} symmetry with methane lying on the benzene C_6 axis and one C−H bond pointing to the center of the benzene ring.

Electrostatic interactions, polarization, and charge transfer interactions seem to play a role in determining the orientation of the components. Many theoretical studies since followed,[64] supporting the suggestion of Sakaki et al. AIM (atoms-in-molecule) analyses[65−67] demonstrated the hydrogen bond nature of this molecular force. A number of combined spectroscopic and theoretical studies have appeared.[68]

The interaction energy depends on the nature of the molecular fragments, CH as well as π-groups. For typical cases involving aliphatic and aromatic CH groups as the hydrogen donor, the energy of a one unit CH/π hydrogen bond is ca. 1.5−2.5 kcal mol^{-1}. The stronger the proton donating ability of the CH, the larger the stabilizing effect. For stronger CH/π bonds involving acetylenic C−H or X_3C−H (X = electron-withdrawing atom or group), the energy of interaction becomes comparable to the conventional hydrogen bond. As for the acceptor, the electron density of the π-group is relevant. The energy components of CH/π and related weak hydrogen bonds are given in Table 1 (the contributions from polarization and charge-transfer energies are not included).

The interaction energy involving an aromatic CH is somewhat stronger than that of the aliphatic ones. Nakagawa and co-workers suggested that interaction between the quadrupoles of aromatic groups is important.[73] The CH/π hydrogen bond involving aromatic CHs is often referred to as the edge-to-face or T-shape π/π, arene/arene, or polar/π interaction, etc. We prefer to refer this as the "aromatic CH/π hydrogen bond", in view of its nature.

2.4. Directionality and Cooperativity of the CH/π Hydrogen Bond

Directionality is a requisite for hydrogen bonding, distinguishing it from the mere London dispersion force.[74] Orientation dependence of an interacting system follows the order of the strength: the stronger the bond, the stronger the trend for the linearity. Figure 9 shows this. Table 2 summarizes the results. Notice that the directionality and the CH/π-plane distance (D_{PLN}) correlate and depend on the strength of the proton donor. Analogous plots are reported also for other hydrogen bonds.[75]

Another noteworthy feature of the CH/π hydrogen bond is that it works cooperatively. Wong studied the CH/π hydrogen bond by calculations, at the CCSD(T)/aug-cc-pVTZ//MP2/aug(d,p)-6-311G(d,p) level, between benzene and various alkanes.[76] A number of CH groups concurrently interact with the benzene aromatic ring in many cases.

Kobayashi and Saigo studied, by the periodic *ab initio* MO method, the property of CH/π hydrogen bonds in crystals of 1-phenylethylamine salts of mandelic acid derivatives.[77] The characteristics of the aromatic CH/π hydrogen bond resemble the conventional hydrogen bond in view of the energy and the polarization of the C−H bond.

Sozzani reported that cooperation of CH/π hydrogen bonds greatly increases the stability of organic compounds, including synthetic polymers. Competing with the tendency to take multiple conformations, CH/π hydrogen bonds induce a single structure to fit the aromatic nanocylinders, consisting of tris-(*o*-phenylenedioxy)spirocyclotriphosphazene (Figure 10), adopting the entropically unfavorable extended-chain

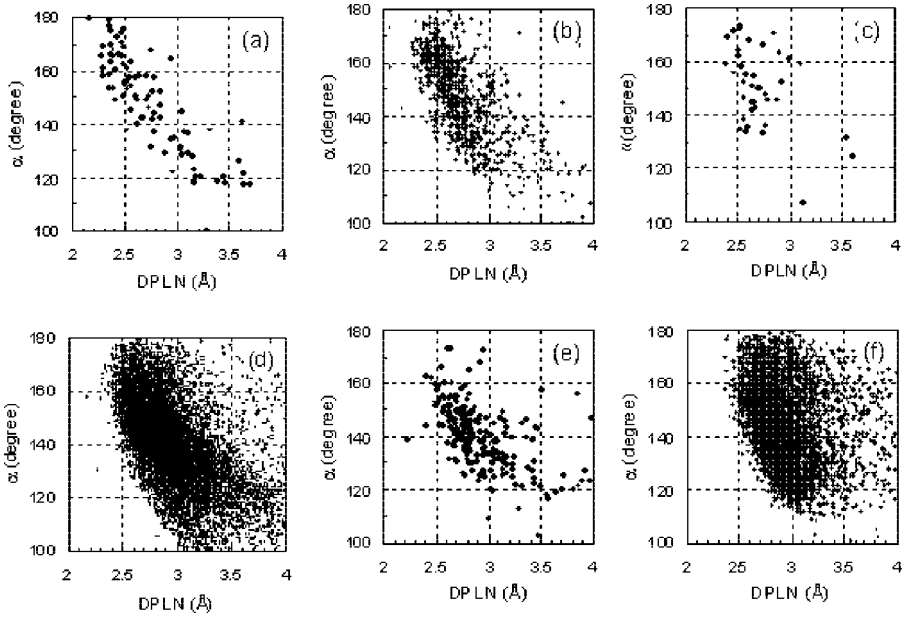


Figure 9. Orientation dependence of the CH/π hydrogen bond: (a) Cl_3CH/π; (b) Cl_2CH_2/π; (c) sp-CH/π; (d) sp^2-CH/π; (e) sp^2-CH/π (neutron data); (f) CCH_3/π. Figure 7 of ref 55, Takahashi et al., *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2421−2430. Reproduced with permission from the Chemical Society of Japan.

Table 2. Distance and Orientation Dependence of the CH/π Hydrogen Bond

	N^a	d,[b] Å	α,[c] deg	α,[d] deg
Cl_3CH/π	67	2.53 ± 0.17	157 ± 12	169 ± 11
Cl_2CH_2/π	648	2.62 ± 0.15	151 ± 13	159 ± 14
sp-CH/π	37	2.62 ± 0.13	152 ± 13	159 ± 13
sp^2-CH/π	11579	2.73 ± 0.13	148 ± 11	154 ± 13
sp^2-CH/π[e]	161	2.70 ± 0.11	146 ± 9	149 ± 11
CCH_3/π	2391	2.75 ± 0.10	148 ± 13	157 ± 15

[a] Number of observations. [b] Mean CH/π plane distance, D_{PLN}. [c] C−H−π-plane angle. [d] C−H−π-plane angle, corrected. [e] Neutron data including organometallic compounds.

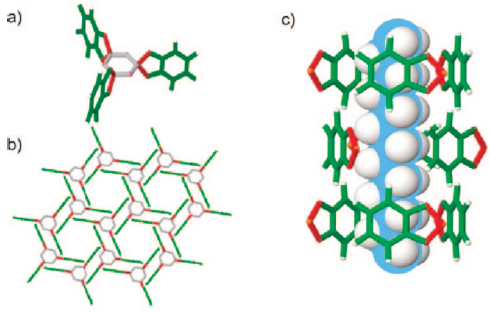


Figure 10. (a) Tris-(*o*-phenylenedioxy)spirocyclotriphosphazene, (b) aromatic nanochannel, (c) polyethylene included in the nanochannel. Figure 1 of ref 78, Sozzani et al., *Chem. Commun*. **2004**, 768−769. Reproduced with permission from the Royal Society of Chemistry.

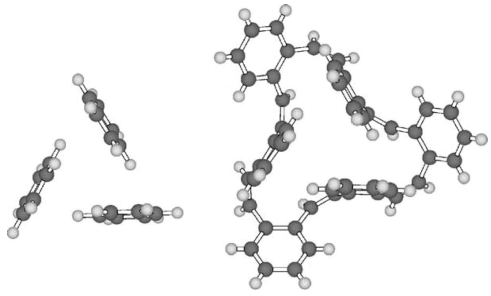


Figure 11. Benzene trimer (left) optimized by the MP2/6-31G* level calculation and crystal conformation of *all-Z*-hexabenzo-[24]annulene (right). Figure 3 of ref 80, Kuwatani et al., *Tetrahedron Lett.* **2004**, *45*, 359−362. Reproduced with permission from Elsevier Ltd.

conformation of polyethylene, etc.[78] Inclusion of organic compounds into the aromatic nanochannel forms robust structures melting at temperatures some 200 K higher.[79]

The following three topics illustrate how the CH/π hydrogen bond effectively works when cooperated.

Kuwatani et al. studied the structure of *all-Z*-hexabenzo[24]annulene.[80] Its crystal conformation has a C_3-symmetry, in which three benzene rings were assembled inside (Figure 11). A similar conformation has been shown to prevail in solution by NMR experiments. This is consistent with the result obtained by *ab initio* calculations for a benzene trimer; the stabilization energy was estimated to be ca. 5 kcal mol^{-1} by a CCSD(T)/cc-pVDZ level calculation.[81] Notice that the benzene trimer takes almost the same geometrical disposition of the three inner benzene rings of *all-Z*-hexabenzo[24]annulene. They attributed the stability of the C_3-symmetric structure to CH/π hydrogen bonds, concurrently operating among the three benzene rings.

Furuta et al. found that an N-confused metalloporphyrin forms both C_3- and C_1-symmetric structures in solution,

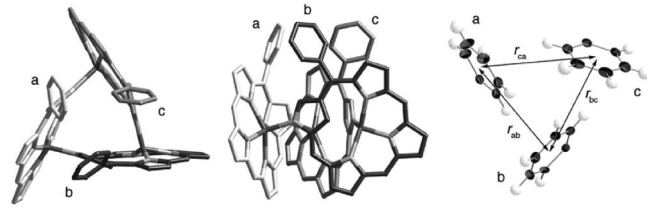


Figure 12. Crystal structure of a phenyl-substituted N-confused metalloporphyrin. Figure 3 of ref 82, Morimoto et al., *Angew. Chem. Int. Ed.* **2007**, *46*, 3672−3675. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

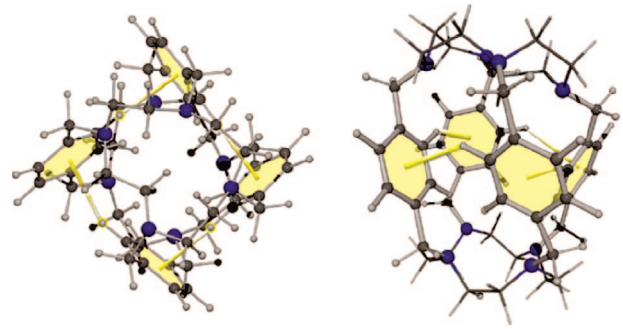


Figure 13. Calculated structure (DFT-based MD simulation) of the most stable conformer of a cyclophane compound. Yellow arrows indicate aromatic CH/π hydrogen bonds. Figure 5 of ref 84, Hill et al., *Phys. Chem. Chem. Phys.* **2009**, *11*, 6038−6041. Reproduced with permission from the Royal Society of Chemistry.

whereas its phenyl-substituted analogue exclusively forms a C_3-symmetric substructure, in solution and crystals (Figure 12).[82] The stabilization enthalpy and the Gibbs energy of the benzene ring trimer were estimated, by NMR measurements, as 3.8 and 2.6 kcal mol^{-1}, respectively. The above data are in good agreement with calculated values.[83] They argued the results in the context of the CH/π hydrogen bond, concurrently operating among the three benzene rings.

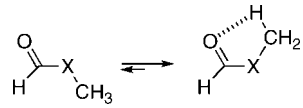
Hill, Ariga, and their co-workers synthesized a cyclophane compound composed of two cyclen and four 1,4-xylyl units and studied the conformation by NMR and STM (scanning tunneling microscopy) imaging.[84] By molecular dynamics simulation, a conformer containing a highly symmetric cyclic benzene tetramer has been found to be the most stable (Figure 13). The result has been attributed to CH/π hydrogen bonds, concurrently operating among the four aromatic groups.

3. Preference of the Folded Conformer in Synthetic Organic Compounds

3.1. Relevance of the CH/*n* Hydrogen Bond in Organic Compounds

3.1.1. CH_3/C=O Eclipsed Conformation

There is ample evidence in the literature that the CH_3/C=O eclipsed conformation prevails in compounds such as methyl formate **1** (Figure 14, X = O),[85] *N*-methylformamide **2** (NH),[86] and propanal **3** (CH_2).[87,88] Since we felt that this phenomenon is a consequence of the CH/O hydrogen bond, we calculated the conformational energies of these compounds.[89] The geometry optimizations were performed at the MP2/6-311++G(d,p) level and single-point calculations were performed at the CCSD(T)/6-311++G(d,p) level.



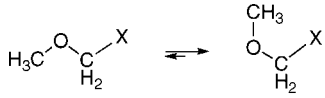
E *Z*

Figure 14. Conformational equilibrium of CH_3XCHO-type compounds **1**−**3**.

The minimum energy was obtained in every case at $CH_3-X-C=O$ torsion angle ϕ ca. 0° (geometry *Z*). In the next stable conformation, ϕ is 180°, 180°, and 120° (geometry *E*), respectively, for **1**, **2**, and **3**. In these geometries, the shortest distance between a CH in the methyl group and the carbonyl oxygen is 2.65, 2.68, and 2.81 Å, respectively, for **1**, **2**, and **3**. In every case, the electron density at the carbonyl oxygen is maximal, whereas that of CH_3 is minimal at geometry *Z*. This is consistent with our hypothesis that the CH/O hydrogen bond is contributing to stabilizing the $CH_3/C=O$ eclipsed or *gauche* conformation. The calculated Gibbs energy differences ΔZE fit quite well with the experimental data: 4.30 vs 4.75 kcal mol^{-1} for **1**, 1.07 vs 1.4−1.6 kcal mol^{-1} for **2**, and 0.63 vs 0.7−1.2 kcal mol^{-1} for **3**. We interpreted the results on the basis of the CH/O hydrogen bond. A recent X-ray photoelectron spectroscopic study has revealed that the methyl group in **3** is eclipsed to C=O.[90]

3.1.2. Conformation of Methyl Ethers CH_3OCH_2X

The conformational equilibrium of molecules such as CH_3OCH_2-X, **4** (X = OH, OCH_3, halogen), was studied, in view of its similarity to the anomeric effect in carbohydrate chemistry. The folded or *gauche* conformer has been found more stable in every case; this is called the generalized anomeric effect.



anti-**4** *gauche*-**4**

In the 1970s, MO calculations at the Hartree−Fock (HF) level were performed for compounds including methoxymethanol **4** (X = OH)[91] and dimethoxymethane (OCH_3).[92] The results were argued in terms of the delocalization of the lone pair on the oxygen atom to the antibonding orbital of the CH_2-O bond.

We carried out *ab initio* MO calculations, at the MP4/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) level, for a series of methyl ethers **4** (X = OH, OCH_3, F, Cl, Br, C≡N, C≡CH, C_6H_5, CHO).[93] Table 3 lists the results. The Gibbs energy of the *gauche* conformers has been shown to be lower in every case (except for X = CHO) than that of the *anti* conformers. In the *gauche* conformers, the interatomic distance between X and the interacting hydrogen atom was found to be shorter than the sum of the van der Waals radii. The natural bonding orbital (NBO) charges of the group X are more negative in the *gauche* conformers than those in the *anti* conformers. The effect may well be explained, at least partly, in terms of the CH/X (OH, OCH_3, F, Cl, Br) and CH/π (C≡N, C≡CH, C_6H_5, CHO) hydrogen bonds.

Table 3. Difference in the Conformational Energy, Interatomic Distance between H and X in the *gauche* conformer, and Natural Bonding Orbital (NBO) Charges of Relevant Atoms for a Series of Methyl Ethers 4

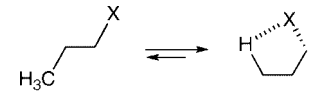
X	$\Delta G_{anti-gauche}$[a]	$d_{H/X}$[b]	Δd[c]	NBO_{anti}[d]	NBO_{gauche}[e]	$\Delta NBO_{anti-gauche}$[f]
OH	2.35	2.58	0.14	−0.748	−0.769	0.021
OCH_3	5.24	2.59	0.13	−0.620	−0.640	0.021
F	4.00	2.57	0.10	−0.417	−0.446	0.029
Cl	4.46	2.85	0.10	−0.080	−0.149	0.069
Br	4.05	2.93	0.12	−0.027	−0.117	0.090
C≡N	1.68	2.61	0.36	0.327	0.299	0.028
C≡CH	0.98	2.63	0.34	−0.023	−0.050	0.027
C_6H_5	1.09	2.63	0.34	−0.043	−0.063	0.020
CHO	−0.83	2.68	0.29	0.542	0.519	0.023

[a] $\Delta G_{anti-gauche} = G_{anti} - G_{gauche}$ (in kcal mol^{-1}, at 298.15 K). [b] Distance between H and X in the *gauche* conformer (in Å). [c] $\Delta d = d_{vdW} - d_{H/X}$. [d] NBO charge of X for the *anti* conformer. [e] NBO charge of X for the *gauche* conformer. [f] Difference in the NBO charges of X between the *anti* and *gauche* conformers.

3.1.3. Conformation of Alkyl Halides

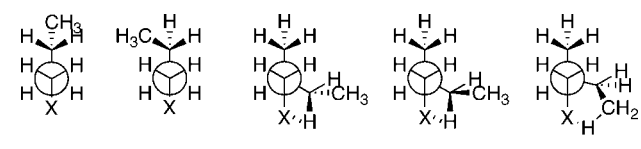
Spectroscopic evidence for the preference of the folded, CH/X hydrogen-bonded conformers has accumulated. Thus Morino and Kuchitsu studied, by electron diffraction spectroscopy, the conformation of 1-propyl chloride, $CH_3CH_2CH_2Cl$, and found that the *gauche* conformer is favored, though slightly.[8,94] Hirota obtained a similar result for 1-propyl fluoride, $CH_3CH_2CH_2F$.[9] Similar conclusions were reported by far-infrared and low-frequency Raman,[95] electron diffraction,[96] FT-IR,[97] and X-ray photoelectron spectroscopy.[90]

In every case, the *gauche* conformation has been found to be preferred. The experimental data are consistent with the results obtained by high-level *ab initio* calculations.[98,99] The effect of solvent,[100] pressure, and temperature[101] on the conformational equilibrium of 1-propyl chloride has been reported.



anti *gauche*

Ukaji and Bonham studied, by electron diffraction spectroscopy, the conformation of 1-butyl chloride, $CH_3CH_2CH_2CH_2Cl$.[102] Studies by Raman and IR[103] and microwave spectroscopies followed.[104,105] In 1-butyl halides, the result is somewhat controversial since these molecules have five possible conformations and the analysis is rather difficult. However, the importance of conformers bearing a CH/C *gauche* relationship has been confirmed in every case; the CH/X hydrogen-bonded conformers (*ga*, *gg*, *gg′*) have been suggested to prevail.



aa *ag* *ga* *gg* *gg'*

1-butyl halides

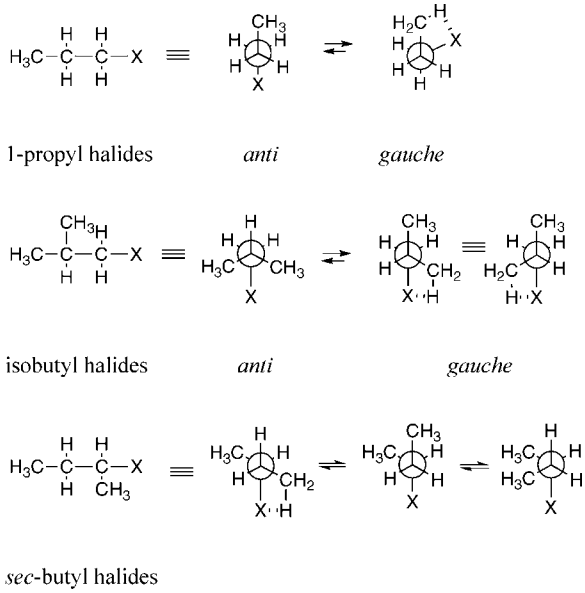
To investigate the generality of the phenomenon, we carried out *ab initio* MO calculations, at the MP2/6-

Table 4. Relative Proportion of the Stable Conformers of 1-Butyl Halides, $CH_3CH_2CH_2CH_2X$

X	*aa*	*ag*	*ga*	*gg*	*gg′*
F[a]	16	10	46	22	6
Cl[a]	17	12	42	28	1
Br[b]	23	21	38	18	0
Cl (exptl)[c]	13	12	60	12	0
Br (exptl)[c]	36	24	24	16	0

[a] G3 theory. [b] MP2/6-311G(d,p). [c] Experimental values: X = Cl,[107] X = Br.[107]

311G(d,p) and G3 level, of 1-propyl halides, isobutyl halides, *sec*-butyl halides, and 1-butyl halides.[106] It has been found in every case that the conformer in which a methyl group is close to the halogen atom is favored. One of the methylene or methyl hydrogens interacts with the group X in the stable conformers. The results are consistent with documented experimental data. Table 4 summarizes the data obtained for 1-butyl halides.



The proportion of the *gauche* conformers ($ga + gg + gg'$) increases in the increasing order of the electronegativity of X (Br < Cl < F). The inverse is true for the *anti* conformers ($aa + ag$). The agreement with the experimental values is satisfactory. The distance between X and one of the hydrogens in the interacting CH_2 or CH_3 has been shown to be shorter than the sum of the van der Waals radii (Figure 15). Considerations on the NBO charges of interacting atoms gave results consistent with the above conclusion.

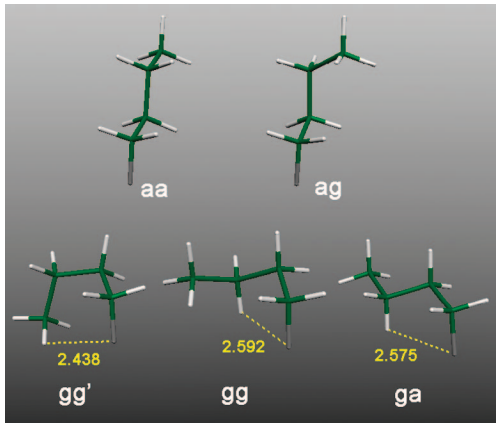


Figure 15. Calculated geometries of the stable conformers of 1-butyl fluoride. The numbers refer to the H/F distance (in Å). See also Figure 1 of ref 106.

3.1.4. Conformation of Alcohols and Ethers

Yoshida et al. studied the conformation of 1-butanol,[108] 1,2-dimethoxyethane,[109] and 1-methoxy-2-(dimethylamino)-ethane[110] by matrix-isolation IR spectroscopy and found that the CH/O-interacted geometry is favored (Chart 1A).

Houk et al. reported the preference for the CH/O hydrogen-bonded conformer in *n*-propanol and 2-methylpropanol by MP2/6-31+G(d) level calculations.[111] Maeda et al. analyzed the millimeter- and submillimeter-wave spectra of 1-propanol and found that the *gauche* conformer prevails in the equilibrium (Chart 1B).[112]

Favero et al. found the *gauche* conformation of dimethoxymethane to be stable by microwave spectroscopy and attributed the result to intramolecular CH/O hydrogen bond (Chart 1C).[113]

Tsuzuki et al. studied 1,2-dimethoxyethane [MP3/6-311+G(d)//HF/6-31G(d)][114] and *o*-dimethoxybenzene [MP2/6-311G(d,p)//HF/6-311G(d,p)] and reported that the CH/O-interacted geometries are stable (Chart 1D).[115]

Shin-ya et al. studied the conformation of benzyl methyl ether by matrix isolation IR spectroscopy and MO calculations [MP2/6-311++G(d,p)].[116] Cooperation of the CH/O hydrogen bond with the CH/π hydrogen bond was suggested to be important, since replacement of O by CH_2 significantly reduced the *gauche* preference in the equilibrium (Chart 1E).

Chart 1

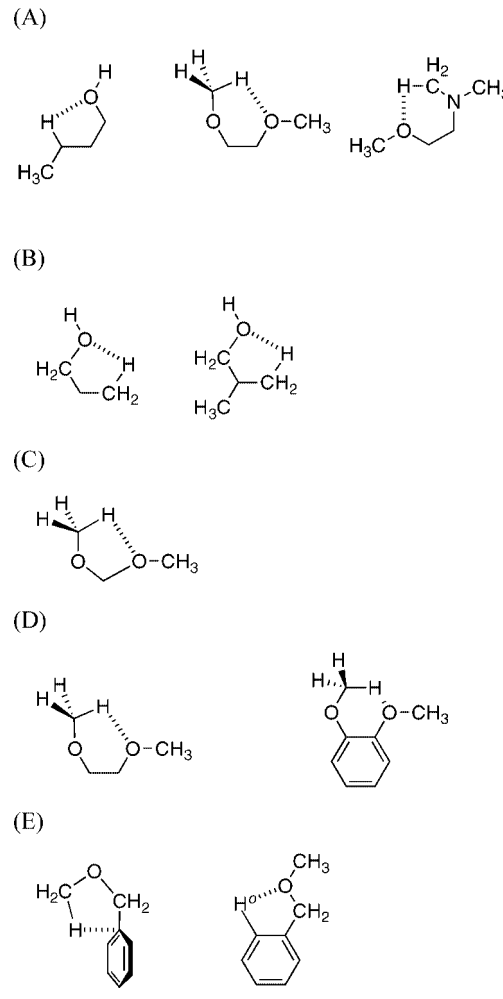


Table 5. Difference in the Conformational Free Energies (in kcal mol^{-1}) in Substituted Cyclohexanes 5 and Cyclohexanones 6

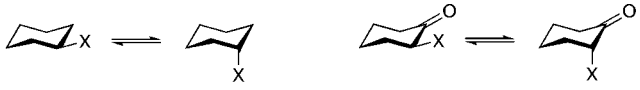
X	OH	OCH_3	F	Cl	Br	C≡CH	C≡N
A-value[a]	0.60	0.55−0.75	0.25−0.42	0.53−0.64	0.48−0.67	0.41−0.52	0.2
5	−0.28	0.22	0.18	0.49	0.69	−0.16	−0.39
6	3.26	−1.02	−0.58	−1.20	−1.52	−1.56	−1.35

[a] From ref 117, Table 11.7.

3.1.5. Conformation of Cyclohexane and Cyclohexanone Derivatives

The difference in the Gibbs energies between the axial and equatorial conformers of alkyl cyclohexanes $C_6H_{11}-R$ ($-\Delta G_{eq\text{-}ax}$, *A*-value) is 1.74−4.9 kcal mol^{-1}, depending on the nature of the alkyl group. The *A*-value for halogenated cyclohexanes $C_6H_{11}-X$, **5** (0.25−0.67 kcal mol^{-1}), is much smaller than might be expected from the size of group X.[117] This effect has been attributed to the longer length of the C−X bond compared with that of the C−C bond.[118]

To make clear the origin of the above phenomenon, we calculated the conformational Gibbs energy of a series of substituted cyclohexanes **5** and cyclohexanones **6**, at the MP2/6-311++G(d,p) level calculations. Table 5 summarizes the results.[119]



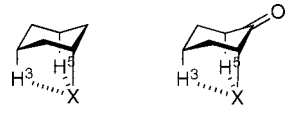
cyclohexane derivatives **5** 2-substituted cyclohexanones **6**

For **5**, it has been shown that the conformer bearing an electron-withdrawing group (X = OH, OCH_3, F, Cl, Br) at the axial orientation is relatively stable compared with alkyl cyclohexanes; the result is consistent with documented experimental data. For X = C≡CH and C≡N, the axial conformer has been suggested to be slightly more stable. We do not know at present the reason for this discrepancy, but the calculated data correspond to the gas-phase conformation, while the experimental values were obtained in solution.[118]

For 2-substituted cyclohexanones **6**, the axial conformer has been found to be more stable than the equatorial conformer, except for X = OH. Short nonbond distances have been disclosed in every axial conformer of **5** and **6**, between the axial CH's and group X (Figure 16). Natural bonding orbital charges of the relevant atoms are consistent with the above suggestion. We conclude that a considerable part of the relative stability of the axial conformation is attributed to intramolecular CH/*n* and CH/π hydrogen bonds.[106]

3.1.6. The Anomeric Effect Revisited

The anomeric effect refers to the tendency of an electronegative substituent at C^1 of pyranosides to assume the axial rather than the equatorial conformation, contrary to the expectation from ordinary stereochemical considerations.[120] This phenomenon is not limited to carbohydrate chemistry but extends to stereochemistry of six-membered heterocyclic compounds such as 2-substituted oxanes **7** and 1,3-dioxanes **8**.



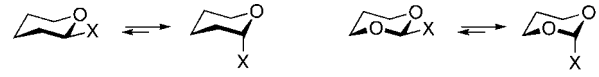
5 **6**

Figure 16. CH/X hydrogen bonds suggested for **5** and **6**.

Table 6. Difference in the Gibbs Energy[a], Calculated at the MP2/6-311++G(d,p) Level, between the Axial and Equatorial Conformers of 2-Substituted Oxanes 7 and 1,3-Dioxanes 8

X	**7**	**8**
OCH_3	1.25	1.94
F	2.47	3.42
Cl	2.57	4.31
Br	3.08	5.45

[a] $\Delta G_{eq-ax} = G_{eq} - G_{ax}$, in kcal mol^{-1}.



2-substituted oxanes **7** 2-substituted 1,3-dioxanes **8**

Several interpretations have been presented to explain the anomeric effect. In 1955, Edward advanced an explanation in terms of the interaction between lone pairs of the endocyclic oxygen and the dipole of the exocyclic C−O bond of a pyranoside.[121] This reasoning has been accepted in view of its consistency with experimental data of the solvent effect. Thus, a more polar solvent favors the equatorial conformer, the dipole moment of which is larger than that of the axial conformer. This mechanism, however, does not explain the variation of the bond lengths, X−C and C−O, associated with the anomeric effect. Another explanation has been advanced on the basis of the orbital interaction.[122]

Since we felt that the anomeric effect is a consequence of the CH/*n* hydrogen bond, we calculated the conformational energy of **7** and **8**.[123] Table 6 gives the results.

The axial conformer has been found to be more stable than the corresponding equatorial conformer in every case. In the axial conformers, the interatomic distance between X and the axial C−H has been found to be appreciably shorter than the van der Waals distance, suggesting the importance of the five-membered CH/O or CH/halogen hydrogen bond in stabilizing these conformations. Figure 17 illustrates this for 2-substituted oxanes **7**, X = OCH_3 and F. NBO charges of the relevant atoms have been shown to be more positive for H and more negative for C in the axial conformers than in the corresponding equatorial conformers. In view of the above findings, we consider that the CH/*n* hydrogen bond plays an important role, at least partly, in stabilizing the axial conformation in 2-substituted oxanes **7** and 1,3-dioxanes **8** and, by implication, in the anomeric effect in carbohydrate chemistry. (It remains to be explored, however, to what extent this factor is contributing to the anomeric effect, compared with the dipolar and orbital interaction mech-

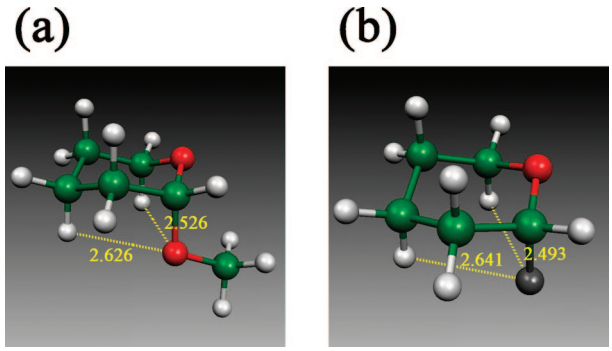
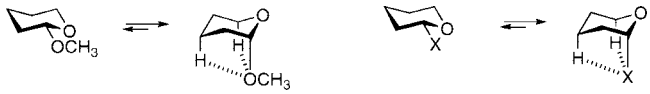


Figure 17. CH/X hydrogen bonds calculated for (a) 2-axial methoxyoxane and (b) 2-axial fluorooxane. The numbers indicate nonbond distances (in Å).

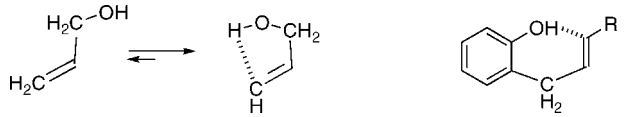
anisms. Reexamination of the cause of the anomeric effect seems necessary.)



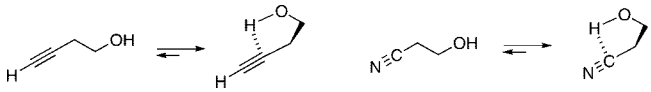
3.2. Relevance of the XH/π (X = O, S, Se) Hydrogen Bond in Organic Compounds

3.2.1. Conformation of Simple Unsaturated Molecules

3.2.1.1. OH/π Hydrogen Bond. Dominance of the OH/π hydrogen-bonded *gauche* conformers was reported for the conformational equilibria of allyl alcohol (CH_2=$CHCH_2OH$),[124] *o*-propenylphenols ($HOC_6H_4CH_2CH$=$CH-R$ (R = H, C_6H_5)),[125] 3-hexyn-1,6-diol,[126] and cumyl hydroperoxide.[127]

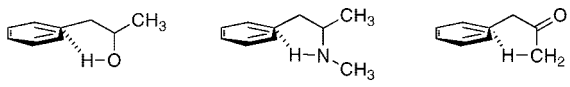


Stability of the folded, OH/π hydrogen-bonded conformation has also been shown, by microwave spectroscopy, for compounds bearing a C≡C or C≡N triple bond, such as 3-butyne-1-ol (CH≡CCH_2CH_2OH)[128] or N≡CCH_2CH_2OH.



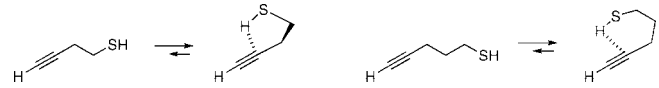
Møllendal et al. examined the conformational equilibrium of 4-pentyne-1-ol (CH≡$CCH_2CH_2CH_2OH$)[129] by microwave and MO calculations. In this case, the conclusion remains somewhat ambiguous since this type of molecule has three freedoms of rotation.

Tubergen et al. studied the rotational spectra of 1-phenyl-2-propanol, methamphetamine, and 1-phenyl-2-propanone.[130] The conformers depicted below have been suggested to prevail; the result was attributed to the OH/π, NH/π, and CH/π hydrogen bonds, respectively.

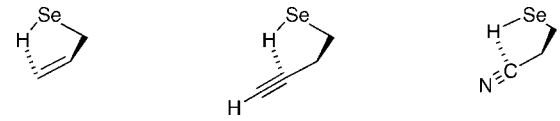


1-phenyl-2-propanol methamphetamine 1-phenyl-2-propanone

3.2.1.2. SH/π Hydrogen Bond. The nature of SH/π hydrogen bond has been studied only recently.[131] Møllendal and his co-workers examined, by microwave spectroscopy, the conformation of 3-butyne-1-thiol (CH≡CCH_2CH_2SH), cyclopropanemethanethiol ($C_3H_5CH_2SH$), 2-furanmethanethiol ($C_4H_3OCH_2SH$), 3-mercaptopropionitrile (N≡CCH_2CH_2SH), allyl mercaptan (CH_2=$CHCH_2SH$), 3-butene-1-thiol (CH_2=$CHCH_2CH_2SH$), and related nitriles.[132] The importance of the folded conformation has been suggested in every case.



3.2.1.3. SeH/π Hydrogen Bond. Møllendal, Guillemin, and their groups studied, by microwave spectroscopy and high-level *ab initio* MO calculations, the conformation of a number of selenols[133] including 2-propene-1-selenol (CH_2=$CHCH_2SeH$),[134] 3-butene-1-selenol (CH_2=$CHCH_2CH_2SeH$), cyclopropylmethylselenol ($C_3H_5CH_2SeH$),[135] propargyl selenol (HC≡CCH_2SeH),[136] and 3-butyne-1-selenol (CH_2≡$CHCH_2CH_2SeH$).[137] Structurally related nitriles were also studied. The importance of the folded conformation has been suggested in every case. High-level MO calculations gave results consistent with the experimental data.



3.3. CH/π Hydrogen Bonds

3.3.1. Conformation of Simple Unsaturated Molecules

Gung et al. first studied the conformation of simple unsaturated compounds by *ab initio* calculations including the electron correlation.[138] Table 7 gives the conformational energy of 1,5-hexadiene, calculated at the MP2/6-31G(d) and MP4/6-31G(d) level. Conformer **d** (= **f**) was found to be the most stable. Notice that the vinylic hydrogen in conformer **d** can be involved in a CH/π hydrogen bond (Figure 18).

On the basis of the above findings, Gung attributed the origin of high diastereoselectivity in several diastereoselective reactions[139] to the CH/π hydrogen bond. Implication in the mechanism of Cope rearrangement was also suggested. It was further pointed out that the stability of such a conformation bears implication in the folding of squalene, a precursor in cholesterol biosynthesis. Thus the high yield (with good stereoselectivity) of a one-pot synthesis in the cyclization of squalene to a cholesterol precursor in nonenzymatic conditions[140] may find its origin in the stability of the *gauche* conformation of 1,5-hexadiene. Hess discussed the recent advance in computer technology in solving such problems in organic chemistry[141] and biochemistry.[142]

Trætteberg et al. found, by electron diffraction spectroscopy, that 1-pentyne coexists in the *gauche* (69%) and *anti* (31%) conformations.[143] *n*-Propyl cyanide, which is isoelectronic to 1-pentyne, has been shown to take a similar conformation (*gauche/anti* = 75/25); calculations at the MP2/6-31(d) level supported the above conclusions.[144] They attributed the prevalence of the *gauche* conformer to the CH/π hydrogen bond. Durig et al. provided results consistent

Table 7. Conformational Energy (in kcal mol^{-1}) of 1,5-Hexadiene

	a	b	c	d = f	e
MP2/6-31G*//HF/6-31G*	0.36	1.01	0.55	0.0	0.13
MP4/6-31G*//HF/6-31G*	0.30	0.05	0.57	0.0	0.10

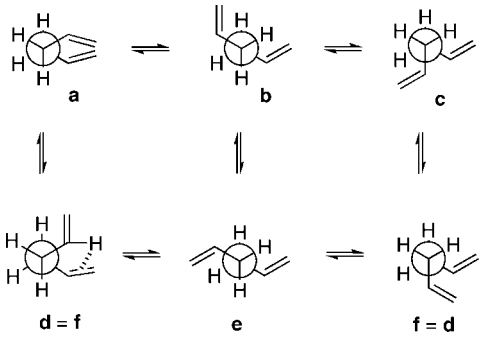
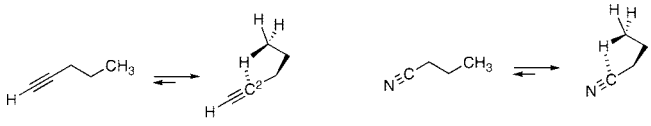
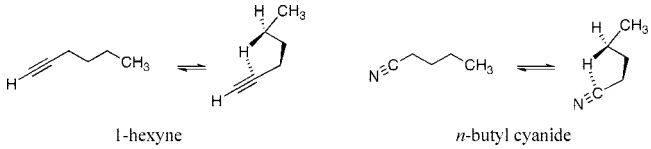


Figure 18. Possible conformers of 1,5-hexadiene.

with the above findings by IR and Raman experiments and MP2/6-311+G(2df,2pd) level calculations.[145] Thomas, Sæthre, and Børve substantiated this conclusion by X-ray photoelectron spectra of *n*-propyl cyanide.[90] (In 1-propyl fluoride and propanal, the CH/F- and CH/O-interacted conformer, respectively, was found to prevail.) Holme et al. examined the X-ray photoelectron spectrum of 1-pentyne and found that a CH/π hydrogen-bonded species prevails (*gauche*/*anti* = 71/29); the interatomic distance between one of the methyl hydrogens and C^2 was found to be smaller, by 0.48 Å, than the van der Waals distance.[146]

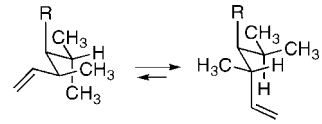


Bohn et al. found that the *gauche* and *anti* conformations coexist in the conformational equilibrium of *n*-butyl cyanide.[147] A similar conclusion was obtained for 1-hexyne by microwave measurements and calculations [6-311+G(d,p)]; the result was explained in terms of the CH/π hydrogen bond.[148] A similar folded conformer has been suggested for cyclopropylmethylsilane (*cyclo*-$C_3H_5SiH_2CH_3$).[149]

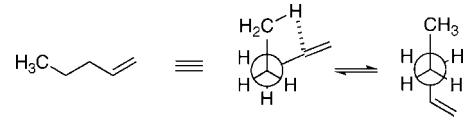


Tsuzuki et al. calculated 3-methoxyprop-1-ene and prop-2-enyl phenyl ether at the MP2/6-311G(d,p)//HF/6-311G(d,p) level and found that the CH/π hydrogen-bonded structure is predominant.[150]

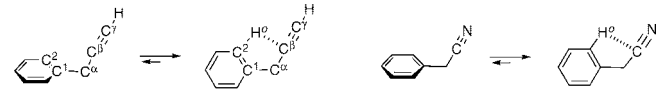
Derivatives of 3,5-dimethyl-1-hexene have been shown to prevail in the folded conformations in solution by NMR. The experimental data were compared with the results obtained by molecular mechanics; the agreement was fair but not necessarily very good.[151]



Roussel et al. calculated the conformational energy of 1-pentene with different methods [DFT (B3LYP), MP2, MP4, CISD, CCSD(T)] and a large basis set [up to 6-311++G(d,p)].[152] These calculations converged to the importance of a folded, CH/π-interacted *syn* conformer, even though it is slightly less stable than the other *anti* one (by 0.2 kcal/mol).

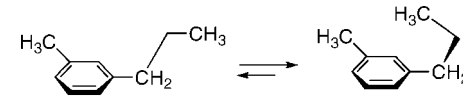


Bohn et al. showed that propargyl benzene (3-phenyl-1-propyne) exists in the structure as depicted below: C^1, C^α, C^β, and C^γ are in a same plane.[153] This is contrasted with the conformation reported for *n*-alkyl benzenes where the bond $C^\alpha-C^\beta$ is at ca. 120° to the benzene plane (section 3.3.2). A similar conformation was reported for benzyl cyanide.[154] They presented a rationale for this irregular result: the *ortho* C−H is pointing to the π-system of the acetylenic triple bond.

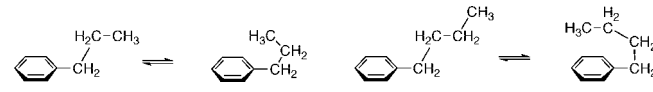


3.3.2. Conformation of Alkylbenzenes and Related Molecules

In 1980, Hopkins, Powers, and Smalley determined the fluorescence excitation spectra of a series of alkylbenzenes cooled in a supersonic free jet. They suggested that two (*anti* and *syn*) conformers coexist when the alkyl group is *n*-propyl or *n*-butyl.[155] In 1987, Breen et al. studied the conformation of alkylbenzenes by supersonic molecular jet spectroscopy and demonstrated that, in 3-propyltoluene, the *syn* conformer is at least equally stable, compared to the *anti* conformer.[156]

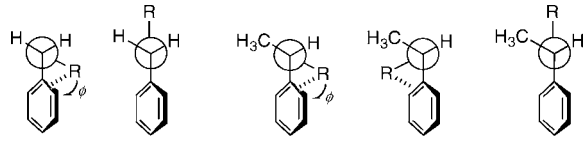


The above works were followed by a number of experimental studies on *n*-propylbenzene and *n*-butylbenzene by laser-induced fluorescence excitation spectroscopy,[157] microwave spectroscopy,[158] high-resolution electronic spectroscopy,[159] and dispersed fluorescence spectroscopy,[160] accompanied with *ab initio* calculations; existence of the *syn* conformer has been suggested in every case.



We investigated, by calculations at the MP2/6-311G(d,p)//MP2/6-31G(d) level, the relative conformational Gibbs energy of the conformers of a series of alkylbenzenes

Table 8. Relative Abundance (%) of the Conformers of 9 and 10[a]



a	c	a	b	c

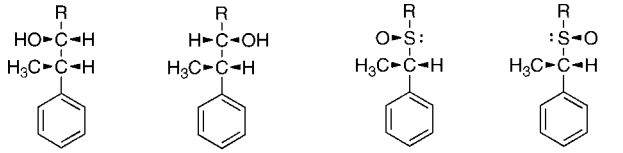
	9		10		
R	a (=b)	c	a	b	c
CH_3	68 (62)[b]	32 (180)	82 (58)	5 (−62)	13 (173)
C_2H_5	69 (62)[c]	31 (180)	86 (59)	3 (−62)	11 (172)
i-C_3H_7	65 (59)	35 (176)	92 (53)	1 (−63)	7 (177)
t-C_4H_9	13 (65)	87 (180)	95 (63)	0 (−72)	5 (136)

[a] R/C_6H_5 torsion angle ϕ (deg) is given in parentheses. [b] 1-propylbenzene. [c] 1-butylbenzene.

$C_6H_5CH_2CH_2$-R (**9**)[161] and $C_6H_5CH(CH_3)CH_2$-R (**10**).[162] The relative abundance of the stable conformers are listed in Table 8. The conformer with R/C_6H_5 torsion angle ϕ around 60° (conformer **a**) prevails, except for the *t*-butyl derivative of **9**. The result is compatible with the above spectroscopic data and the computational results. Introduction of a methyl group at position α to the phenyl group significantly increases the proportion of the folded conformer.

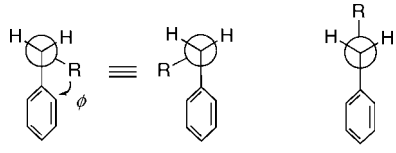
Table 9 lists the abundance of conformers in various benzylic type compounds $C_6H_5CH_2-X-R$ (**11**) estimated by MP2/6-311G(d,p) level calculations.[161] In every case, the proportion of the R/Ph-*gauche* conformer is much larger than the *anti* conformer, except for the *t*-butyl compounds.

Table 10 summarizes the abundance of the conformers calculated for 1-alkyl-2-phenylethylpropan-1-ols, $C_6H_5CHCH_3CH(OH)$-R (**12**),[162] and alkyl 1-phenylethyl sulfoxides, $C_6H_5CHCH_3S(O)$-R (**13**).[163] (To avoid confusion, the conventional *threo*−*erythro* notation is used, because the IUPAC notation does not necessarily correspond the stereochemical relationship of the isomers).



threo-**12** *erythro*-**12** *threo*-**13** *erythro*-**13**

Table 9. Relative Abundance (%) of the Conformers of $C_6H_5CH_2-X-R$, 11 (X = O, S, SO_2)[a]

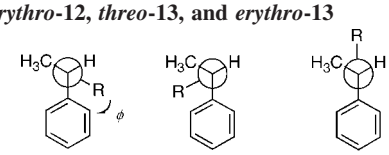


a	b	c

	X					
X	O		S		SO_2	
R	a (=b)	c	a (=b)	c	a (=b)	c
CH_3	88 (68)	12 (177)	91 (58)	9 (189)	95 (54)	5 (180)
C_2H_5	89 (70)	11 (177)	90 (54)	10 (176)	94 (51)	6 (180)
i-C_3H_7	93 (71)	7 (165)	88 (54)	12 (174)	90 (56)	10 (180)
t-C_4H_9	69 (92)	31 (166)	34 (72)	66 (180)	56 (59)	44 (180)

[a] The R/Ph torsion angle ϕ (deg) is given in parentheses.

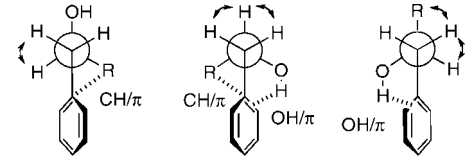
Table 10. Relative Abundance (%) of the Conformers of *threo*-12, *erythro*-12, *threo*-13, and *erythro*-13



a (ϕ ca. 60°) **b** (ϕ ca. 300°) **c** (ϕ ca. 180°)

R	a	b	c
	$C_6H_5CHCH_3CHOH-R$, *threo*-**12**		
CH_3	53	4	43
C_2H_5	56	3	41
i-C_3H_7	47	0	53
t-C_4H_9	100	0	0
	$C_6H_5CHCH_3CHOH-R$, *erythro*-**12**		
CH_3	65	14	21
C_2H_5	65	10	25
i-C_3H_7	76	1	23
t-C_4H_9	76	0	24
	$C_6H_5CHCH_3SO-R$, *threo*-**13**		
CH_3	77	14	9
C_2H_5	89	6	5
i-C_3H_7	90	4	6
t-C_4H_9	88	0	12
	$C_6H_5CHCH_3SO-R$, *erythro*-**13**		
CH_3	85	15	0
C_2H_5	89	11	0
i-C_3H_7	94	6	0
t-C_4H_9	100	0	0

Table 11. Proportion (%) of the Three Stable Conformers in Substituted Benzyl Alcohols 14[a]



a	b	c

R	a	b	c
CH_3	20 (64)	29 (295)	51 (178)
C_2H_5	18 (64)	26 (296)	56 (177)
i-C_3H_7	13 (65)	14 (285)	73 (175)
t-C_4H_9	1 (69)	1 (294)	98 (180)

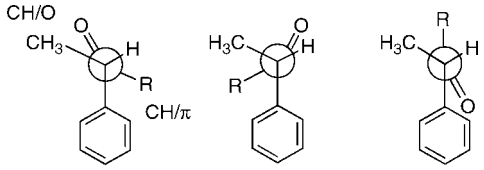
[a] R/Ph torsion angle ϕ (deg), estimated by MP2/6-311G(d,p) level calculations, is given in the parentheses.

In every case, the Ph/R-synclinal conformer (ϕ ca. 60°) has been shown to be dominant. Conformer **b**, where R is flanked by the benzylic methyl group and Ph (ϕ ca. 300°), exists in a perceptible concentration, except for R = *t*-butyl. The above results were interpreted in the context of the compromise of CH/π, OH/π, and CH/O hydrogen bonds, as well as unfavorable steric effects R vs CH_3 and between vicinal CH groups, and dipolar interactions between S−O and Ph.

Table 11 lists the relative abundance in the conformational equilibrium of alkyl-substituted benzyl alcohols, $C_6H_5CH_2CH(OH)-R$ (**14**).[164]

It was found that conformer **c**, where the OH group is *gauche* to Ph, is the most stable. The result can be attributed to the OH/π hydrogen bond occurring between OH and C_6H_5. Conformers **a** and **b** are less stable but still exist in an appreciable concentration, except for R = *t*-C_4H_9. The conclusions deduced by nuclear Overhauser effects, $^3J_{HH}$ spin-coupling constants, and IR spectral data are consistent with the above results. The conformational equilibrium of the benzyl alcohols seems to be determined by the compro-

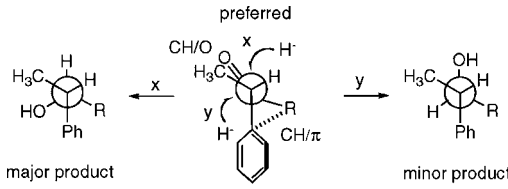
Table 12. Gibbs Energies (in kcal mol^{-1}) of Conformers a, b, and c of 15[a]



a **b** **c**

R	a	b	c
H	0 (64)	1.58 (302)	2.06 (171)
CH_3	0 (77)	2.16 (283)	
C_2H_5	0 (79)	2.19 (282)	
i-C_3H_7	0 (71)	2.08 (297)	
t-C_4H_9	0 (93)	4.89 (289)	

[a] R/Ph torsion angles (deg) are given in parentheses.



erythro-**12** **15** *threo*-**12**

Figure 19. Hydride attack to $C_6H_5CHCH_3COR$ **15**, giving diastereomeric alcohols **12**.

mise of OH/π and CH/π hydrogen bonds and repulsive interactions H vs H and H vs R.

3.3.3. Conformation of Alkyl 1-Phenylethyl Ketones

We calculated, at the same level of approximation, the conformational Gibbs energies of 2-phenylpropanal and homologues, $C_6H_5CHCH_3COR$ (**15**).[165] Table 12 shows the results. In every case, conformer **a**, whereby R is synclinal to Ph, has been shown to be the most stable. The second most stable conformer **b** bears R flanked by the benzylic methyl and Ph. Difference in the enthalpy between these conformers ($\Delta G_{\mathbf{a-b}}$) was estimated to be 1.58 kcal mol^{-1} for 2-phenylpropanal. $\Delta G_{\mathbf{a-b}}$ is 2.16, 2.19, 2.08, and 4.89 kcal mol^{-1}, respectively, for R = CH_3, C_2H_5, *i*-C_3H_7, and *t*-C_4H_9; the R/Ph *anti* conformation has been shown not at the energy minimum. Absence of conformer **c** may be ascribed to the unfavorable dipolar interaction C=O/Ph. Conformer **a** seems to be stabilized by CH/π and CH/O hydrogen bonds.

Experimentally, conformer **a** was suggested to be the most abundant in solution, irrespective of the nature of R;[166] this is consistent with the above computational result. Maris and Caminati determined the conformation of 2-phenylpropanal by free jet millimeter-wave absorption spectroscopy and MP2/6-31G(d,p) level calculations.[167] Their result agrees with our conclusion and shows that the gas-phase conformation resembles that in solution.

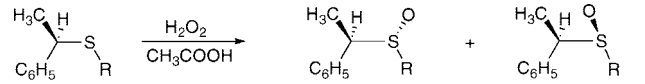
3.3.4. Cram Rule Revisited

We estimated the diastereomeric ratio of the product secondary alcohols **12**, obtained by the nucleophilic addition to **15** (Figure 19), on the basis of the ground-state conformer distribution;[168] the result was compared with the experimental data reported by Felkin and co-workers.[169] Table 13 summarizes the results. Agreement of the calculated data with the experimental values is satisfactory. In view of this, we suggest that the mechanism of Cram rule is understood on the basis of a simple premise that the geometry of the transition state (TS) resembles the ground state conformation of the substrate **15**, and the reagent attacks from the less hindered side. In other words, the transition state is reactant like, and not product like.

Table 13. Isomer Ratios (Major/Minor) in Diastereofacial Reactions, Estimated on the Basis of Conformer Distributions of 15, 16, and 17

	15 to **12**[a]		**16** to **13**[b]		**17** to alcohols[c]	
R	exptl	calcd	exptl	calcd	exptl	calcd
CH_3	2.9	3.7	3.0	3.0	1.6	1.3
C_2H_5	3.2	3.9	3.2	3.2	2.0	1.6
i-C_3H_7	4.9	4.3	3.6	3.4	4.1	2.3[d]
t-C_4H_9	49	49	49	49.1	1.6	1.9

[a] $LiAlH_4$ in ether. [b] **16**: $C_6H_5CHCH_3$−S-R; H_2O_2 in acetic acid. [c] **17**: *cyclo*-$C_6H_{11}CHCH_3CO$-R; $LiAlH_4$ in ether. [d] We do not know the exact reason for this apparent anomaly. Notice, however, the isopropyl group often behaves exceptionally in view of the conformational preference. See discussion raised in later sections dealing with the conformational equilibria of alkylketone and α-phellandrene.



16 **13** (major product) **13** (minor product)

Figure 20. Oxidation of sulfides **16**, giving rise to diastereomeric sulfoxides **13**.

A similar argument on the oxidation of related sulfides $C_6H_5CHCH_3$−S−R (**16**) to diastereomeric sulfoxides **13** gave results compatible with the experimental data (Table 13, columns 4 and 5). Notice that the model depicted in Figure 20 is similar to Cram open-chain model (Figure 3 in Chapter 1). The ratio of the diastereomeric secondary alcohols *cyclo*-$C_6H_{11}CHCH_3CHOH$−R produced in the nucleophilic addition to *cyclo*-$C_6H_{11}CHCH_3CO$−R (**17**) was also estimated on the basis of the conformer distribution (Table 13, columns 6 and 7).[170] There, importance of the CH/π(C=O) hydrogen bond has been suggested.

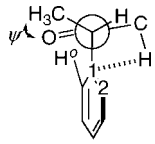
We further calculated the Gibbs energy of the diastereomeric transition states for a model reaction, $C_6H_5CHCH_3COR$ (**15**) + LiH. The difference in the Gibbs energies between the transition state leading to the predominant product (TS1) and the transition state leading to the minor product (TS2) was 1.37 kcal mol^{-1} for R = CH_3, whereas it was 4.13 kcal mol^{-1} for R = *t*-C_4H_9. Table 14 shows that the geometry of TS1 is not much different from that of the ground-state (GS) conformation. In the TS2 geometry; on the contrary, the geometrical parameters were significantly distorted to avoid unfavorable steric interactions. Therefore, CH/π and CH/O hydrogen bonds seem to cooperate in stabilizing the GS and TS structures (Figure 21).

To summarize this section, the transition state geometry of the reactions (1,2-asymmetric induction) does not significantly differ from the ground state conformation of the substrates.[171]

3.4. Aromatic CH/π Hydrogen Bond

As shown in the preceding section, there are sufficient data showing the importance of the CH/π hydrogen bond in

Table 14. Geometrical Parameters of the Ground State (GS), the Transition State Leading to the Predominant Product (TS1), and the Transition State Leading to the Minor Product (TS2) in the LiH Addition to 15, Estimated by MP2/6-311G(d,p) Level Calculations



R		$d_{CH/\pi}$/Å[a]	Ψ/°[b]	$d_{CH/O}$/Å[c]	α/°[d]	$d_{H°/C}$/Å[e]
CH_3	GS	2.85	23	2.54	56	2.77
	TS1	2.83	27	2.63	59	2.82
	TS2	2.60	−39	2.59	73	3.19
t-C_4H_9	GS	2.91	36	2.57	50	2.73
	TS1	2.60	29	2.60	58	2.84
	TS2	2.47	−33	2.50	71	3.19

[a] Distance between CH and C1. [b] CH_3/O torsion angle. [c] Distance between one of the three protons in the benzylic methyl group and the carbonyl oxygen atom. [d] Dihedral angle defined by C2−C1−C−C(=O). [e] Distance between H° and carbonyl C(=O) atom.

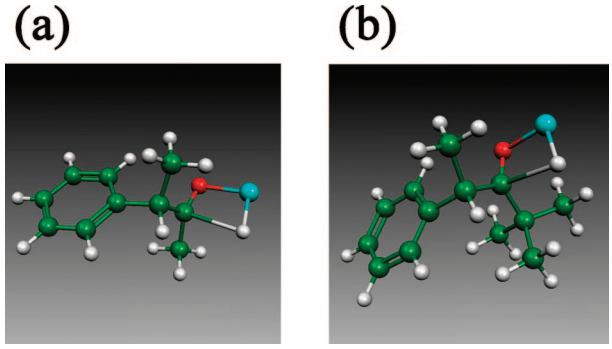


Figure 21. Geometries of the transition states leading to the predominant product TS1 in (a) R = CH_3 and (b) R = *t*-C_4H_9. H in white, C in green, O in red, and Li in light blue. See also Figure 4 of ref 168, Takahashi et al., *New J. Chem.* **2004**, *28*, 355−360.

making the folded structure stable. Recent papers reporting on the relevance of CH/π hydrogen bonds include a polycyclic succinimide,[172] a crown ether derivative,[173] an azacalix[4]arene derivative,[174] molecular tweezers with long-chain alkyl chains and naphthalene rings,[175] a rhenium complex (*fac*-[Re(bpy)$(CO)_3(PR_3)]^+$),[176] a crown-tetrathia-[3.3.3.3]metacyclophane,[177] 2,11-dithia[3]paracyclo[3](4,4′)-2,2′-bipyridinophane,[178] *N*,*N*′-bis(2-tosylaminobenzylidene)-1,4-xylylenediamine complexes,[179] [Pd(η^3-2-Me-allyl)(μ-$Ph_2PPy)]_2(BF_4)_2$,[180] [Pd(C^2,*N*-dmba)(μ-$N_3)]_2$,[181] 1,4-bis(2-hydroxymethyl-5,5-dimethyl-1,3-dioxan-2-yl)benzene,[182] metal complexes of H(Aib-ΔPhe)$_2$-Aib-OCH_3,[183] and a hemin-derived porphyrin compound.[184] In every case, when examined, the crystal conformation was found to be maintained in solution. (See our previous reviews[43−45] for other examples in more complex molecules.)

3.4.1. Folded Ar/Ar Conformation

Here, we will discuss the CH/π hydrogen bond in which an aromatic CH is the hydrogen donor. In 1983, Kunieda et al. studied the conformation of $C_6H_5CHCH_3CH_2CO$-Ar[185] and $C_6H_5CHCH_3SO$-Ar[186] and found that the *gauche* C_6H_5/Ar conformation is preferred. To explore the generality of the phenomenon, they examined papers reporting the prevalence of the folded Ar/Ar conformation and showed that such a phenomenon is by no means exceptional.

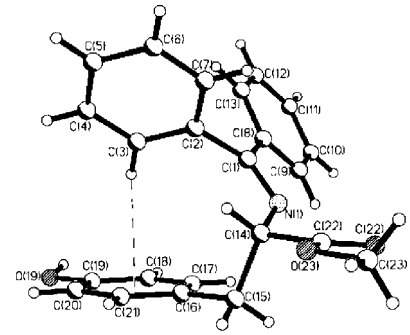


Figure 22. Crystal structure of **20**. Figure 4 of ref 189, Jennings et al., *Org. Biomol. Chem.* **2009**, *7*, 5156−5162. Reproduced with permission from the Royal Society of Chemistry.

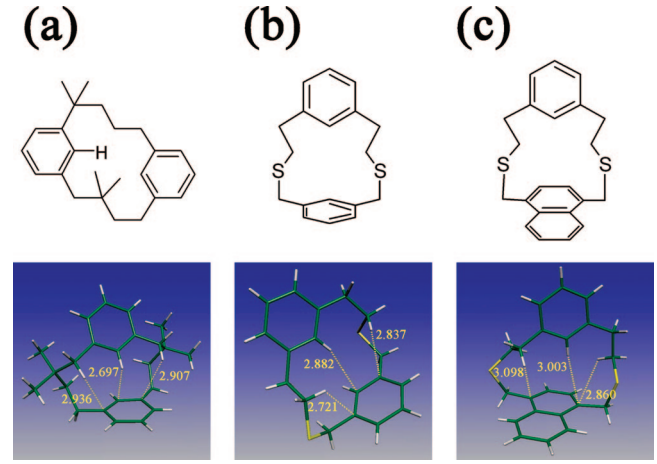
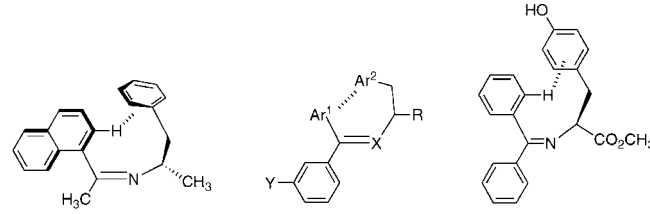


Figure 23. Crystal structures of (a) **21** (CSD refcode POHZOB), (b) **22** (ZAQPAI), and (c) **23** (ZAQPOW).

In 1990, Jennings and their co-workers found that compound **18** takes the *gauche* conformation in crystals and in solution.[187] This was followed by studies of similar flexible organic compounds **19** (X = C, N, NO; R = CH_3, C_6H_5, etc.).[188] Figure 22 gives the crystal structure of **20**, reported in a recent paper.[189] The folded crystal conformation has been shown to be maintained in solution by NMR measurements.



18 **19** **20**

Jennings et al. reviewed aromatic CH/π hydrogen bonds in compounds bearing at least two aromatic moieties.[190] The distance between one of the hydrogens on an aromatic ring and another π plane has been reported to be short in every crystal structure. Examples include 2,2,13,13-tetramethyl-[4,4]metacyclophane **21**[191] and a series of [4,4]thiocyclophanes such as **22** and **23**.[192] In every case, the folded conformation has been shown, both in the crystal and in solution. Notice that in Figure 23, aromatic as well as aliphatic CHs are contributing in a cooperative manner.

To cite other recent examples, Viñas and her co-workers determined the crystal structure of a series of poly(1-pyrrolymethyl) benzene derivatives.[193] Figure 24 shows

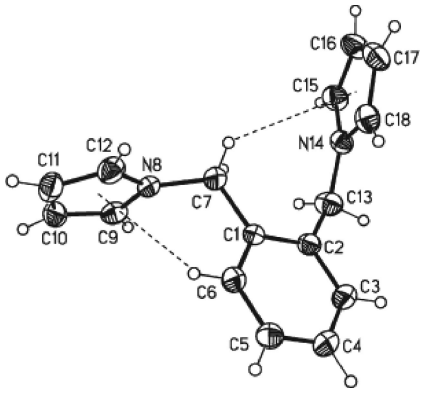


Figure 24. Crystal conformation of di(1-pyrrolymethyl)-*o*-benzene. The nonbond distances are 3.30 and 3.03 Å, respectively, for C^6-H and C^7-H vs the center of the pyrrole ring. Figure 10 of ref 193, Planas et al., *CrystEngComm* **2006**, *8*, 75−80. Reproduced with permission from the Royal Society of Chemistry.

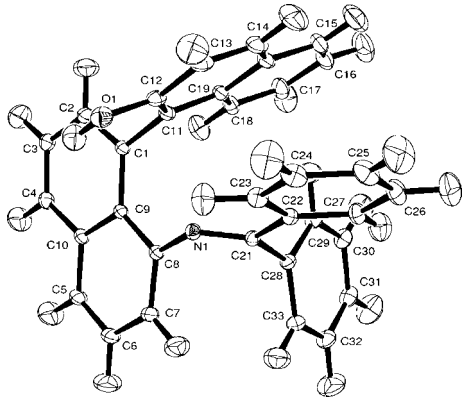
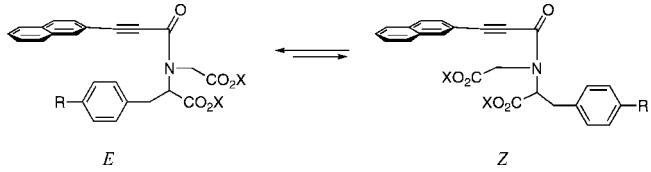


Figure 25. Crystal conformation of 8′-benzhydrylideneamino-1,1′-binaphthyl-2-ol. Figure 1 of ref 194, Farrugia et al., *Acta Crystallogr.* **2009**, *B65*, 757−769. Reproduced with permission from Oxford University Press.



E *Z*

Figure 26. Conformational equilibrium of **24** (X = Na or CH_3).

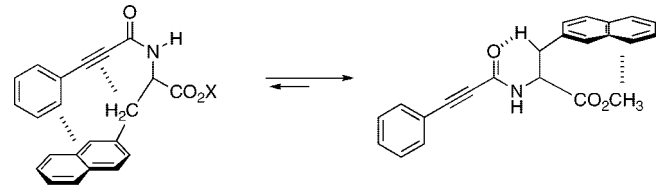
that aliphatic and aromatic CHs in di(1-pyrrolymethyl)-*o*-benzene are both contributing to maintain this conformation stable.

Farrugia et al. reported that an intramolecular CH/π hydrogen bond contributes in maintaining the folded conformation of 8′-benzhydrylideneamino-1,1′-binaphthyl-2-ol, as shown in Figure 25.[194] An aromatic CH on the benzhydrylyl moiety points itself to the center of a naphthyl group (distance 2.63 Å).

3.4.2. Nature of the Aromatic CH/π Hydrogen Bond

Gellman and co-workers analyzed the *Z* vs *E* equilibrium of a series of tertiary amide **24** (X = Na, CH_3; R = H, Me, Et, *i*-Pr, *t*-Bu, Phe, cyclohexyl) by Monte Carlo simulations and NMR (NOESY) experiments. In this case, they found that the *E* conformer prevails (Figure 26).[195]

In secondary amides **25**, in contrast, the *Z* conformer has been found to be the dominant contributor. They compared



E *Z*

Figure 27. Conformational equilibrium of **25**.

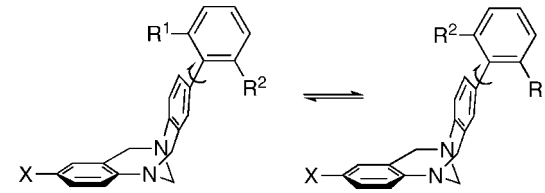


Figure 28. Molecular torsion balance of Wilcox.

the *E*/*Z* ratio for sodium salts (X = Na) in water and methyl esters (X = CH_3) of **25** in $CDCl_3$ (interactions with the solvent chloroform (a strong CH-donor) involve the effect of CH/π hydrogen bonds and thus might influence the conformational equilibria) to investigate whether the so-called "hydrophobic effect" is contributing.[196] They argued that such an effect might occur, though slightly, since the concentration of the *E* conformer increases in water.

Our suggestion is that the contribution from nonconventional hydrogen bonds should not be ignored in the interpretation of the experimental results. Possible intramolecular interactions include CH/π hydrogen bonds (C_6H_5 vs $C_{10}H_7$ and CH_2 vs C≡C) in the *E* conformer and CH/O (CH vs O═C) and CH/π hydrogen bonds (CH_3 vs $C_{10}H_7$) in methyl esters of the *Z* conformer. Figure 27 illustrates this.

The energy involving an aromatic CH is somewhat stronger than that involving an aliphatic CH; this type interaction is often referred to as the edge-to-face or T-shape π/π, edge-to-face aromatic, arene/arene, or polar/π interaction. We prefer to refer this as the "aromatic CH/π hydrogen bond".

The nature of the aromatic CH/π hydrogen bond has long been a subject of debate[197] but remains undecided yet. A number of workers attacked this problem. Wilcox and coworkers devised a "molecular torsion balance"[198] for measuring the folding energies of the aromatic CH/π hydrogen bond and to examine the effect of substituents (Figure 28). The influence of various factors has been studied by the use of this useful model: the effect of bulkiness or surface area of R^1 and R^2,[199] the nature of X (electron-donating vs electron-withdrawing),[200] and solvent[201] (polar vs nonpolar). In any event, contribution from the London dispersion force is the most important, but the Coulombic, dipole, and quadrupole interactions[202] are also considerable.

Hunter and his group developed a methodology called the "chemical double mutant cycles"[203] to measure exactly the energy of the aromatic CH/π hydrogen bond in hydrogen-bonded zipper complexes as a function of substituent on aromatic rings (Figure 29). By using this ingenious method, Carver et al. estimated the interaction energy to vary, depending on the combination of the substituents (X and Y in Figure 29), from ca. +0.24 kcal mol^{-1} to ca. −1.2 kcal mol^{-1}.[204] The results fit well to the Hammett relationship indicating that electrostatic interactions are responsible for the CH/π hydrogen bond.

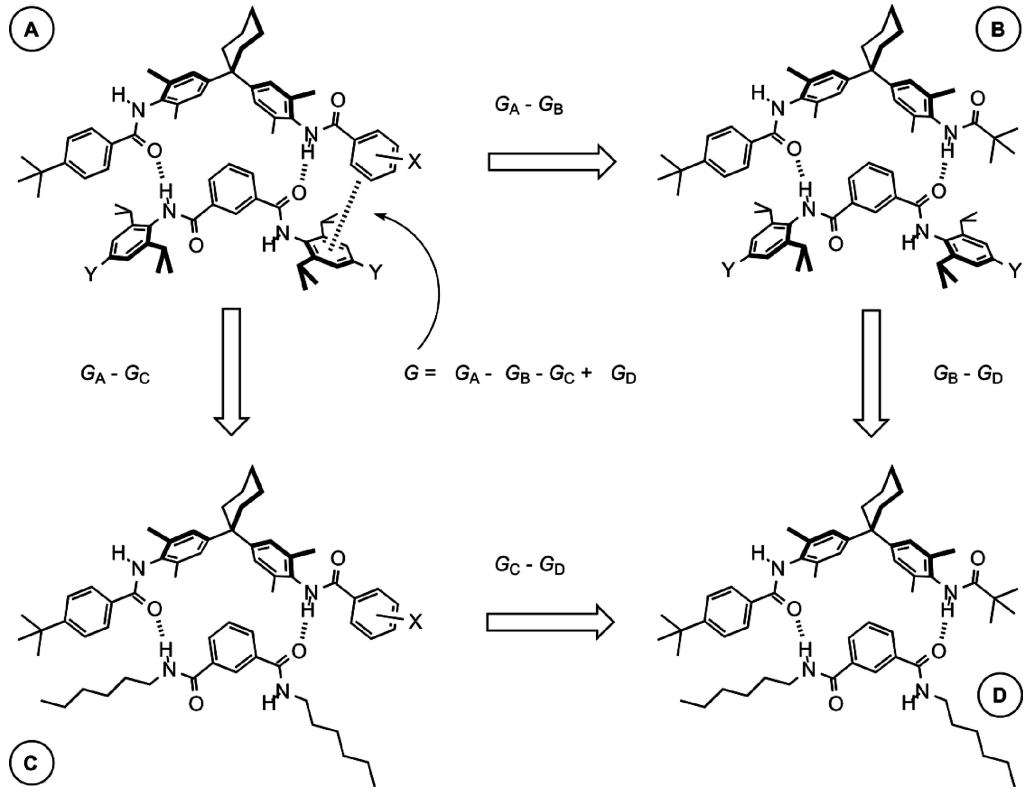


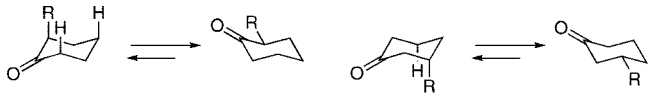
Figure 29. A chemical double mutant cycle for determining the magnitude of the terminal aromatic hydrogen bond in complex A. Scheme 1 of Carver et al., *Chem.—Eur. J.* **2002**, *8*, 2847−2859. Reproduced with permission from Wiley-VCH Verlag GbmH.

4. Conformation of Natural Organic Compounds Studied by ab Initio MO Calculations

Hereafter we examine the possibility that the relative stability of an axial alkyl substituent in cyclohexanones and the folded conformations, occasionally observed in terpenic and steroidal compounds, is rationalized in terms of the CH/π hydrogen bond.

4.1. The Alkylketone Effect Revisited

Increase in the ratio of the axial conformer is noted in 2-alkyl (**26**) and 3-alkyl cyclohexanones (**27**), compared with the parent hydrocarbons.[205] More specifically, a shift is observed in the conformational equilibrium of 2-ethyl- and 2-isopropyl-**26**, and 3-methyl-, 3-ethyl-, and 3-isopropyl-**27**. This is known as the alkylketone effect. Since its discovery in 1955, effort has been made to find the origin of this phenomenon. Previous interpretations were based, fundamentally, on the relief of a severe 1,3-diaxial repulsion that might be brought about by replacing a CH_2 with a flat carbonyl group.



26 **27**

We hypothesized that the alkylketone effect is one of the consequences of the CH/π hydrogen bond that occurs between CH(s) of an axial alkyl group and π(C═O) in cyclohexanones.[206] Table 15 gives the results of our calculations. It is noted that the alkylketone effect does not occur in 2-methyl-cyclohexanone **26** (R = CH_3) while it does in 3-methyl-cyclohexanone **27** (R = CH_3). This is consistent with the experimental data[207] and is reasonable, since formation of a five-membered CH/π(C═O) hydrogen bond is impossible in the former, whereas it may occur in the latter (Figure 30).

Table 15. Conformational Gibbs Free Energies of 2-Alkyl Cyclohexanones 26 and 3-Alkyl Cyclohexanones 27 [MP2/6-311G(d,p)]

R	*A*-value[a]	ΔG_{ax-eq}, **26**	2-alkylketone effect[b]	ΔG_{ax-eq}, **27**	3-alkylketone effect[b]
CH_3	1.74	1.94	−0.20	1.00	0.74
C_2H_5	1.79	1.33	0.46	0.87	0.92
i-C_3H_7	2.21	0.80	1.41	1.19	1.02
t-C_4H_9	4.7	3.88	0.82	3.81	0.89

[a] *A*-value = ΔG_{ax-eq} (experimental values in kcal mol^{-1}), data from ref 117, Eliel et al., *Stereochemistry of Organic Compounds*, Wiley-Interscience, 1993, New York, Table 11.7. [b] *A*-value − ΔG_{ax-eq} (calculated values).

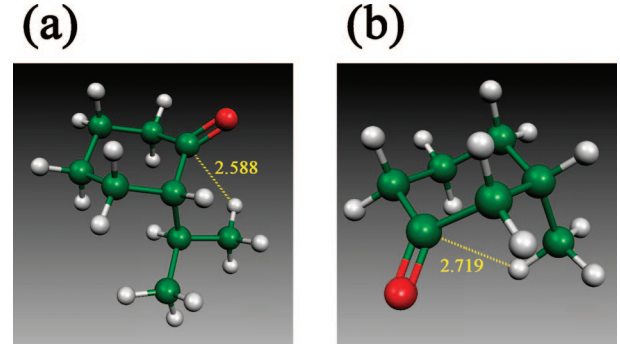


Figure 30. (a) 2-Alkylketone effect (R = i-C_3H_7) and (b) 3-alkylketone effect (R = CH_3). Numbers indicate the distances between relevant atoms (in Å). Figures 2 and 3 of ref 206, Takahashi et al., *Tetrahedron* **2008**, *64*, 2433−2440. Reproduced with permission from Elsevier Ltd.

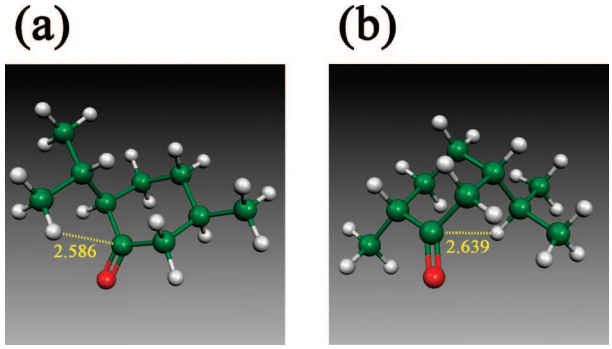
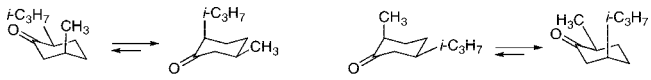


Figure 31. Short CH/π(C═O) distances disclosed in axial isopropyl conformers of (a) isomenthone **28** and (b) isocarvomenthone **29**. The numbers indicate distances between relevant atoms (in Å). Figures 2 and 5 of ref 206, Takahashi et al., *Tetrahedron* **2008**, *64*, 2433−2440. Reproduced with permission from Elsevier Ltd.

4.2. Conformation of Isomenthone and Isocarvomenthone

In isomenthone **28**, it has been known that the axial isopropyl conformer prevails. In isocarvomenthone **29**, ca. 75% has been suggested to be in the axial isopropyl conformation.



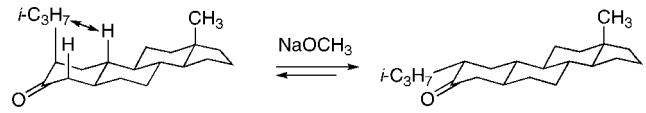
28 **29**

We calculated the conformational energy of **28** and **29**. The most stable conformer has been found to have the axial isopropyl group in these compounds. Figure 31 illustrates this. Short CH/π(C═O) distances are disclosed in **28** (2-alkylketone effect) and **29** (3-alkylketone effect).

4.3. Stability of the Axial Isopropyl Group in Ketosteroids

Djerassi and his group studied the equilibrium of 2-isopropyl-19-nor-5α-androstan-3-one, **30**.[208] Alkali treatment of either axial isopropyl **30a** or equatorial isopropyl diastereomer **30b** gave a mixture of the isomers in a ratio ca. 20:80. This is extraordinary in view of the seemingly unfavorable 1,3-diaxial interactions (*i*-C_3H_7 vs Hs) involved in **30a** (Figure 32).

To make clear the reason for this phenomenon, we calculated the conformational energy of model tricyclic ketones **31** at the MP2/6-311G(d,p) level. Table 16 gives the difference in the Gibbs energy, ΔG_{ax-eq}, and the ratios



30a (ca. 20%) **30b** (ca. 80%)

Figure 32. Equilibrium of 2-isopropyl-19-nor-5α-androstan-3-one **30**. The arrow indicates unfavorable 1,3-diaxial interaction.

Table 16. Difference in the Gibbs energy, ΔG_{ax-eq} (in kcal mol^{-1}), and the Ratio (%) of the Axial and Equatorial Conformers of Model Compounds 31

R	ΔG_{ax-eq}	axial	equatorial
CH_3	1.68	5.5	94.5
C_2H_5	1.03	14.9	85.1
i-C_3H_7	0.41	33.2	66.8
t-C_4H_9	2.69	1.0	99.0

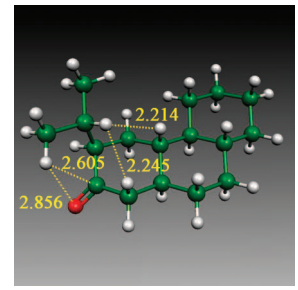
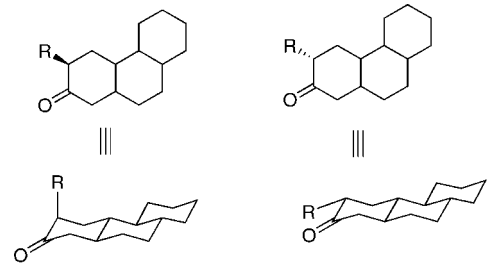


Figure 33. Structure of the most stable conformer of axial **31** (R = *i*-C_3H_7). Numbers indicate the distances between the relevant atoms (in Å). Unfavorable 1,3-diaxial interactions (*i*-C_3H_7 vs Hs) seem to be minimized.

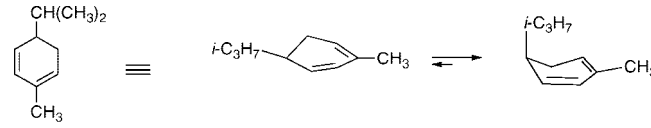
of the axial and equatorial conformers of model compounds.[209] The proportion of the axial *i*-C_3H_7 conformer (ca. 33%) compares with the experimental value (ca. 20%). Figure 33 gives the structure of the most stable one among three axial isopropyl conformers. Short CH/π distances are noted between CH hydrogens in *i*-C_3H_7 and C═O.



31 (axial-alkyl) **31** (equatorial-alkyl)

4.4. Conformation of α-Phellandrene

In α-phellandrene (**32**), the conformer bearing a quasi-axial isopropyl group has been known to prevail. To make clear the reason for this apparently peculiar phenomenon, we calculated the conformational Gibbs energy of a series of 5-alkyl-1,3-cyclohexadienes **33**.[210] Table 17 lists the results. It has been found that the conformer bearing the 5-alkyl group in the axial orientation is more stable than the equatorial congener.



32

Table 17. Relative Gibbs Free Energies (ΔG_{eq-ax}, in kcal mol^{-1}) of the Conformational Isomers of 2-Methyl-5-alkyl-1,3-cyclohexadienes 33 [MP2/6-311++G(d,p)//MP2/6-311G(d,p)] and the Proportions (%) of the Conformers

R	ΔG_{eq-ax}	axial	equatorial
CH_3	0.07	53.0	47.0
C_2H_5	0.34[a]	64.0	36.0
i-C_3H_7[b,c]	1.27[a]	89.6	10.4
t-C_4H_9	0.36	64.7	35.3

[a] Calculated by taking account of the abundance of three axial and equatorial conformers. [b] α-Phellandrene. [c] Isopropyl derivatives often give exceptional data in conformational equilibria. The reason remains uncertain, but it may be pointed out that in *i*-C_3H_7, we have one CH and two diastereotopic methyl groups (each CH_3 has three CHs). The number and chance of the interaction increase, accordingly.

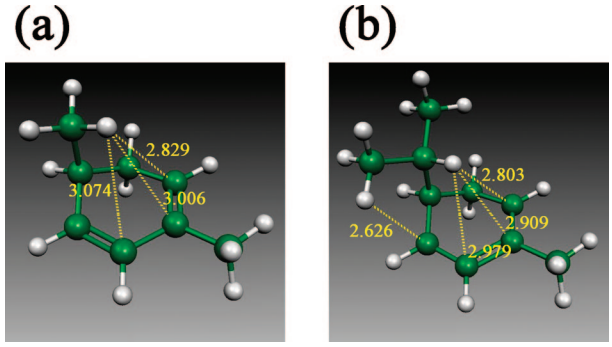


Figure 34. Calculated geometries of (a) 2-methyl-5-methylcyclohexa-1,3-diene (**33**, R = methyl) and (b) α-phellandrene (**33**, R = isopropyl). Numbers indicate the distances between relevant atoms (in Å). From Figure 2 of ref 210, Takahashi et al., *Tetrahedron* **2008**, *64*, 5773−5778. Reproduced with permission from Elsevier Ltd.

Figure 34 shows the most stable axial conformers of **33** (R = CH_3, *i*-C_3H_7). A number of short distances are disclosed between CHs in the 5-alkyl group and sp^2-carbons. This explains the experimental finding that the axial isopropyl conformer prevails in the equilibrium of α-phellandrene.

4.5. Conformation of Levopimaric Acid

In 1961, Burgstahler et al. reported that levopimaric acid **34** exists in the folded conformation **34a**, as opposed to the extended conformation **34b** (Figure 35).[13] Later, the crystal conformation of **34** was shown to be similar to that found in solution.[14]

We felt that the stability of the folded conformation comes from CH/π hydrogen bonds occurring between 10β angular methyl group and the 1,3-cyclohexadiene moiety of **34a**. The difference in the conformational energy of **34**, $\Delta G_{\text{folded-extended}}$, was calculated to be −3.32 kcal mol^{-1}, at the MP2/6-311G(d,p) level calculations.[211] In the calculated structure of **34a**, the dihedral angle τ defined by $C^8-C^{14}-C^{13}-C^{12}$ has been shown to be −10.2°; this compares with the experimental values (−9.1°, −11.8°) found in the crystal structure of levopimaric acid.[212] Figure 36 illustrates the calculated structure of levopimaric acid **34** (CH_3 instead of *i*-C_3H_7).

To investigate the effect of the 10β methyl group in stabilizing the folded conformation, the conformational energy of a series of model compounds was calculated for 10β-methyl **35**, 9α-methyl **36**, 9α,10β-dimethyl **37**, and 9,10-nor-compound **38**. Table 18 compares the results.

In 10β-Me compound **35**, the folded conformation (τ −10.2) has been calculated to be more stable than the extended (τ +9.8) conformation. The conformation with negative τ has also been shown more stable than the positive-τ conformation in 9α-Me compound **36**. Similar results are obtained for 9α,10β-dimethyl **37** and 9,10-nor-compounds **38**, but in these cases, ΔG becomes smaller, due to the compensation or the nonexistence of the effect. Figure 37 illustrates short intramolecular CH/π distances noted between the relevant atoms in **35** and **36**. Notice that the methyl group is interacting from the opposite sides of the molecular plane. (The more stable **36** (τ −12.2) is in the folded conformation.)

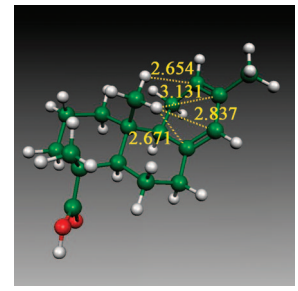
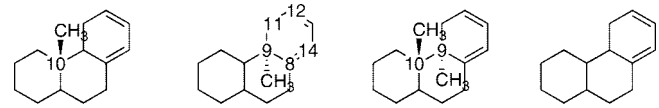


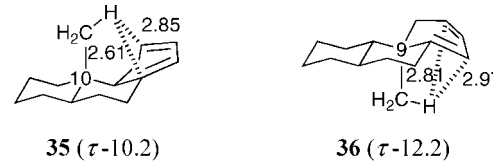
Figure 36. Calculated structure of levopimaric acid **34** (CH_3 instead of *i*-C_3H_7). Numbers indicate the distances between relevant atoms (in Å). From Figure 1 of ref 211, Takahashi et al., *Tetrahedron* **2009**, *65*, 3525−3528. Reproduced with permission from Elsevier Ltd.

Table 18. Relative Conformational Gibbs Energies (ΔG, in kcal mol^{-1}) of 10β-Me 35, 9α-Me 36, 9α,10β-diMe 37, and 9,10-nor compound 38[a]



35	**36**	**37**	**38**
35	**36**	**37**	**38**
−2.33 (−10.2) 0 (+9.8)	0 (+14.4) −1.90 (−12.2)	0 (+12.0) −0.89 (−7.8)	0 (+15.6) −0.31 (−12.5)

[a] The dihedral angle τ (deg) defined by the sequence of atoms $C^8-C^{14}-C^{13}-C^{12}$ is given in parentheses.



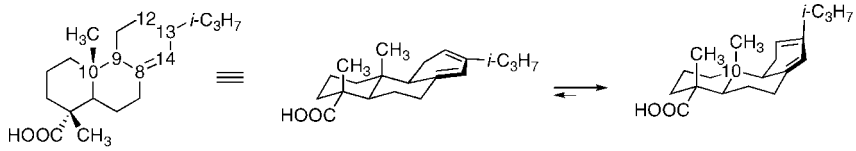
35 (τ-10.2) **36** (τ-12.2)

Figure 37. CH/π short contacts in **35** and **36**; the numbers correspond to the interatomic distances (in Å).

5. Preference of the Gauche Alkyl−Aromatic Conformation as Evidenced by Crystallographic Database Studies

5.1. Organic Compounds

We analyzed XH/π contacts (X = C, O, N) in organic crystals in the Cambridge Structural Database (CSD).[213] Among entries bearing at least a C−H group and a C6-aromatic ring, a considerable fraction have been shown to bear a short CH/π distance (Table 19).



34b (extended) **34a** (folded)

Figure 35. Conformation of levopimaric acid.

Table 19. XH/π Contacts Disclosed in the Crystal Structure of Organic Compounds

	entries[a]	hits[b]	ratio, %	distances[c]	D_{atm}, Å[d]
			Intermolecular		
CH/Ar	32669	24523	75.1	112553	2.91 ± 0.12
OH/Ar	8448	431	5.1	512	2.80 ± 0.21
NH/Ar	8827	825	9.3	1059	2.78 ± 0.19
			Intramolecular		
CH/Ar	32669	9520	29.1	22937	2.72 ± 0.18
OH/Ar	8448	126	1.4	168	2.48 ± 0.26
NH/Ar	8827	239	2.7	285	2.58 ± 0.22

[a] Number of entries bearing at least one XH (X = C, O, N) and a C6 aromatic group. [b] Number of entries with at least one short XH/Ar contact (cutoff = 3.05 Å). [c] Number of short XH/Ar distances. [d] Mean H/C atomic distance.

It is noted that the ratio of entries bearing short CH/π contacts is much larger than that of the OH/π and NH/π hydrogen bonds. As for the intramolecular interaction, ca. 29% of compounds have at least one CH/Ar short contact in their crystal structure, while corresponding values for the OH/Ar and NH/Ar interactions are 1.4% and 2.7%, respectively (these values are minimum estimates since structures bearing no atomic coordinates are included in these entries. A longer cut off distance gave a higher proportion of the hit entries). This is comprehensible because the CH group is more abundant than the OH and NH groups. Another reason is that OH and NH prefer O or N to form ordinary hydrogen bonds. The CH/π distance has been found to be shortest in the five-membered CH/π bond and increases on going to a larger-membered interactions. (Formation of the five- or six-membered ring has been known to be general in the conventional hydrogen bond and XH/π, and CH/O hydrogen bonds.) Suezawa et al. analyzed CH/π hydrogen bonds in crystals involving C_{60} fullerene.[214]

5.2. Coordination and Organometallic Compounds

Janiak,[215] Suezawa et al.,[216] Reger,[217] Xi and Niclós-Gutiérrez,[218] Zaric,[219] and their co-workers analyzed organometallic crystals by CSD surveys. CH/π hydrogen bonds have been found to be important in most cases; π/π- stacking prevails, however, in cases where such an interaction is only possible for stereochemical reasons.

5.3. Peptides

Umezawa et al. performed a database study to examine the role of the CH/π interaction in peptides.[220] A number of short intramolecular CH/π distances have been disclosed in the crystal structures of peptides bearing at least one aromatic residue in the sequence (Table 20). Among 130 entries, the number of crystals bearing at least one intramolecular CH/π hydrogen bond is 55 (42%). The crystal structure was inspected individually to know whether the conformation is merely a consequence of the so-called "packing force" or the CH/π interaction plays an indispensable role. Thus they concluded that the CH/π hydrogen bond constitutes one of the key factors in controlling the conformation of peptides in the solid state.

Table 20. Intramolecular CH/π Contacts Disclosed in the Crystal Structure of Peptides Bearing at Least One Phenylalanine, Tyrosine, or Tryptophan Residue

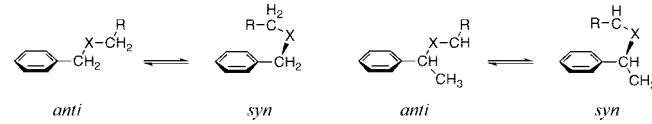
	entries[a]	distances[b]	D_{atm}, Å[c]
CH/π	55	95	2.87 ± 0.15
C_{sp^3}H/π	49	78	2.88 ± 0.15
C_{sp^2}H/π	10	17	2.82 ± 0.11

[a] Number of entries with short CH/Ar contact (3.05 Å cut off). [b] Number of short distances. [c] CH/C(aromatic) interatomic distance.

Bazzicalupi and Dapporto analyzed CH/π hydrogen bonds in peptides by CSD searches.[221] Residues containing aromatic (tryptophan, tyrosine, phenylalanine) and methyl groups (alanine, valine, leucine, isoleucine) were examined as a function of the length of the chain separating the interacting groups. The maximum number of CH/π hydrogen bonds has been found for five-membered chains joining the aromatic and methyl moieties.

5.4. Combined CSD and Computational Study

A combined CSD and computational study was carried out to investigate the crystal conformation of aralkyl compounds, $ArCH_2XCH_2-R$ and $ArCHCH_3XCH-R$.[222] The structure bearing R (R = any group) and Ar (Ar = C6 aromatic group) in the *syn* relationship has often been found in these crystals.

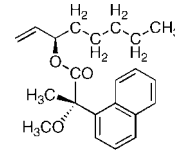


The proportion of crystal structures bearing R and Ar in the *syn* relationship relative to the *anti* conformation ($r_{syn/anti}$) varied from 0.55 for $ArCH_2XCH_2-R$ to 3.68 for $ArCHCH_3XCH-R$. The logarithm of $r_{syn/anti}$ was plotted against the difference in Gibbs energy, $\Delta G_{syn-anti}$, obtained by MO calculations of model compounds $C_6H_5CH_2XCH_3$ and $C_6H_5CHCH_3XCH_3$ (X = O, NH, S, CH_2). A linear correlation has been shown between ln $r_{syn/anti}$ and $\Delta G_{syn-anti}$. In other words, correlation of the crystal conformer distribution with the computed conformational energy difference is statistically significant. This shows that the effect of the so-called "packing forces" is neither large nor systematic in controlling the crystal conformation of these compounds.[223]

6. CH/π Hydrogen Bonds in Biologically Important Molecules

6.1. CH/π Hydrogen Bonds in Enantiomeric Separation

To investigate the mechanism of enantioresolution of secondary alcohols, Ichikawa et al. determined the crystal structure of esters bearing an (*S*)-2-methoxy-2-(1-naphthyl)-propanoic acid moiety [(*S*)-MαNP acid], such as **39**.[224]



39

The crystal conformation of **39** was found as shown in Figure 38. Notice that two CH/π hydrogen bonds concurrently occur between the *n*-pentyl group in the alcoholic part and the naphthyl group. NMR experiments showed that a

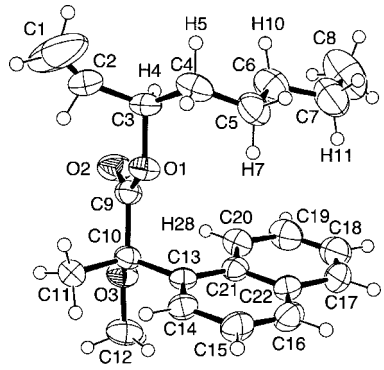


Figure 38. Crystal structure of **39**. Figure 3 of ref 224, Ichikawa et al., *Tetrahedron: Asymmetry* **2008**, *19*, 2693−2698. Reproduced with permission from Elsevier Ltd.

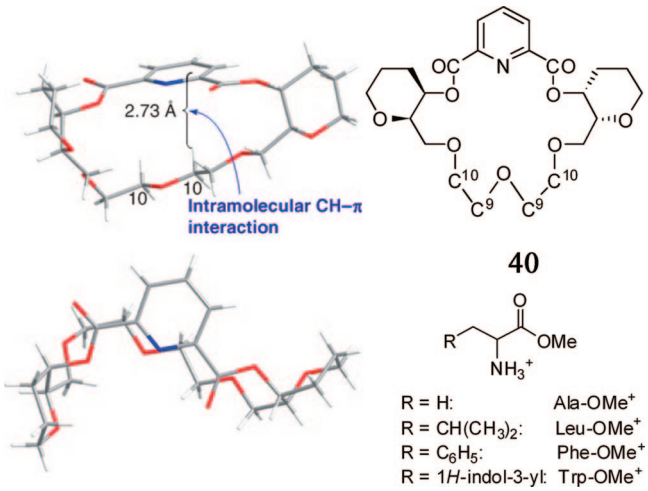


Figure 39. Crystal structure of **40**. Figure 2 of ref 226, Carrillo et al., *Angew. Chem., Int. Ed.* **2009**, *48*, 7803−7808. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

Table 21. Ratio of the Association Constants, K_D/K_L, and Gibbs Free Energy Changes $\Delta\Delta G_{D-L}$ (in kcal mol^{-1}) in the Chiral Discrimination by 40 of Amino Acid Esters D-AA-OMe$^+$ vs L-AA-OMe$^+$[a]

guest	K_D/K_L[b]	$\Delta\Delta G_{D-L}$
Ala-OMe$^+$	1.80	0.35
Leu-OMe$^+$	3.32	0.71
Phe-OMe$^+$	4.55	0.90
Trp-OMe$^+$	10.39	1.39

[a] Edited from Table 1 of ref 226, Carrillo et al., *Angew. Chem. Int. Ed.* **2009**, *48*, 7803−7808. [b] Enantioselectivity.

similar conformation is maintained in solution. They argued that the CH/π hydrogen bond plays a key role in the effective enantioseparation. Excellent separation of the diastereomers has been accomplished in HPLC, by using esters of (*S*)-MαNP acid.[225]

In the course of exploring useful methods for the optical resolution of amino acid esters, Martin et al. determined the structure of a synthetic receptor, **40**, which bears a *cis*-2-oxymethyl-3-oxy-tetrahydropyran unit as a key motif.[226] The crystal conformation of **40** is shown in Figure 39. A similar folded conformation was found in solution by NMR ROE experiments.

Table 21 shows that the association constant is higher with the D-enantiomers of amino acid esters (AA-OMe$^+$) than the L-congener, especially for esters that bear an aromatic side chain. Replacement of the hydrogens at C^{10} by fluorine significantly reduced the efficiency of the resolution. In view of the above findings, they proposed a mechanism of this chiral discrimination and argued that the CH/π hydrogen bond is an important factor in bringing about such a remarkable chiral recognition. The methods presented as above are useful in studying the nature of weak molecular forces and designing systems for enantioseparation.

6.2. Conformation of Peptides

6.2.1. Solution Conformation

In 1967, Kopple reported on the preference of the folded conformation for cyclic dipeptides bearing an aromatic residue such as *cyclo*(Gly-Tyr) and *cyclo*(Ala-Tyr).[227] Preference of the CH/Ar proximate conformation was suggested also for peptide derivatives such as D-AA-L-Phe-Bzl (AA = Leu, Val, or Ala), D-Arg-L-Phe-NHBzl, D-Leu-L-Phe-NHBzl,[228] and so on;[229] the result was interpreted in terms of the CH/π interaction.

In 1972, Deber and Joshua showed, on the basis of a systematic NMR study, that the folded conformer prevails in a series of dipeptides bearing phenylalanine: L-Phe-D-AA (AA = asparagine, aspartate, glutamine, glutamate, arginine, lysine, amino butyric acid (Aba), norvaline (Nva)).[230] Significant upfield shifts were observed for methylene hydrogens of the residue AA, compared with those of dipeptides bearing alanine (L-Ala-D-AA). The results indicate the presence of an attractive interaction between the phenylalanine aromatic ring and β-CHs in the side chain group.

Trp cage, a 20-residue peptide, Asn-Leu-Tyr-Ile-Gln-Trp-Leu-Lys-Asp-Gly-Gly-Pro-Ser-Ser-Gly-Arg-Pro-Pro-Pro-Ser, has been known to exist in a compact, coiled structure. The reason for the compact structure of this peptide was investigated by calculations at the BHandHLYP/cc-pVTZ level.[231] It was found that CH/π and NH/π hydrogen bonds involving the aromatic rings of tyrosine and tryptophan as acceptors are concurrently working to stabilize the coiled conformation of this peptide.

A 21-residue antimicrobial cyclic peptide, arenicin-2, was studied by molecular dynamics simulation. Contribution to the hairpin stabilization from several weak molecular forces, like nonpolar interactions between aliphatic side chains and aromatic CH/π hydrogen bonds, has been suggested.[232]

Computational studies (PCILO) were performed for CH_3-CO-Aib-ΔPhe-$NHCH_3$, CH_3CO-(Aib-ΔPhe)$_3$-$NHCH_3$ (Aib = α-amino-isobutyric acid, ΔPhe = dehydrophenylalanine), and their derivatives bearing leucine at either the N- or C-terminus.[233] These peptides have been found to adopt helical structures. The methyl group of CH_3CO was involved in CH/π hydrogen bonds with the π-group of ΔPhe, and the amino group of ΔPhe is involved in an NH/π hydrogen bond with its aromatic ring. The methyl groups of the Aib residues are also involved in CH/π hydrogen bonds.

6.2.2. Solid Conformation

In 1971, Webb and Lin reported on the crystal structure of *cyclo*(Gly-Tyr).[234] L-Asp-L-Phe and L-His-Gly[235] have been shown to be in the folded conformation. Figure 40 gives two examples from a CDS study. There we see CH/π and NH/π hydrogen bonds keeping the compact structures stable.

Evidence for the folded conformation was provided in other peptides such as enkephalin,[236] Boc-Gly-Gly-Gly benzyl ester,[237] synthetic unnatural peptides,[238] and so on. The crystal structure of Boc-Val-ΔPhe-Leu-Ala-ΔPhe-Ala-

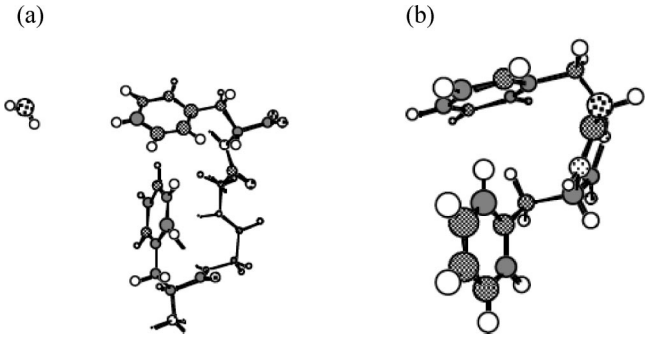
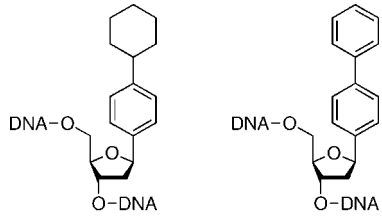


Figure 40. Crystal structures of (a) L-Phe-Gly-Gly-D-Phe·$3H_2O$ (FEYZEO) and (b) *cyclo*(L-Phe-L-Phe) (DUZDUX). See also Figures 3−9 in ref 220, Umezawa et al., *Bioorg. Med. Chem.* **1999**, *7*, 2021−2026.

OCH_3 was examined.[239] The overall conformation of the molecule is a 3_{10}-helix, unwound at the C-terminus. The NMR data suggested that the peptide maintains its helical structure in solution. The aromatic ring of ΔPhe formed the hub of multicentered interactions, using CH/π and CH/O hydrogen bonds. In summary of this section, CH/π hydrogen bonds are often found in peptides, and by implication, this effect seems to be crucial in the consideration of the 3D structure of proteins.

6.3. Relevance of CH/π Hydrogen Bonds in Bioconjugates

Leumann examined the thermal melting and thermodynamic properties of a DNA-duplex model system, 5′-d(GATGAC-$(X)_n$-GCTAG)/3′−d(CTACTG-$(Y)_n$-CGATC, which bears one or three phenyl-cyclohexyl nucleosides (PhC) or biphenyl nucleosides (Bph) at the center of each strand.[240] Table 22 summarizes the thermal melting and thermodynamic data.



PhC Bph

It is remarkable that the duplex containing three PhC nucleosides in the center of the strand is more stable by 3.7 °C than a control duplex with three T−A base pairs. Further, it is noted that the PhC/PhC interactions stabilize the triple-modified duplexes by 14.6 kcal mol^{-1}, while the Bph/Bph interaction only contributes 2.9 kcal mol^{-1} to the stability. The NMR and CD data gave results consistent with this conclusion. Contribution from the CH/π hydrogen bond is apparent (Figure 41).

Table 22. Thermal Melting Data and Thermodynamic Parameters of the Duplex Formation in the Mutual Recognition of 5′-d(GATGAC-$(X)_n$-GCTAG)/3′-d(CTACTG-$(Y)_n$-CGATC[a]

n	X	Y	T_m, °C	ΔG^b	ΔH^b	ΔS^c
1	T	A	47.9			
1	PhC	PhC	45.4	−15.3	−95.9	−208
1	Bph	Bph	42.5	−13.5	−79.7	−221
3	T	A	51.0			
3	PhC	PhC	54.7	−19.1	−110.5	−307
3	Bph	Bph	49.9	−15.7	−82.6	−225

[a] Edited from Tables 1, 2, and 3 of ref 240, Kaufmann et al., *Angew. Chem. Int. Ed.* **2009**, *48*, 3810−3813. [b] In kcal mol^{-1}. [c] In cal mol^{-1} K^{-1}.

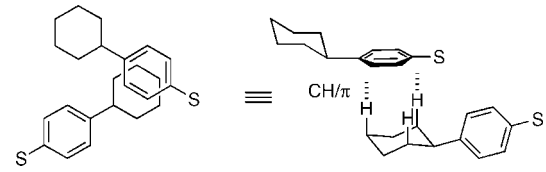


Figure 41. Schematic representation of a cyclohexyl/phenyl interaction. S = deoxyribose.

Table 23. Carbohydrate/Benzene Interactions, As Determined in a DNA-Duplex Context[a]

dangling moiety[b]	T_m, °C	ΔG^c	ΔH^c	ΔS^d	$\Delta\Delta G^{c,e}$
HO-C2	50.0	−9.4	−56.1	−150	
β-D-glucose-C2	51.6	−9.9	−63.1	−171	−0.25
β-D-galactose-C2	50.4	−9.7	−59.1	−159	−0.15
β-L-fucose-C2	51.8	−10.1	−67.4	−185	−0.40
β-D-2-deoxyglucose-C2	50.7	−9.7	−61.0	166	−0.15
α-Δ-2-deoxyglucose-C2	51.0	−9.8	−60.9	165	−0.20

[a] Edited from Table 1 of ref 241, Morales et al., *Chem.−Eur. J.* **2008**, *14*, 7828−7835. [b] Core sequence BCGCGCG, where B is the benzene nucleoside and C2 is $CH_2CH_2-OPO_2^-$. [c] In kcal mol^{-1}. [d] In cal mol^{-1} K^{-1}. [e] Carbohydrate/benzene stacking.

Morales et al. studied carbohydrate/aromatic interactions using a dangling-end DNA model system (Figure 42).[241] Table 23 lists the thermodynamic parameters for systems bearing a variety of carbohydrates. The presence of the ethylene glycol linker destabilizes the DNA conjugates due to the entropy cost because of its high mobility. Table 23 shows, however, that all of the conjugates that contain a carbohydrate moiety show higher stability than the control conjugate. Undoubtedly, the interaction is enthalpy-driven.

By NMR experiments, it has become clear that the interaction of the hydrogens (H^1, H^3, H^5) at the α-face of the carbohydrate with the benzene π-system contributes in stabilizing the structure of the dangling-end DNA (Table 24). Contribution from CH/π hydrogen bonds between the carbohydrates and the benzene ring seems apparent (Figure 43). Neither conventional hydrogen bonds nor the so-called "hydrophobic effects"[242] play a part in driving the interaction.

Waters and co-workers examined a carbohydrate/π interaction using a β-hairpin peptide model system. Thus they determined, by NMR experiments, the ratio of the folded conformation of a number of peptides, incorporated with an aromatic residue at position 2 and Ac_4Glc at position 9 (Figure 44).[243]

Table 25 summarizes the results. Comparison of tryptophan (or β-(1-naphthyl)-L-alanine (1-Nal), β-(2-naphthyl)-L-alanine (2-Nal)) to phenylalanine shows that the surface area of the aromatic ring impacts the magnitude of the interaction. The axial CHs on the α-face in the sugar moiety were all shifted upfield, indicating that these hydrogens pack against the π plane of the aromatic ring; NOE experiments gave results consistent with this conclusion. Figure 45 illustrates this for the Ac_4Glc vs tryptophan and Ac_4Glc vs phenylalanine interactions. Contribution from the CH/π hydrogen bond is apparent. The so-called "hydrophobic interaction" does not play any role.

They also studied, by using the same β-hairpin peptide model, the interactions between tryptophan and lysine and

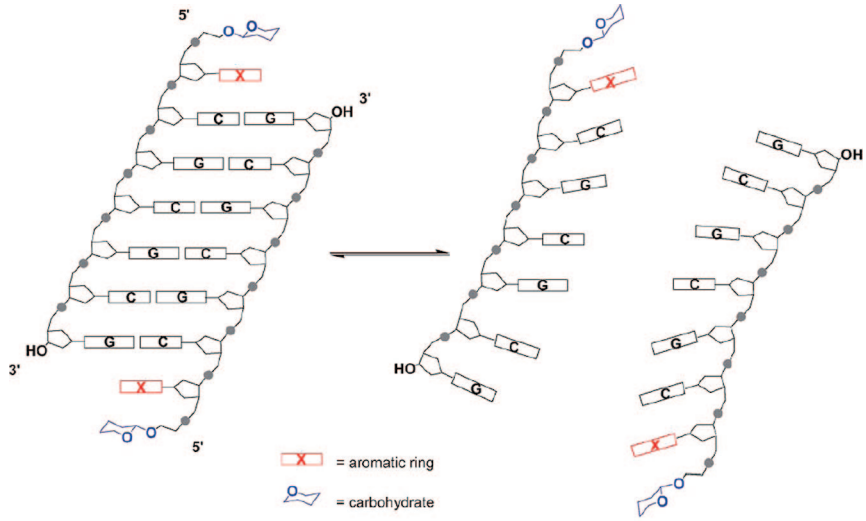


Figure 42. Dual carbohydrate/aromatic interaction in a dangling-DNA model. Scheme 1 of ref 241, Morales et al. in *Chem.—Eur. J.* **2008**, *14*, 7828−7835. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

Table 24. ^{1}H NMR Chemically Induced Shift Differences (in ppm) between the Sugar Residues and the Corresponding Monosaccharide Controls in D_2O[a]

	β-D-glucose	β-D-galactose	β-L-fucose
H^1	−0.112	−0.102	−0.144
H^2	−0.056	−0.059	−0.084
H^3	−0.074	−0.087	−0.082
H^4	−0.048	−0.051	−0.093
H^5	−0.120	−0.116	−0.178
H^6	−0.069	−0.058	
$H^{6'}$	−0.086	−0.050	
CH_3			−0.122

[a] Edited from Table 2 of ref 241, Morales et al., *Chem.—Eur. J.* **2008**, *14*, 7828−7835.

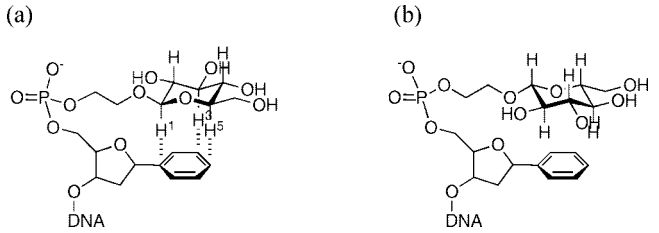


Figure 43. Schematic representation of the β-D-glucose/aromatic interaction: (a) interaction of the benzene ring through the α-face of the sugar; H^1, H^3, and H^5 are cooperatively contributing; (b) interaction of the benzene ring through the β-face of D-glucose.

norleucine (Nle). The tryptophan versus lysine and tryptophan versus norleucine combinations gave comparable data with regard to the proportion of the folded conformer and the stability of the peptide.[244] Peptides bearing acetyl, formyl, or trifluoroacetyl lysine at position 9 gave almost identical results[245] (Table 26, Figure 46); this demonstrates that the positive charge has little effect if any on the binding.[246] Aoyama and co-workers reported that neutral compounds are effectively included in synthetic receptors bearing π-groups such as calix[4]arenes.[247] Being consistent with this suggestion, it has been known that neutral compounds devoid of N^+ close to CH_2 or CH_3 groups are effective in the binding to acetylcholine esterase, where the binding site is lined with many aromatic residues.[248]

The above results are consistent with the findings that mutation of an aromatic residue to an aliphatic one abolishes the biological activity of enzymes such as lysozyme,

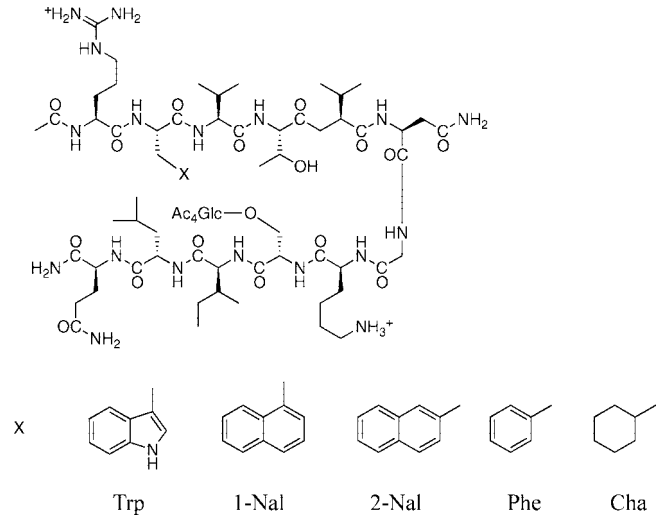


Figure 44. β-Hairpin peptide model designed to measure carbohydrate/aromatic interactions.

Table 25. Proportion of the Folded Conformation and ΔG of β-Hairpin Peptides Arg^1-Aaa^2-Val^3-Thr^4-Val^5-Asn^6-Gly^7-Lys^8-Ser^9(Ac$_4$Glc)-Ile^{10}-Leu^{11}-Gln^{12}-NH$_2$[a]

position 2	position 9	fraction folded[b]	ΔG^c
Trp	Ac_4Glc	85	−1.03
1-Nal[d]	Ac_4Glc	86	−1.08
2-Nal[e]	Ac_4Glc	83	−0.94
Phe	Ac_4Glc	57	−0.17
Cha[f]	Ac_4Glc	45	+0.12

[a] Aaa = residues with an aromatic side chain or cyclohexylalanine (Cha). Edited from Table 1 of Laughrey et al., *J. Am. Chem. Soc.* **2008**, *130*, 14625−14633. [b] Proportion of the folded conformer (%). [c] In kcal mol^{-1}. [d] 1-Naphthylalanine. [e] 2-Naphthylalanine. [f] Cyclohexylalanine.

carbohydrate-binding proteins, and lectins.[249] With regard to the interaction of an aromatic system with the lysine side chain,[250] it seems pertinent to comment on the results obtained by a mutagenesis study. Thus Imamoto et al. reported that a single CH/π hydrogen bond occurring between the side-chain methylene groups of Lys123, $-CH_2CH_2CH_2CH_2NH_3^+$, and the aromatic ring of Phe6 governs the stability and the biological activity of photoactive yellow protein (PYP).[251] They found that K123L and K123E retain the 3D structure and biological activity of the wild-

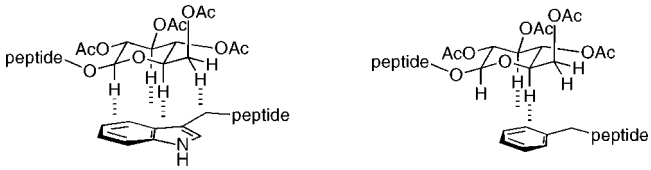


Figure 45. Schematic representation of the interactions in β-hairpin peptides: (a) Ac_4Glc vs tryptophan; (b) Ac_4Glc vs phenylalanine.

Table 26. Proportion of the Folded Conformation of β-Hairpin Peptides Arg^1-Trp^2-Val^3-Thr^4-Val^5-Asn^6-Gly^7-Lys^8-Aaa^9-Ile^{10}-Leu^{11}-Gln^{12}-NH_2[a]

position 2	position 9	fraction folded[b]
Trp	Lys	77
Trp	Nle	86
Trp	CH_3CO-Lys	87
Trp	HCO-Lys	86
Trp	CF_3CO-Lys	87

[a] Aaa = Lys or analogs. [b] Proportion of the folded conformer (%).

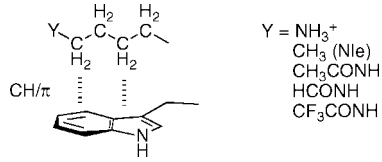


Figure 46. Schematic representation of the interactions of tryptophan with lysine and analogs.

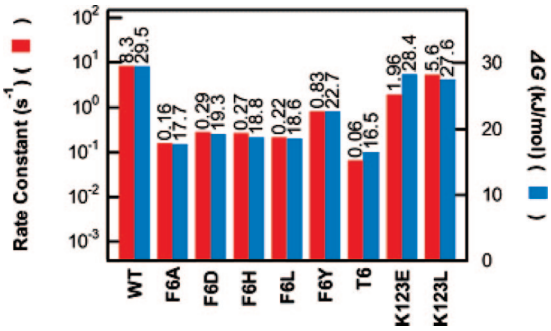


Figure 47. Bioactivity and stability of mutant proteins. Figures 1 and 2 of ref 251, Harigai et al., *J. Am. Chem. Soc.* **2006**, *128*, 10646−10647. WT = wild type. T6 = truncated at position 6.

type PYP (Figure 47). This indicates that the isobutyl group in leucine and methylene groups in the glutaminic acid side chain $-CH_2CH_2COO^-$ are almost equally effective as those in lysine side chain (Figure 48). In contrast, F6L and F6D completely abolish the stability and the activity of the protein. Neither the so-called "hydrophobic interaction" nor Coulombic force seems to play a role.

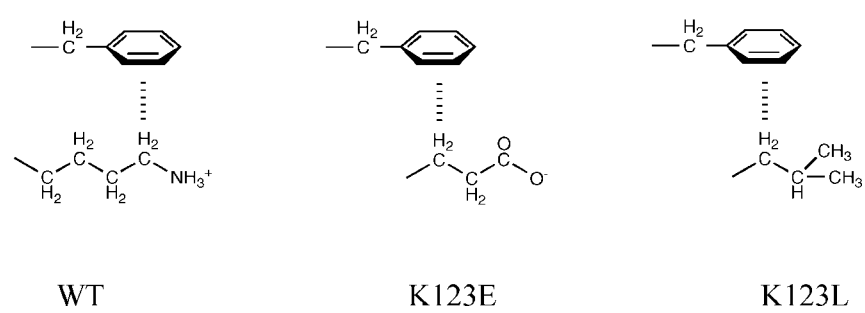
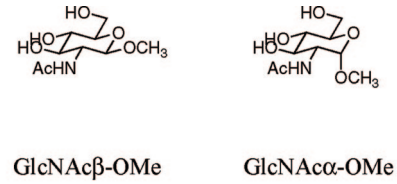


Figure 48. Schematic drawings illustrating the interaction between the aromatic ring of phenylalanine and side-chain CH_2 groups in (a) lysine, (b) glutaminic acid, and (c) leucine.



GlcNAcβ-OMe GlcNAcα-OMe

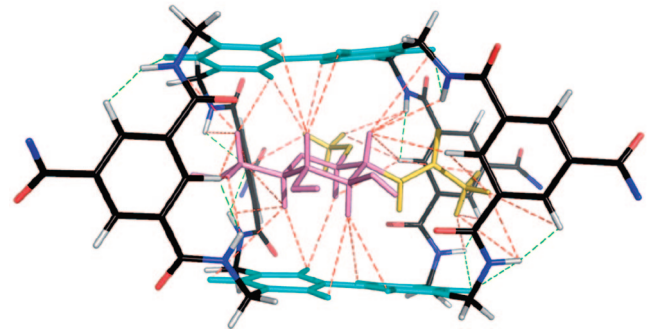


Figure 49. Derived structure by NOESY experiments and Monte Carlo molecular mechanics conformational search for the complex of **41** with GlcNAcβ-OMe (Figure 2 of ref 252, Ferrand et al., *Angew. Chem., Int. Ed.* **2009**, *48*, 1775−1779. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

Davis and co-workers designed a synthetic receptor (a lectin model), composed of two biphenyl and four isophthalamide moieties **41** (Figure 49).[252] Methyl glycosides of *N*-acetyl-D-glucosamine have been shown to be good substrates; the association constant in water, K_a, is 630 M^{-1} for GlcNAcβ-OMe and 24 M^{-1} for GlcNAcα-OMe, respectively. The former value well compares with K_a of wheat germ agglutinin for GlcNAcβ-OMe (730 M^{-1}). The specificity for the β-isomer is remarkable. Notice that, in Figure 49, many CH/π hydrogen bonds are contributing in the binding of the guest GlcNAcβ-OMe.

With regard to CH/π hydrogen bonds involving carbohydrates, Muraki presented a comprehensive review.[253] Spiwok,[254] Balaji,[255] Cuevas,[256] and co-workers reported on their computational results. Jiménez-Barbero,[257] Roelens,[258] Mazik[259] (NMR), Davis and Simons (IR),[260] and their coworkers studied the issue by spectroscopic determinations.

Before closing this chapter, we suggest that the concept of CH/π hydrogen bond is useful in the consideration of the folding mechanisms of proteins.[261] The specificity of the ligand binding will also be understood on this basis.[248,262,263] These topics, however, are out of the scope of this review and will be dealt with elsewhere.

7. Summary and Outlook

Evidence has accumulated that the *gauche* or folded conformation prevails in a number of organic compounds. It has been shown that many kinds of molecular forces contribute in stabilizing these conformations. In this review, we focused on the importance of weak hydrogen bonds. The role of nonconventional hydrogen bonds such as CH/π, CH/O, CH/X, and XH/π has been shown to be the most significant. Implication of the CH/π hydrogen bond, in particular, extends to crystal packing,[46] crystal conformation,[43,45] specificity of molecular recognition or host/guest chemistry,[47,264,265] selectivity of organic reactions,[48,266] 3D structure of proteins[49,50,267−269] and DNA,[270] substrate specificities of proteins, and structure-based drug design.[271,272]

Stereochemical problems, unsettled to date, will become clearer in the light of the paradigm of nonconventional hydrogen bonds. The topics dealt with in this review are limited to those noticed by the authors; it is certain that many papers escaped their attention. More up-to-date information is available from the literature list in the author's Web site (http://www.tim.hi-ho.ne.jp/dionisio; The papers included in the list are grouped into several categories such as conformation, crystal packing, host/guest chemistry, chiral recognition, stereoselective organic reaction, theoretical calculation, protein, biochemistry, database analysis, etc. The literature list is accompanied with the title of papers and is constantly updated.). We hope that this review will show the importance of weak hydrogen bonds and stimulate interest in conformational analysis, one of the most fascinating fields in physical organic chemistry.

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