Electronic substituent effect on intramolecular CH/π interaction as evidenced by NOE experiments

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In order to demonstrate the hydrogen-bond-like character of the CH/π interaction, electronic substituent effects on the equilibria between the stretched and the folded conformers of series of compounds capable of forming CH/π interactions were examined by measurements of NOE enhancements of ^{1}H NMR signals. Nuclear Overhauser enhancement is shown to be useful to determine the abundance of the CH/π proximate folded conformer. The Hammett plots of all series of the compounds capable of having CH/π interaction gave negative ρ values. Together with other substituent effects (effects of electronegative substituents, on the CH donor, of ring size, and of α-alkyl substituent), the involvement of delocalization interaction and the hydrogen-bond-like character of the CH/π interaction were established.

Introduction

Non-covalent inter- and intra-molecular interactions have been shown to play important roles in understanding conformational preferences and behaviours of organic molecules. These intermolecular forces are very often attractive but far weaker than those of covalent bonds. Among such attractive intermolecular interactions the hydrogen bond is usually the strongest.[1] In the past few decades evidence has been accumulated that hydrogen-bond-like attractive forces weaker than typical hydrogen bonds are also important in the fine tuning of organic and biochemical reactions and molecular recognition. In these weak hydrogen bonds, hydrocarbon moieties are often shown to be involved. They are the CH/O and CH/N interactions[2,3] on the one hand, and the OH/π[4] and NH/π[5] interactions on the other. In the former cases the CH group acts as a hydrogen donor; while the aromatic or olefinic π-moiety acts as a hydrogen acceptor in the latter cases.

These facts lead to the assumption that the hydrogen bond between the CH donor and π-acceptor can persist when the circumstances are favourable. This sort of interaction is termed as "CH/π interaction" and can be regarded as a weakest extreme of the hydrogen bond persisting between a soft CH acid and a soft π-base.[6] The energy of the hydrogen-bond-type interaction decreases approximately in the following order OH/O > OH/N > NH/N > OH/π > NH/π > CH/π and consequently the presence of the weakest CH/π interaction has not been verified until recently.

The enthalpy per CH/π bond has been estimated to be at most 9 kJ mol^{-1} for intermolecularly interacting CH-donor/aromatic π-base system by temperature dependence measurements of the NMR chemical shifts.[7] Even if it is very weak the CH/π interaction can persist and sometimes play an important role because it has a unique feature that many CH groups can participate simultaneously in the interaction with π-bases without considerable loss of entropy. In other words, it becomes more advantageous when the energy of the interaction increases by incorporating CHs and π-groups into an organized chemical structure. The total free energy may become sizable as a combined effect of such multiple interactions.[6] Thus, the CH/π proximate arrangement often occurs in organic and biological systems, which suggests the participation of an attractive force attributable to CH/π interaction.[6,8,9]

Just like intramolecular hydrogen bonds, CH/π interaction can occur between CH and aromatic or olefinic π-groups which are appropriately situated within a molecule. Intramolecular CH/π interaction often affects the conformational properties because it can be formed without a large loss of entropy and because the gain of 1–2 J mol^{-1} in stabilization free energy can reverse the conformational preference. As a result, the folding tendency of the chain is quite general in a wide variety of aralkyl compounds.[6,8]

Very weak CH/π interaction is often misjudged as a mere dispersion interaction or that it is a sort of hydrophobic interaction. The criterion to classify the CH/π interaction as a hydrogen bond is the contribution of the delocalization term, which implies the formation of a weak chemical bond. In the case of a typical hydrogen bond, the charge transfer from the non-bonding orbital of the hydrogen acceptor atom (usually electronegative) to the antibonding orbital of the hydrogen donor X–H bond produces the delocalization interaction energy.[10] In the case of CH/π interaction, charge transfer from π to σ*(CH) occurs instead. The charge-transfer interaction is usually accompanied by weakening of the X–H bond, which can be observed by spectroscopic and other methods.

It is generally difficult to observe the perturbation of physical properties caused by an extremely weak interaction such as CH/π. Infrared, NMR and other spectroscopy, as well as X-ray crystallography, could not be applied in the same manner as in the cases of typical hydrogen bonds. For example, the hydrogen bond shift of the CH stretching absorption is very small even in the interaction of chloroform and π-bases.[11] A reverse high frequency shift is often observed in the intramolecular cases.[12,13] In proton NMR studies, the expected hydrogen bond shift is obscured by the strong high field shift due to the magnetic anisotropy induced by the aromatic ring.[14]

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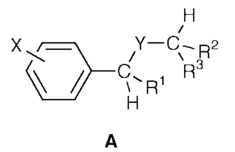
In this situation, the substituent effect becomes a very good probe to show the hydrogen-bond-like character of the CH/π interaction. Electron-withdrawing substituents on the CH carbon should lower the level of the antibonding CH orbital and electron-donating substituents on the π system should raise the highest occupied π orbital; both substituent effects should increase the partial charge transfer from the highest occupied π orbital to the lowest unoccupied σ* orbital of the CH bond[15] and, hence, favour the CH/π interaction by narrowing the energy gap of the interacting orbitals. If steric and other circumstances are similar, electronegative substituents on the CH donor and electron-donating substituents on the π-acceptor should favour the CH/π interacted conformer in the intramolecular case. Thus, the electronic substituent effect on equilibrium constants and enthalpies of formation can be a good criterion to show the contribution of the delocalization or charge-transfer term to the CH/π interaction. In a very favourable case of isopropyl-1-*d* 1-(4-substituted phenyl)ethyl ketones, the amounts of free and intramolecularly CH/π interacted species were determined by measuring the intensities of their C–D stretching bands separately and the substituent effect was examined.[12] However, it is rather difficult to apply this method generally.

In order to examine the substituent effect on the conformational preference of a wide range of possibly CH/π interacted compounds, a generally applicable method to determine the amount of the CH/π interacted folded conformer is required. The nuclear Overhauser effect[16] is a convenient tool to search for nuclei located proximate to each other. Its magnitude (hereafter called NOE enhancement) is solely dependent on the distance between the two nuclei and not dependent on the bond connectivity. The NOE enhancement ($f_{\mathrm{I}}(\mathrm{S}) = K(\gamma_{\mathrm{S}}/\gamma_{\mathrm{I}})r^{-6}$, where $f_{\mathrm{I}}(\mathrm{S})$, γ_{S} and γ_{I} are the fractional NOE enhancement, gyromagnetic ratios of protons S and I. K is an arbitrary constant) decreases very abruptly as the inter-nuclear distance (r) increases; in other words, it is a very short-range effect. Thus, it is a powerful tool to detect the through-space proximity of two atoms which are separated by a number of bonds.

NOE has been applied to determine the geometries of many organic molecules which are conformationally labile. In the case of slow exchange between the two conformers, the signals of each conformer reflect its geometry and the population-weighted enhancement was observed.[17] NOE of the equilibrium mixtures of conformers was discussed extensively in relation to the distance geometry method in the determination of peptide conformation.[18] Many experiments showed that the NOE enhancement of a rapidly exchanging mixture of conformers is proportional to the population averaged NOE of the relevant conformer. This implies that the NOE is proportional to the population of the conformer when other conformers are inert.

NOE itself shows us only the proximity and does not imply the presence of any interaction. If a hydrogen-bond-like interaction is operating between CH and π-groups, an electron-donating substituent enriches the electron density of the aromatic ring and, as a result, favours the CH/π interacted folded conformer. Thus, the examination of the substituent effect on NOE can provide a clue to the CH/π interacted species.

In this paper we report the electronic substituent effect on the NOE of several series of compounds $XC_6H_4CHR^1$–Y-CHR^2R^3 **A** (R^1 = H or CH_3, R^2, R^3 = H or alkyl) and their homologues in



A

order to give a general survey on the electronic and steric effects of substituents (X, Y, R^1, and R^2), as well as the ring size effect. The substituent effect is discussed quantitatively by applying the Hammett equation. The gradient of the plot ρ is shown to serve as a measure for the strength of the delocalization interaction.

Table 1 Calculated nearest H(CH-donor)···H(π-acceptor) distances and expected ratios of NOE of aromatic H (H_{ortho}) upon irradiation of the donor H of the folded conformers

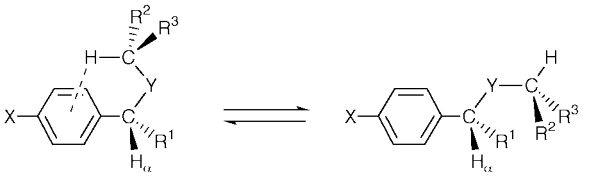
Compound	$H_{donor}\cdots H_{ortho}$ Distance/Å Folded	Stretched	Ratio of NOE, R^a (folded/stretched) (%)
1a $C_6H_5CH_2OCH{=}O$	3.471	5.035	10
3a $C_6H_5CH_2NMeCHMe_2$	3.206	4.527	12
6a $C_6H_5CH_2CONMeCHMe_2$	2.782	4.527	5

[a] The calculated ratio enhancements per molecule are given: $R = [f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CH\text{-}donor}})]_{\mathrm{folded}}/[f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CH\text{-}donor}})]_{\mathrm{stretched}}$.

Results and discussion

The CH/π distances in folded and stretched conformers from MM

In order to estimate the distance between the donor CH and the aromatic acceptor, molecular mechanics (MM) calculations were carried out with the folded (**B**) and stretched (**C**) conformers of typical $C_6H_5CHR^1$–Y–CHR^2R^3 molecules capable of forming intramolecular CH/π interaction. The compounds **1a** and **3a** are capable of forming five-membered CH/π interaction and bearing different CH donor groups, while **6a** can form a six-membered interaction. Among several folded conformers, only the most stable CH/π proximate conformer was considered. The calculated distances between the donor CH and the nearest aromatic H (H_{ortho}) are given in Table 1.



B **C**

In the CH/π interacted folded conformers, the proton(s) of the CH donor groups are located within the sum of van der Waals radii (<2.9 Å) to the nearest *ipso* sp^2-carbon; this is close enough to the aromatic ring protons to induce a considerable NOE enhancement of one or a few of the aromatic ^1H (or ^{13}C) signals upon irradiation of the donor C–H proton. Actually the nearest H_{donor}/H_{ortho} distance (r) in the folded conformer is within 3.2 Å for the compounds bearing an isopropyl CH donor as exemplified by **3a** in Table 1. As NOE is a very short-range effect and tends to decrease proportionally to r^{-6}, it should be attenuated to less than one tenth and become undetectable in the stretched conformer devoid of such interaction. This was confirmed by MM3 calculations. Calculated NOE enhancements per molecule of the stretched conformers **C** of **1a**, **3a**, and **6a** are about 10% or less those of the folded CH/π proximate conformers **B**, respectively. Thus, NOE can serve as a means to determine the CH/π proximate conformer without interference from the stretched conformer.

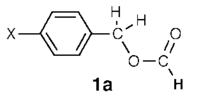
Substituent effect on the NOE of possibly CH/π interacted compounds

Many possibly CH/π interacted compounds showed NOE enhancements of aromatic H signal(s) when the possible donor H atom was irradiated. As discussed previously, the enhancement should originate mostly from the intramolecularly CH/π interacted folded conformer (such as **B**) taking a CH/π proxim-

Table 2 The NOE enhancements $f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{donor}})$ (%)[a] of aromatic protons induced by irradiation of CH donor protons measured at 30 °C in DMSO-d_6 and chloroform-d[7,8]

Compound[b]	Solvent	CH_3O	CH_3	H	Cl	Br	CF_3	NO_2
1a	DMSO	5.1	4.1	3.6	3.3			
	$CDCl_3$	4.2	3.4	3.0	2.8			2.2
1b	DMSO		5.5	4.9	3.7			
	$CDCl_3$		4.2	3.8	3.2			2.5
2a	$CDCl_3$	7.4	5.6	4.6		4.4		
2b	$CDCl_3$	8.2		5.5		4.7		
3a	$CDCl_3$	4.6	4.3	3.7	3.2			2.0
5[c]	DMSO	14.6	12.6	11.8	11.2			10.5
	$CDCl_3$	8.8	7.4	6.1	5.8			5.0
6a[c]	DMSO	8.7	7.2	7.0	6.4			5.0
	$CDCl_3$	6.9	6.5	5.6	3.9			3.5
6c[c]	DMSO		10.5	9.7				6.7
	$CDCl_3$		8.0	7.3				4.7
7	DMSO	0.8	0.3	0.4	0.2		0.2	0.7
8[c]	DMSO	3.8	3.3	3.1	3.1		3.0	2.2
9[c]	DMSO	2.0		1.9	1.6			0.6

[a] Average NOE of three measurements on each sample is given. See Experimental part. [b] Structural formulae (CH donor in bold type):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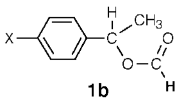
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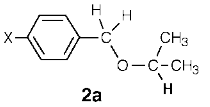
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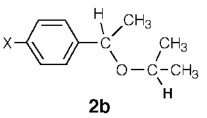
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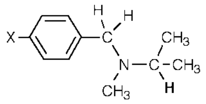
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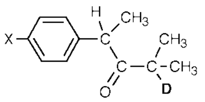
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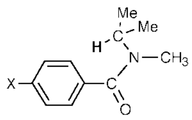
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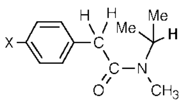
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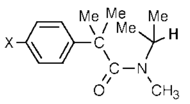
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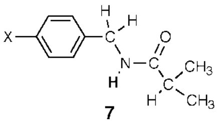
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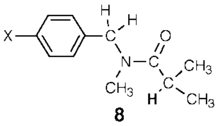
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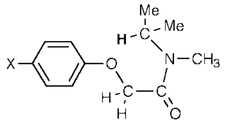
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[c] NOE enhancement of the isopropyl CH of the (*E*) conformer.

ate arrangement. If the measurements are carried out under the same conditions, the comparison of the NOE enhancements through a series of structurally similar compounds bearing different polar substituents allows us to estimate the electronic substituent effect. The steric or ring-size effect can similarly be estimated if the measurement is done with a series of electronically similar compounds bearing differently bulky alkyl group(s) or bearing a bridge of different chain length connecting the CH donor and the π-groups.

In this investigation the electronic substituent effect on CH/π interaction will be evaluated from the substituent effect on the NOE enhancements of several series of possibly intramolecularly CH/π-interacted molecules $XC_6H_4CHR^1–Y–CHR^2R^3$. Intramolecular CH/π interaction is restricted by the conformation and can persist only in the CH/π proximate conformers (**B**). When the CH/π proximate conformers are formed, a very large proportion of them should be involved in CH/π interaction because it results in some additional stabilization. By this assumption, the NOE between the donor CH and π-base moieties can be connected with the relative population of the CH/π interacted conformer (**B**).

The reliability of the observed substituent effect was examined with the series of *para*-substituted benzyl formates ($XC_6H_4CH^{\alpha}_2$–O–CHO **1a**). The NOE enhancement ($f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CHO}})$) of **1a** is dependent regularly on the electronic properties of the *para*-substituent (X) in contrast to those of the benzyl protons ($f_{\mathrm{H\alpha}}(\mathrm{H}_{\mathrm{CHO}})$) which are almost substituent-independent throughout the series [$f_{\mathrm{H\alpha}}(\mathrm{H}_{\mathrm{CHO}}) = 1.8\%$ for $X = CH_3O$ and 1.9% for $X = NO_2$ of **1a**]. Since the distance between the donor H and α-H does not change considerably upon conformational change, $f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CHO}})$ can be used as an intramolecular standard of NOE and, hence, the $f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CHO}})/f_{\mathrm{H\alpha}}(\mathrm{H}_{\mathrm{CHO}})$ ratio should be more reliable as a measure of the population of the interacted species. In this case, $f_{\mathrm{H\alpha}}(\mathrm{H}_{\mathrm{CHO}})$ is nearly constant through the series of formates, which implies that the NOE per molecule is nearly constant. A similar trend was observed with other series of compounds, which justifies the use of $f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{donor}})$ as a measure of the population of the CH/π interacted conformer. The NOE enhancements (in %) are denoted as $f_{\mathrm{H_{obs}}}(\mathrm{H}_{\mathrm{irr}})$, where H_{obs} and H_{irr} are the observed and the irradiated protons in the NOE experiment.

The substituent effects on NOEs of various compounds are given in Table 2, where the enhancements of aromatic CH signals upon irradiation of the donor CH protons [$f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{CH\text{-}donor}})$] are given. The first five compounds (**1a**–**5**) in this table are capable of forming five-membered (with respect to the *ipso* carbon atom) intramolecular CH/π interactions. Compounds **6** to **9** form six- or seven-membered rings in contrast.

With all series of compounds in Table 2, the $f_{\mathrm{HAr}}(\mathrm{H}_{\mathrm{donor}})$ increases as the substituent becomes more electron-donating, suggesting that the CH/π contiguous folded conformer (**B**) should become more favourable than the stretched conformer (**C**) in this order.

The donor hydrogen atom is expected to lie just above the aromatic ring and to be subjected to the diamagnetic anisotropy effect[14] of the aromatic π-acceptor in the CH/π interacted conformer. Thus, the high-field shift of the donor CH signal can be another probe to detect the CH/π interaction. The chemical shifts of donor hydrogen atoms are collected in Table 3. The chemical shift proved to be a less trustworthy measure of the CH/π proximate conformer than NOE.

Hammett plots of substituent effect on the CH/π interaction

In order to evaluate the substituent effect more quantitatively it was analysed by use of the Hammett equation[19] written in terms of equilibrium constants ($\log_{10} K = \rho\sigma + \log_{10} K_0$). First, the gradients of the Hammett plots (ρ) were tested as a scale to estimate the strengths of CH/π interaction. As revealed by a vast amount of data accumulated on the reactivity of aromatic

Table 3 Chemical shifts of donor CH protons at 30 °C

Compound[a]	Solvent	CH_3O	CH_3	H	Cl	Br	CF_3	NO_2
1a	$CDCl_3$	8.11	8.12	8.14	8.17			8.19
1b	$CDCl_3$		8.03	8.07	8.09			8.14
2a	$CDCl_3$	3.66	3.67	3.68	3.65			
2b	$CDCl_3$			3.48				
3a	$CDCl_3$	2.87	2.88	2.89	2.89			2.90
5	DMSO *E*	3.8br	3.84	3.81	3.76			3.66
	Z	4.6br	4.68	4.72	4.69			4.73
	$CDCl_3$ *E*	4.0br	4.01	3.97	3.92			3.80
	Z	4.9br	4.94	4.96	4.92			4.95
6a	DMSO *E*	4.16	4.15	4.16	4.15			4.18
	Z	4.68	4.69	4.70	4.69			4.67
	$CDCl_3$ *E*	4.11	4.10	4.09	4.07			4.10
	Z	4.89	4.91	4.90	4.89			4.88
6c	DMSO *E*			3.63				3.43
	Z			4.74				4.71
	$CDCl_3$ *E*			3.72				3.47
	Z			4.93				4.83
7	DMSO	2.41	2.41	2.42	2.42		2.45	2.45
8	DMSO	2.87	2.89	2.92	2.92		2.93	2.95
9	DMSO *E*	4.08		4.08	4.05			4.02
	Z	4.61		4.62	4.61			4.61

[a] Structural formulae are given in footnote [b] of Table 2.

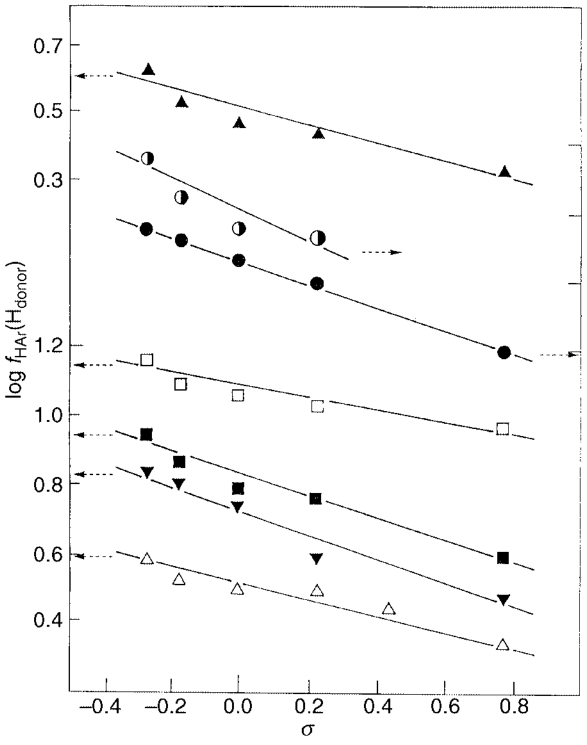


Fig. 1 The $\log_{10} f_{HAr}(H_{CH\text{-}donor})$ *vs.* σ plots for various series of $XC_6H_4CHR^1$–Y–CHR^2R^3. The plotted lines correspond to **1a** (▲), **2a** (◑), **3a** (●), **5*** (□), **5** (■), **6a** (▼), and **8*** (△) from the top to the bottom. The measurements were carried out in $CDCl_3$ except for those asterisked which were measured in DMSO-d_6.

compounds,[20] ρ is a reliable empirical scale for the sensitivity of the reaction to the electronic substituent effect.

In the case of intramolecular interactions, the population (N_i) of the interacted conformer can be correlated to the equilibrium constant (K) by $K = N_i/(N - N_i)$, where N is the total population of the compound capable of forming intramolecular CH/π interactions. Under the condition that the interacted species (N_i) constitutes only a small portion of the total (N), *i.e.* $N_i \ll N$, the variation in the interacted species induced by the electronic substituent effect can be directly related to the variation in equilibrium constant, and, in turn, to the free energy (ΔF_i) variation induced by the electronic substituent effect, eqn. (1). Thus, ρ is a scale for the sensitivity ($\partial(\log N_i)\partial\sigma$) of the

$$\rho = \partial(\log N_i)/\partial\sigma = \partial(\log K)/\partial\sigma = \partial\Delta F_i\partial\sigma \qquad (1)$$

population of CH/π interacted conformer to the electronic substituent effect in this case. Stabilization energies of hydrogen bonds and similar interactions are treated conveniently as the sum of coulombic, delocalization (charge transfer), van der Waals and other energy terms.[10] Among these energy terms, only the delocalization term concerns the electronic substituent effect explicitly. As the sensitivity is expected to increase as the charge-transfer term becomes large, ρ should be used as a reasonable relative scale for the strength of the hydrogen-bond-like character of the CH/π interaction.

This conclusion is quite general and can be extended to various experiments as far as the relative abundance of the interacted species is not large. Since the NOE enhancement $f_{HAr}(H_{donor})$ has been shown to be proportional to the concentration of the CH/π interacted species (N_i), the logarithm of $f_{HAr}(H_{donor})$ was plotted against σ, eqn. (2). The Hammett plots

$$\log_{10} f_{HAr}(H_{CH\text{-}donor}) = \rho\sigma + [\log_{10} f_{HAr}(H_{CH\text{-}donor})]_0 \qquad (2)$$

of $f_{HAr}(H_{CH\text{-}donor})$ gave two quantities, namely ρ and the statistically most probable value of the equilibrium constant for the unsubstituted compound K_0 (actually $[\log_{10} f_{HAr}(H_{CH\text{-}donor})]_0$ in the cases of NOE), both of which can be used as a scale for the strength of CH/π interaction. These values for various series of $XC_6H_4CHR^1$–Y–CHR^2R^3 are collected in Table 4.

Evidence for the hydrogen-bond-like character of CH/π interaction. In the cases of hydrogen bonds, the electron-donating substituent on hydrogen acceptor favours the interaction, giving negative ρ values.[21,22] This trend has been interpreted in terms of the charge-transfer (delocalization) interaction between the σ^* orbital of donor XH and the n orbital of the acceptor atom. The same trend of the substituent effect is clearly observed in the Hammett plots, *i.e.* the $\log_{10} f_{HAr}(H_{donor})$ *vs.* σ plot (eqn. (2)) for intramolecular CH/π interaction; typical examples are shown in Fig. 1.

In order to examine whether ρ is pertinent to a scale for the evaluation of the strength of the hydrogen-bond-like interaction, the ρ values of the Hammett plots for various intramolecularly interacted systems are collected in Table 5. The table includes some examples of typical hydrogen bonding and

Table 4 Substituent effect on the NOE enhancements of intramolecularly CH/π interacted systems (H donor atoms are shown by the bold letters **H**)

Compound	Ring size[a]	Solvent	n	Linear correlation parameters[b] ρ[a]	$(\log_{10} f)_0$[c]	r
$XC_6H_4CH_2OC\mathbf{H}{=}O$ (**1a**)	5	DMSO-d_6	4	−0.35(0.09)	0.58(0.02)	0.93
		$CDCl_3$	5	−0.34(0.04)	0.51(0.02)	0.95
$XC_6H_4CH(CH_3)OC\mathbf{H}{=}O$ (**1b**)	5	DMSO-d_6	4	−0.44(0.06)	0.68(0.01)	0.99
		$CDCl_3$	4	−0.24(0.02)	0.58(0.01)	0.99
$XC_6H_4CH_2OC\mathbf{H}(CH_3)_2$ (**2a**)	5	DMSO-d_6	4	−0.50(0.12)	0.70(0.02)	0.97
$XC_6H_4CH(CH_3)OC\mathbf{H}(CH_3)_2$ (**2b**)	5	DMSO-d_6	3	−0.58(0.02)	0.81(0.002)	(0.999)[d]
$XC_6H_4CH_2N(CH_3)C\mathbf{H}(CH_3)_2$ (**3a**)	5	$CDCl_3$	5	−0.35(0.01)	0.57(0.003)	0.998
$XC_6H_4CH(CH_3)C({=}O)C\mathbf{D}(CH_3)_2$ (**4b**)[e]	5	CCl_4	7	−0.19(0.02)	0.16(0.01)[f]	0.91
$XC_6H_4C({=}O)N(CH_3)C\mathbf{H}(CH_3)_2$ (**5**)	5	DMSO-d_6	5	−0.16(0.03)	1.09(0.02)	0.95
		$CDCl_3$	5	−0.30(0.03)	0.83(0.02)	0.97
$XC_6H_4CH_2C({=}O)N(CH_3)C\mathbf{H}(CH_3)_2$ (**6a**)	6	DMSO-d_6	5	−0.20(0.03)	0.85(0.01)	0.97
	6	$CDCl_3$	5	−0.30(0.04)	0.74(0.02)	0.94
$XC_6H_4CH_2NHC({=}O)C\mathbf{H}(CH_3)_2$ (**7**)	6	DMSO-d_6	6	−0.07(0.32)	−0.42(0.13)	0.12
$XC_6H_4CH_2N(CH_3)C({=}O)C\mathbf{H}(CH_3)_2$ (**8**)	6	DMSO-d_6	6	−0.18(0.04)	0.51(0.02)	0.907
$XC_6H_4OCH_2C({=}O)N(CH_3)C\mathbf{H}(CH_3)_2$ (**9**)[g]	7(6)	DMSO-d_6	4	−0.52(0.07)	0.24(0.05)	0.950

[a] Size of the chelate ring of the CH/π interacted conformer is given; calculated by assuming that the interaction takes place at the *ipso*-position of the phenyl group. [b] The gradient (ρ) and the intercept $(\log_{10} f)_0$ of the $\log_{10} f$ *vs.* σ plot are given together with the correlation coefficient (r). Here, f refers to the $f_{\mathrm{HAr(H_{donor})}}$ value in %. [c] Standard errors of ρ and $(\log_{10} f)_0$ are given in parentheses. [d] Regression line from only three data. [e] The $\log_{10}(\varepsilon_i/\varepsilon_f)$ from IR spectroscopy was plotted against σ. This quantity is also proportional to the logarithm of the abundance of CH/π interacted conformer and the gradient ρ can be compared with that from NOE. [f] The intercept $[\log_{10}(\varepsilon_i/\varepsilon_f)]_0$ is entirely different in scale from $(\log_{10} f)_0$; hence it cannot be compared with the other values in this column. [g] CH/O hydrogen bonding involving aryloxy oxygen atom.

Table 5 The ρ values of the Hammett plots for various intramolecularly hydrogen-bonded molecules

Compound	Solvent	Ring size	Interaction	ρ
$XC_6H_4OCH_2COOH$[19]	CCl_4	5	OH/O	−0.94
$XC_6H_4OCMe_2COOH$[19]	CCl_4	5	OH/O	−1.01
$XC_6H_4CH_2OH$[4]	CCl_4	5	OH/π	−0.43
$XC_6H_4(CH_2)_2OH$[4]	CCl_4	6	OH/π	−0.45
$XC_6H_4CH_2NHC_6H_5$[5]	CCl_4	5	NH/π	−0.39
$XC_6H_4(CH_2)_2NHC_6H_5$[5]	CCl_4	6	NH/π	−0.85
$XC_6H_4(CH_2)_3NHC_6H_5$[5]	CCl_4	7	NH/π	−0.24
$XC_6H_4CHMeCOCDMe_2$[9]	CCl_4	5	CD/π	−0.19
$XC_6H_4CH_2NMeCHMe_2$	$CDCl_3$	5	CH/π	−0.35
$XC_6H_4CH_2OCH{=}O$	$CDCl_3$	5	CH/π	−0.34
$XC_6H_4CHMeOCH{=}O$	$CDCl_3$	5	CH/π	−0.24
$XC_6H_4CH_2CONMeCHMe_2$	$CDCl_3$	6	CH/π	−0.30
$XC_6H_4CH_2NHCOCHMe_2$	DMSO-d_6	6	CH/π	−0.18

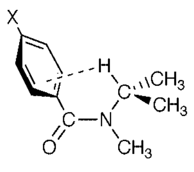
OH/π interactions which are obviously stronger than CH/π interaction. As the substituent effect is assumed to originate from the charge-transfer (delocalization) interaction between σ^*(XH) of the H donor and HOMO of the H acceptor, the absolute value of ρ is expected to become larger as the delocalization interaction becomes stronger. In accordance with this expectation, the ρ value in Table 5 becomes large for strong OH/O hydrogen bonds. At a glance, it decreases in the order OH/O > OH/π > CH/π.

The second quantity which can serve to evaluate the CH/π interaction is the $[\log_{10} f_{\mathrm{HAr}}(\mathrm{H_{CH\text{-}donor}})]_0$ value. It is the statistically calculated $\log_{10} f_{\mathrm{HAr}}(\mathrm{H_{CH\text{-}donor}})$ value for $\sigma = 0$ (unsubstituted compound) and can be substituted by the observed $\log_{10} f_{\mathrm{HAr}}(\mathrm{H_{CH\text{-}donor}})$ of the unsubstituted compound. It is an easily accessible scale for the population of the CH/π interacted conformer and can be used to measure the steric effect. However, the steric effect is rather complicated and the $[\log_{10} f_{\mathrm{HAr}}(\mathrm{H_{CH\text{-}donor}})]_0$ is affected by (i) the stereo structure of the chain (–CHR–Y–) linking the CH and the π-counterparts, (ii) the substitution of hydrogen atoms on the linking chain (benzylic hydrogen atoms) by alkyl and other bulkier groups, (iii) the ring size of the intramolecular interacted system, and other steric factors can affect the population of the CH/π proximate conformer. In addition, the populations can be perturbed by change in acidity of the donor CH group caused by the attached electronegative atoms. These factors restrict the general use of $[\log_{10} f_{\mathrm{HAr}}(\mathrm{H_{CH\text{-}donor}})]_0$ as a scale for the neat strength of CH/π interaction.

Returning to Table 2, we should like to examine the individual cases in order to demonstrate the hydrogen-bond-like nature of CH/π interaction by use of the substituent effects.

Effect of the electronegative substituent on the CH donor. If we compare the four series of compounds $C_6H_5CH_2YC\mathbf{H}(CH_3)_2$ (**2a**, **3a**, **4b** and **5**) bearing an isopropyl CH donor and capable of forming five-membered interaction, ρ becomes larger in the order **4** < **3** < **2**, as the attached group Y becomes more electronegative (CO < NMe < O). This sequence of electronegativity was supported by the chemical shifts of the donor CH in Table 2. This reproduces the general trend that the more positively charged and, hence, acidic hydrogen atom should form the stronger CH/π interaction with a π-base.

The amide **5** in DMSO is an exception; it has relatively small ρ, which suggests that the NOE is not very sensitive to the polar substituent effect. In the most favourable (*E*)-conformer of **5** the amide chromophore is expected to keep a nearly planar conformation (**D**), which forces the isopropyl H atom to approach the aromatic ring. In this conformer the aromatic ring



D

is expected to be twisted and α-H of the isopropyl group should be located just above the aromatic ring so as to avoid the approach of the bulky part (two methyls) of the isopropyl group to the aromatic ring and also to the methyl group on the same nitrogen in this molecule. This was also supported from the higher field chemical shift of isopropyl H (δ 3.81) in comparison to **6a** and **9** (δ 4.16 and 4.08, respectively, in DMSO-d_6). The abundance of the CH/π interacted (*E*)-conformer of **5** is shown to be more than 60% from the intensities of its signals and is apparently too high to assume $N_i \ll N$. As a result, *N* becomes less sensitive to *K*, which results in smaller ρ.

The comparison of ρ for compounds **6a** and **8** also supported the electronegativity effect. The amides **6** whose $|\rho|$ is larger than those of the amides **8** have a more electronegative $NCH(CH_3)_2$ donor group in contrast to the $COCH(CH_3)_2$ group in **8**. As evidenced by the ^1H chemical shift of the NH group, the amides **7** adopt an NH/π interacted conformation, which prevents the formation of a CH/π interaction. Evidently meaningful NOE enhancements could not be observed with the amides **7**.

Effect of the ring size of interaction. The compounds **5**, **6a**, and **9** carry a $NCH(CH_3)_2$ group in common. They can form five-, six-, and seven-membered CH/π interactions, respectively. Apparently the $[\log_{10} f_{HAr}(H_{CH\text{-donor}})]_0$ value becomes smaller in the order **5** > **6a** > **9**. This implies that the population of the CH/π proximate conformation decreases as the chelate ring becomes larger. The decrease in $[\log_{10} f_{HAr}(H_{CH\text{-donor}})]_0$ subsequent to the enlargement of the chelate ring can be attributed to the general entropic effect due to the elongation of the chain intervening CH-donor and π-acceptor groups, which increases the number of uninteracted conformations. In contrast, ρ is rather insensitive to the ring size of the interaction. The flexibility of the **6a** molecule allows the isopropyl group to take a position favourable to hydrogen-bond-like interaction. Thus, the isopropyl CH groups of **6a** (and also **9**) can approach favourably from perpendicular to the π-system, allowing the maximum overlap of antibonding σ^*_{CH} and p_π orbitals. Thus, the contribution of the delocalization term is not very different among these three series of compounds.

In the case of compound **9**, however, α-H of isopropyl is suspected to lie above the aryloxy oxygen atom whose electron density is also subjected to the electronic effect of the *para*-substituent in the same manner as the *ipso* carbon, since the chemical shift of the enhanced signal tends to move downfield as the enhancement $\log_{10} f_{HAr}(H_{CH\text{-donor}})$ increases. The stronger CH/O(π) interaction must be reflected in a slightly larger $|\rho|$ for **9** than those for **5** and **6**.

The interaction forming a five-membered ring is more favourable than that forming a six-membered ring. No clear evidence for the presence of a seven-membered interaction is obtained by this experiment.

Effect of α-alkyl substitution. Introduction of an α-alkyl group (R^1 in **A**) to $XC_6H_4CH_2$–Y–CHR^2R^3 usually favours the folded conformation. In accordance with this general trend, intramolecular CH/π interactions of these series of compounds are considerably enhanced by introducing an alkyl (usually methyl) substituent on the benzyl carbon atom. Thus, the 1-phenylethyl series is always more favourable than the benzyl series in forming the CH/π interaction as exemplified by the $[\log_{10} f_{HAr}(H_{CH\text{-donor}})]_0$ values of benzyl and 1-phenylethyl formates (**1a** and **1b**). Additional examples are the **6a**–**6c** and **2a**–**2b** pairs. Thus, the introduction of a methyl group at the benzyl position increases the $[\log_{10} f_{HAr}(H_{CH\text{-donor}})]_0$ in all three examples. This trend in steric effect of the α-alkyl group has been observed in cases of intramolecular hydrogen bonding,[22] which can be reproduced by the populations of conformers calculated by MM.[8g,h] The effect of α-substitution is clearly reflected in the isopropyl ^1H chemical shift differences between the pairs **1a** and **1b**, **2a** and **2b**, and **5a** and **6c**. In all cases, alkyl substitution was shown to result in high-field shifts (Table 2).

The parameter ρ is not affected substantially by the α-alkyl substituents. Thus, the electronic effect of the introduced alkyl group is not important, and can be attributed to the conformational origin mainly of steric nature.

Conclusion

Nuclear Overhauser enhancement of NMR signal is successfully applied to measure the population of the folded conformer without interference of the stretched conformer. This strategy was used to examine the substituent effect on the populations of CH/π interacted conformers. The Hammett plots gave negative ρ in agreement with typical hydrogen bonded systems.

As shown by the experiments on the compounds bearing common isopropyl CH-donor groups bonded to various electronegative atoms, on the amides forming five- and six-membered CH/π interactions, and on the effect of methyl substitution at the benzyl position, the trends of substituent effects shown here are essentially similar to those of typical hydrogen bonded systems. This gives experimental support to the hydrogen-bond-like character of CH/π interaction.

Experimental

Materials

All Ar-unsubstituted (X = H) compounds are known, and most of their substituted derivatives were prepared by methods previously reported for the unsubstituted compounds.[23] Commercially available solvents for NMR measurements were employed without further purification.

^1H NMR measurements

NMR spectra were obtained on a JEOL-EX-270 NMR spectrometer at 30 °C. Difference NOE spectra were measured under the normal conditions and default spectrometer settings. The NOE enhancements $f_{HAr}(H_{CH\text{-donor}})$ were recorded under three different conditions and their reliability was ascertained by the agreement of the three data sets. The accumulation times, irradiation power (dB), and the duration of irradiation(s) were, respectively, 64, 390, and 8 for the first run, 64, 385, and 7 for the second run, and 32, 380, and 8 for the third run. Their average is given in Table 1.

Molecular mechanics calculations were performed by use of the MM3 program.[24,25]

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