derivatives in DMSO-d_6 at probe temperature. Methanolysis required 3–4 h under these conditions and the signals of the OH groups of the dienols were doublets with δ ca. 8.9 and those H-1 were quartets instead of doublets as found with the O-deuteriated dienols.

Registry No. 1, 70411-98-2; **2**, 70415-58-6; (*Z*)-1-(trimethylsilyloxy)-1,3-butadiene, 35694-19-0; (*E*)-1-(trimethylsilyloxy)-1,3-butadiene, 35694-20-3.

Supplementary Material Available: Tables S1–4 of rate and product data (4 pages). Ordering information is given on any current masthead page.

Shape-Specific Weak Interactions Related to a Phenyl Group: Determination of Their Enthalpies by Gas–Liquid Partition Chromatography

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Abstract: When gas chromatography is used, the enthalpies of the interactions between a phenyl group and a variety of sample molecules (alkanes, alkenes, substituted benzenes, ethers, and carbonyl compounds) are evaluated with the uncertainty mostly lower than ±0.04 kcal mol^{-1}. The $\Delta\Delta H^{t}$, a measure of the interaction of a phenyl group in a stationary liquid with a given sample, ranges from −2.7 to +0.1 kcal mol^{-1}. It is found that the interaction of a phenyl group is (i) specific for the three-dimensional shape of the sample molecule and (ii) more attractive with a cyclic molecule, which in three-dimensional shape is similar to the phenyl group, than with the corresponding acyclic molecule. The relation of the shape-specific weak interactions presented here to the charge-transfer interaction, π-electron interactions, dipole–induced-dipole interaction, and so on, is discussed.

There is now much evidence for the existence of weak attractive interactions associated with a phenyl group. These include alkyl–phenyl interactions,[1] a dipole-induced-dipole interaction[2] between the 1,3-dioxane and phenyl rings, aromatic–aromatic interactions[3] between the aromatic side chains in model peptides and proteins, "carbonyl–aromatic interactions"[4] in proteins, and amino–aromatic interactions[5] in proteins. These interactions[1-5] are shown to affect molecular conformations and chemical selectivity.[6,8] Little is known, however, about the *enthalpies* and *specificity* of these weak interactions, which aid a better understanding of the high specificity of molecular recognition in chemical as well as biochemical reactions.

In gas–liquid partition chromatography (GLPC), weak interactions between sample molecules and a stationary phase as well as heat of vaporization of samples play a significant role in the separation of samples.[9] This led us to explore a novel method for determining the interaction enthalpies by using GLPC. We report here the full details of studies on the enthalpies of shape-specific weak interactions of a phenyl group with a wide variety of sample molecules including alkanes,[10a] alkenes,[10b] ethers,[10b] substituted benzenes,[10c] and carbonyl compounds.

Results and Discussion

Evaluation of Interaction Enthalpies. A pair of stationary liquids (**1** and **2**; Chart I) was employed for the determination of retention time. The ratio of the retention time for a given sample (**4–11**) to that for the standard one [*n*-octane (**3**)][11] was defined as the relative retention (α). The ln α is related to the free energy changes for solution (ΔG) of samples in a given stationary liquid (liquid A)[12] (eq 1) where $\Delta\Delta G^{(\mathrm{A})}$ represents the differences in

$$-RT \ln \alpha = \Delta G(4) - \Delta G(3) = \Delta\Delta G^{(\mathrm{A})} \qquad (1)$$

ΔG between samples **4–11** and **3**. Equation 1 can be expressed as[13] eq 2 and 3 where $\Delta\Delta H^{(\mathrm{A})}$ refers to the difference in heat of

$$\ln \alpha = -\Delta\Delta H^{(\mathrm{A})}/RT + \text{constant} \qquad (2)$$

$$\Delta\Delta H^{(\mathrm{A})} = \Delta H^{(\mathrm{A})}(4) - \Delta H^{(\mathrm{A})}(3) \qquad (3)$$

solution in liquid A ($\Delta H^{(\mathrm{A})}$) between samples **4–11** and **3**. As might be expected from eq 2, plots of ln α against T^{-1} give a

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(1) (a) Watson, A. E. P.; McLure, I. A.; Bennett, J. E.; Benson, G. C. *J. Phys. Chem.* **1965**, *69*, 2753. (b) Zushi, S.; Kodama, Y.; Fukuda, Y.; Nishihata, K.; Nishio, M.; Hirota, M.; Uzawa, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2113. (c) Tanaka, N.; Tokuda, Y.; Iwaguchi, K.; Araki, M. *J. Chromatogr.* **1982**, *239*, 267. (d) Hiraki, Y.; Tai, A. *Chem. Lett.* **1982**, 341. (e) Hiraki, Y.; Oda, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2330. (f) Hiraki, Y.; Tai, A. *Ibid.* **1984**, *57*, 1570.

(2) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85, and the references cited therein. Fuller, S. E.; Mann, B. E.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1982**, 1096.

(3) (a) Burley, S. K.; Petsko, G. A. *Science (Washington, D.C.)* **1985**, *229*, 23. (b) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(4) Thomas, K. A.; Smith, G. M.; Thomas, T. B.; Feldmann, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 4843. Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 5921.

(5) Burley, S. K.; Petsko, G. A. *FEBS Lett.* **1986**, *203*, 139.

(6) Attractive interactions are also shown to exist between alkyl groups. These alkyl–alkyl interactions, though suggested to be weaker than alkyl–phenyl interactions,[1e] influence the equilibrium between the conformations of 1,3,5-trineopentylbenzene[7a] and between valence-bond isomers[7b] and the selectivity in solid-state photodimerization.[7c]

(7) (a) Carter, R. E.; Stilbs, P. *J. Am. Chem. Soc.* **1976**, *98*, 7515. (b) Lyttle, M. H.; Streitwieser, A., Jr.; Kluttz, R. Q. *Ibid.* **1981**, *103*, 3232. Allinger, N. L.; Frierson, M.; Van Catledge, F. A. *Ibid.* **1982**, *104*, 4592. (c) Quina, F. H.; Whitten, D. G. *Ibid.* **1975**, *97*, 1602.

(8) For a review on the interactions between two alkyl groups undergoing conformational changes, see: Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80.

(9) Tenney, H. M. *Anal. Chem.* **1958**, *30*, 2. Weinstein, S.; Feibush, B.; Gil-Av, E. *J. Chromatogr.* **1976**, *126*, 97. König, W. A.; Sievers, S.; Schulze, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 910.

(10) Preliminary reports: (a) Endo, T.; Ito, M. M.; Yamada, Y.; Saito, H.; Miyazawa, K.; Nishio, M. *J. Chem. Soc., Chem. Commun.* **1983**, 1430. (b) Endo, T.; Ito, M. M.; Namiki, T. *Ibid.* **1985**, 933. (c) Ito, M. M.; Kato, J.; Takamura, I.; Wakatsuki, K.; Endo, T. *Chem. Lett.* **1987**, 241. Some of the results given here are different from those in Tables I–III; where this is so, the values in Tables I–III are to be preferred.

(11) As a standard sample, *n*-octane was employed instead of *n*-hexane[10b,c] because of high frequency of its use.

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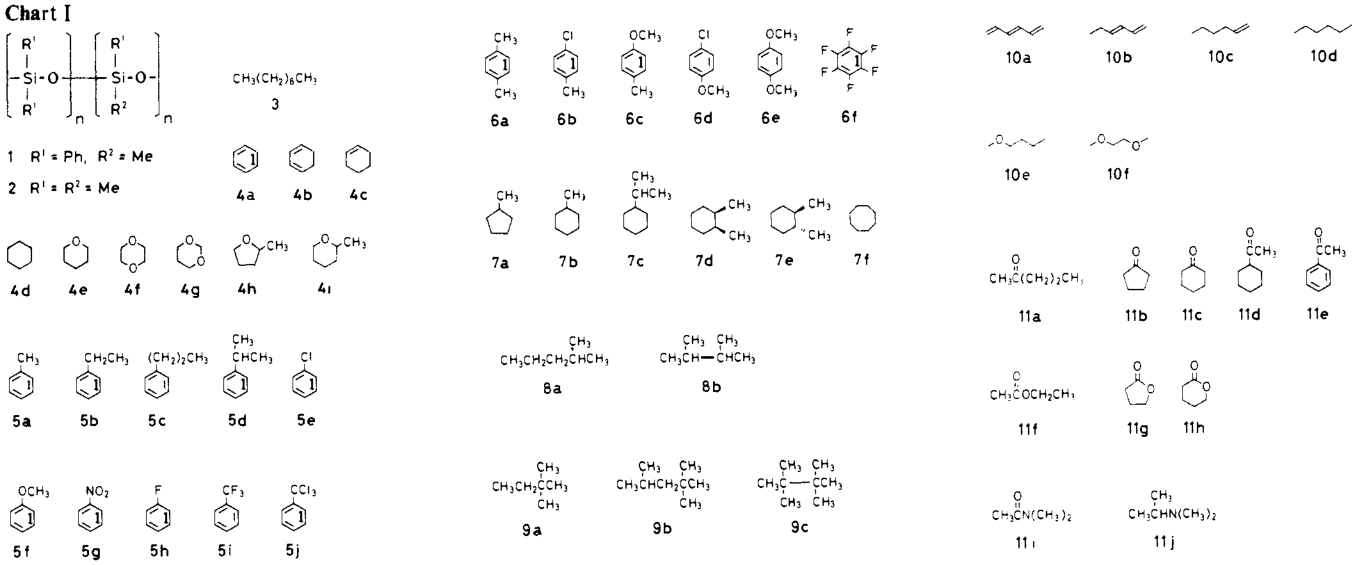
Chart I



straight line for the samples examined, a typical example being shown in Figure 1.

The $\Delta H^{(A)}$ consists of the heat of vaporization (ΔH_v) for a sample and the enthalpy of sample-liquid interaction ($\Delta H_i^{(A)}$) (eq 4). From eq 3 and 4, we get eq 5. Equation 5 shows that

$$\Delta H^{(A)} = -\Delta H_v + \Delta H_i^{(A)} \tag{4}$$

$$\Delta\Delta H^{(A)} = -(\Delta H_v(4) - \Delta H_v(3)) + (\Delta H_i^{(A)}(4) - \Delta H_i^{(A)}(3)) = -\Delta\Delta H_v + \Delta\Delta H_i^{(A)} \tag{5}$$

the difference in heat of vaporization ($\Delta\Delta H_v$) between samples contributes to the $\Delta\Delta H^{(A)}$.

Figure 2 exhibits the dependence of the $\Delta\Delta H^{(2)}$—the $\Delta\Delta H$ in silicone OV-101 (liquid **2**) involving 100% methyl group—for various kinds of samples upon the difference in their heat of vaporization[14] ($\Delta\Delta H_v$) at 25 °C. A linear relationship has turned out to exist between the two (eq 6). Since eq 5 holds for liquid **2**, we get eq 7. From eq 6 and 7, the $\Delta\Delta H_i^{(2)}$ is given by eq 8,

$$\Delta\Delta H^{(2)} = k\Delta\Delta H_v \tag{6}$$

$$\Delta\Delta H^{(2)} = -\Delta\Delta H_v + \Delta\Delta H_i^{(2)} \tag{7}$$

$$\Delta\Delta H_i^{(2)} = (k + 1)\Delta\Delta H_v \tag{8}$$

which indicates that the $\Delta\Delta H_i^{(2)}$ is also proportional to the $\Delta\Delta H_v$. This implies that the $\Delta\Delta H_i^{(2)}$ practically reflects the difference in *nonspecific* interactions,[15] whose enthalpies are related to the ΔH_v. Since the $\Delta\Delta H_i^{(2)}$ is involved in the enthalpies of the interactions with any liquid A ($\Delta\Delta H_i^{(A)}$) whose structure resembles that of liquid **2**, the $\Delta\Delta H_i^{(A)}$ can be expressed as eq 9 where the

$$\Delta\Delta H_i^{(A)} = \Delta\Delta H_i^{(2)} + \Delta\Delta H_{si}^{(A)} \tag{9}$$

$\Delta\Delta H_{si}^{(A)}$ is the $\Delta\Delta H$ reflecting the difference in *specific* interactions with liquid A between a pair of samples. Equation 5 can be rewritten as eq 10. Subtracting eq 7 from eq 10, we obtain eq 11.

$$\Delta\Delta H^{(A)} = -\Delta\Delta H_v + \Delta\Delta H_i^{(2)} + \Delta\Delta H_{si}^{(A)} \tag{10}$$

$$\Delta\Delta H^{(A)} - \Delta\Delta H^{(2)} = \Delta\Delta H_{si}^{(A)} \tag{11}$$

As liquid A we chose silicone OV-25 (**1**), which involves 75% phenyl and 25% methyl groups. Equation 11 holds for liquid **1**.

$$\Delta\Delta H^{(1)} - \Delta\Delta H^{(2)} = \Delta\Delta H_{si}^{(1)} = \Delta\Delta H^{t} \tag{12}$$

Thus, the enthalpy change ($\Delta\Delta H^{(1)} - \Delta\Delta H^{(2)}$), now defined as "$\Delta\Delta H^{t}$",[15] is considered to represent the difference in the specific weak interaction of the phenyl group in liquid **1** between a given sample and *n*-octane. The $\Delta\Delta H^{t}$ consists of the enthalpy of the interaction of a phenyl group with a given sample and that with *n*-octane, namely, is the enthalpy of the specific "sample–phenyl interaction" relative to the enthalpy of "*n*-octane–phenyl

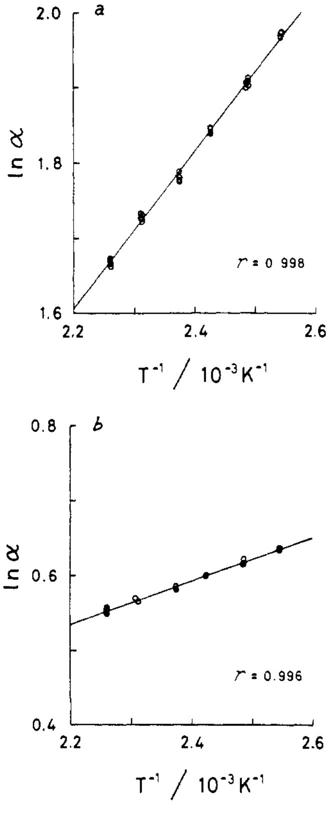


Figure 1. Plot of ln α against T^{-1} for liquid **1** (a) and liquid **2** (b). The relative retention α shown here is for the anisole–*n*-octane pair.

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[12] For simplicity, the ΔG(**4–11**) and $\Delta H^{(A)}$(**4–11**) are typically represented as the ΔG(**4**) and $\Delta H^{(A)}$(**4**), respectively.

[13] Laub, R. J.; Pecsok, R. L. *Physicochemical Applications of Gas Chromatography*; Wiley: New York, 1978.

[14] Dean, J. A.; Ed. *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, 1985; Section 9, pp 142–173. Riddik, J. A.; Bunger, W. B.; Sakano, T. K. *Organic Solvents*, 4th ed.; Wiley: New York, 1986. Timmermans, J. *Physico-chemical Constants of Pure Organic Compounds*; Elsevier: New York, 1950.

[15] One reviewer pointed out that certain compounds (e.g., ethers) fit the regression line (Figure 2) only poorly. These molecules may exhibit specific interactions with the siloxane backbone, or with a methyl group, of liquid **2**. The enthalpies of the former interactions are canceled by subtracting $\Delta\Delta H^{(2)}$ from $\Delta\Delta H^{(1)}$, as mentioned below. On the other hand, the enthalpies of the latter interactions are hardly canceled by the above treatment. However, since the latter enthalpies are considered to make a minor contribution to the $\Delta\Delta H_i^{(2)}$, eq 12 is assumed to hold.

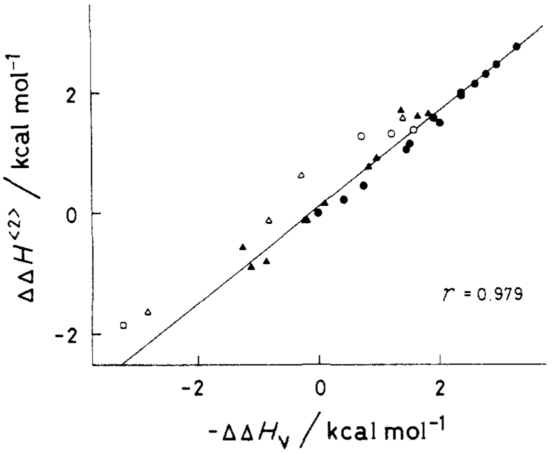

Figure 2. Plot of $\Delta\Delta H^{(2)}$ against $-\Delta\Delta H_{\rm v}$ at 25 °C. The $\Delta\Delta H_{\rm v}$ is the difference between heat of vaporization for a given sample $[\Delta H_{\rm v}(\mathbf{4})]^{12}$ and that for *n*-octane $[\Delta H_{\rm v}(\mathbf{3})]$: $\Delta\Delta H_{\rm v} = \Delta H_{\rm v}(\mathbf{4}) - \Delta H_{\rm v}(\mathbf{3})$. Symbols: ●, alkanes (**3**, **4d**, **7–9**, and **10d**) and alkenes (**4c** and **10c**); ▲, substituted benzenes (**4a**, **5**, and **6a**); ○, ethers (**4** and **10f**); △, carbonyl compounds (**11**); □, nitrobenzene (**5g**). A straight line is drawn through the points for the samples except for polar ones (carbonyl compounds and nitrobenzene), the correlation coefficient (r) being 0.979.

Table I. $\Delta\Delta H^{\rm t}$ Values for Substituted Benzenes[a]

sample	$\Delta\Delta H^{\rm t}$/kcal mol^{-1}
benzene (**4a**)	-1.32 ± 0.02
toluene (**5a**)	-1.18 ± 0.01
ethylbenzene (**5b**)	-1.09 ± 0.04
n-propylbenzene (**5c**)	-1.02 ± 0.02
cumene (**5d**)	-1.08 ± 0.02
chlorobenzene (**5e**)	-1.29 ± 0.02
anisole (**5f**)	-1.51 ± 0.02
nitrobenzene (**5g**)	-1.84 ± 0.04
fluorobenzene (**5h**)	-1.26 ± 0.02
α,α,α-trifluorotoluene (**5i**)	-0.80 ± 0.03
α,α,α-trichlorotoluene (**5j**)	-1.33 ± 0.04
p-xylene (**6a**)	-0.96 ± 0.04
p-chlorotoluene (**6b**)	-1.15 ± 0.02
p-methylanisole (**6c**)	-1.39 ± 0.05
p-chloroanisole (**6d**)	-1.52 ± 0.03
p-dimethoxybenzene (**6e**)	-1.95 ± 0.05
hexafluorobenzene (**6f**)	-1.00 ± 0.02

[a] Errors given are the standard deviations.

interaction". Therefore, the $\Delta\Delta H^{\rm t}$ can be regarded as a measure, though not strict, of the specific weak interaction of a phenyl group with a given sample. Tables I–IV list the $\Delta\Delta H^{\rm t}$ values obtained with various samples (**4–11**).

Phenyl–Phenyl Interaction. Much attention has been devoted to the interaction between electron-rich and electron-deficient aromatic groups, so-called charge-transfer interaction.[16] In contrast, a different type of interaction was recently demonstrated to occur between aromatic side chains[3] in model peptides and proteins.[17] Burley and Petsko reported that the energies of aromatic–aromatic interactions between the aromatic side chains lay between -1 and -2 kcal mol^{-1} (1 cal = 4.184 J) on the basis of nonbonded potential energy calculations.[3a] Furthermore, ab initio quantum mechanical calculations of benzene dimer[3b] for various orientations[18] revealed that the interaction energy minimum was ca. -2.4 kcal mol^{-1}.[19,20]

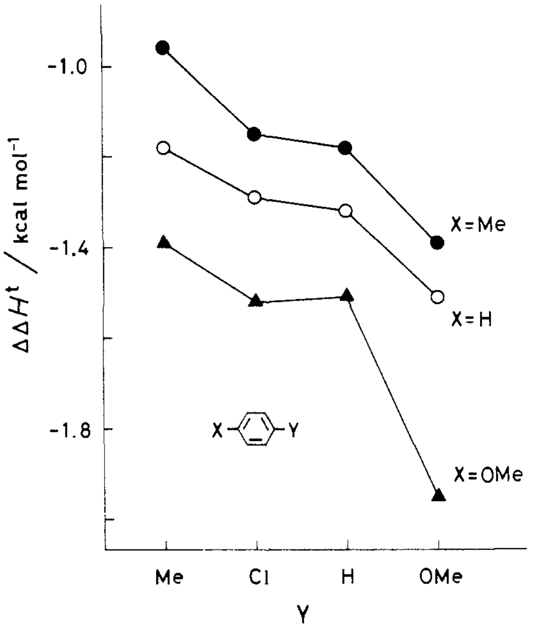

Figure 3. Dependence of $\Delta\Delta H^{\rm t}$ for three sets of substituted benzenes (XC_6H_4Y) on the structures of substituent Y. Symbols: ●, X = Me; ○, X = H; ▲, X = OMe.

Transfer of a benzene molecule from an environment of saturated hydrocarbon molecules into an environment of benzene molecules[22] is energetically favorable to an extent ranging to ca. -1 kcal mol^{-1}. Our experimental result for benzene (**4a**) (i.e., $\Delta\Delta H^{\rm t}$ = -1.32 kcal mol^{-1}, Table I) corresponds to those[22] for the transfer experiment.

Effect of Alkylation of Benzene Rings.[10c] Using a variety of substituted benzenes, we examined the aromatic–aromatic interactions. In Table I are given $\Delta\Delta H^{\rm t}$ values for benzene (**4a**) and monosubstituted benzenes (**5**). It should be noted that, in the case of alkylbenzenes, the $\Delta\Delta H^{\rm t}$ values increase progressively with increasing number of carbon atoms. This result indicates that alkylation, quite a "simple" chemical modification, of a benzene ring leads to weakening in the phenyl–phenyl interaction.

A further attempt was made to investigate the effect of alkylation on weak interactions with various disubstituted benzenes (**6a–e**) as samples. Figure 3 plots the $\Delta\Delta H^{\rm t}$ for three sets of samples (substituted benzenes, para-substituted toluenes, and para-substituted anisoles) against substituent Y. Regardless of the structures of Y, $\Delta\Delta H^{\rm t}$ values become largest for toluenes and smallest for anisoles, the Y-$\Delta\Delta H^{\rm t}$ profiles for the three substituents X (CH_3, H, and OCH_3) being similar to one another. An interesting feature of the data in Figure 3 is that the methylation results in the increment in the $\Delta\Delta H^{\rm t}$ by ca. 0.1–0.2 kcal mol^{-1}.

The order of $\Delta\Delta H^{\rm t}$ values for benzenes **4a** and **5** (Table I) does not agree with that of their ionization potentials[23] [9.24 (benzene), 9.07 (chlorobenzene), 8.82 (toluene), 8.77 (ethylbenzene), and 8.22 eV (anisole)]; this clearly indicates that the $\Delta\Delta H^{\rm t}$ cannot be explained by the charge-transfer interaction, since the energy

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[16] For example, see: Mulliken, R. S.; Person, W. P. *Molecular Complexes*; Wiley: New York, 1969.

[17] In this relation, the interactions between aromatic rings have been suggested to produce a marked influence on molecular conformations and chemical reactivity: Tel, R. M.; Engberts, J. B. F. N. *J. Chem. Soc., Perkin Trans. 2* **1976**, 483. Colter, A. K.; Dack, M. R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 5.

[18] Interplanar angles (dihedral angles) between interacting benzene molecules approaching 90°, the "T-stacked" arrangement, are shown to be enthalpically favorable.[3b] A similar arrangement (interplanar angle of 85°) has also been detected in crystalline macrocycles: Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1070.

[19] Ab initio SCF CI potentials have been calculated for benzene dimer: Karlström, G.; Linse, P.; Wallqvist, A.; Jönsson, B. *J. Am. Chem. Soc.* **1983**, *105*, 3777.

[20] NMR studies[21] showed the enthalpy of the interaction (ΔH) between benzene and chloroform to be -2.0 ± 0.1 kcal mol^{-1}. In this connection, it has been found that the $\Delta\Delta H^{\rm t}$ value for chloroform is -1.25 ± 0.02 kcal mol^{-1}. Provided that the difference in physicochemical nature of the system employed between the two works is negligible, the relationship $\Delta H \simeq \Delta\Delta H^{\rm t} - 0.7$ (in kcal mol^{-1}) holds. Therefore, the $\Delta\Delta H^{\rm t}$ value of -1.3 kcal mol^{-1} for benzene comes to correspond to the enthalpy (ΔH) of phenyl–phenyl interaction of about -2.0 kcal mol^{-1}, in agreement with the results[3b] for potential energy calculations.

[21] Slejko, F. L.; Drago, R. S.; Brown, D. G. *J. Am. Chem. Soc.* **1972**, *94*, 9210.

[22] Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 415.

[23] Reference 16, p 135. Watanabe, K. *J. Chem. Phys.* **1957**, *26*, 542.

Table II. $\Delta\Delta H^t$ Values for Alkanes[a]

sample	$\Delta\Delta H^t$/kcal mol^{-1}
cyclohexane (**4d**)	−0.44 ± 0.03
methylcyclopentane (**7a**)	−0.38 ± 0.02
methylcyclohexane (**7b**)	−0.33 ± 0.02
2-cyclohexylpropane (**7c**)	−0.15 ± 0.03
cis-1,2-dimethylcyclohexane (**7d**)	−0.25 ± 0.02
trans-1,2-dimethylcyclohexane (**7e**)	−0.19 ± 0.03
cyclooctane (**7f**)	−0.46 ± 0.02
2-methylpentane (**8a**)	−0.09 ± 0.02
2,3-dimethylbutane (**8b**)	−0.08 ± 0.02
2,2-dimethylbutane (**9a**)	0.07 ± 0.04
2,2,4-trimethylpentane (**9b**)	0.07 ± 0.02
2,2,3,3-tetramethylbutane (**9c**)	0.04 ± 0.04
n-hexane (**10d**)	−0.04 ± 0.02

[a] Errors given are the standard deviations.

Table III. $\Delta\Delta H^t$ Values for Hydrocarbons and Ethers[a]

sample	$\Delta\Delta H^t$/kcal mol^{-1}
benzene (**4a**)	−1.32 ± 0.02
1,3-cyclohexadiene (**4b**)	−1.02 ± 0.02
cyclohexene (**4c**)	−0.68 ± 0.04
cyclohexane (**4d**)	−0.44 ± 0.03
tetrahydropyran (**4e**)	−1.35 ± 0.02
1,4-dioxane (**4f**)	−1.84 ± 0.02
1,3-dioxane (**4g**)	−1.89 ± 0.03
2-methyltetrahydrofuran (**4h**)	−1.39 ± 0.01
2-methyltetrahydropyran (**4i**)	−1.07 ± 0.02
1,3,5-hexatriene (**10a**)	−0.89 ± 0.03
1,3-hexadiene (**10b**)	−0.74 ± 0.02
1-hexene (**10c**)	−0.39 ± 0.03
n-hexane (**10d**)	−0.04 ± 0.02
1-methoxybutane (**10e**)	−0.90 ± 0.02
1,2-dimethoxyethane (**10f**)	−1.62 ± 0.02

[a] Errors given are the standard deviations.

of this interaction depends on the ionization potential of a donor.[16] Electronic effect of Y also fails to account for the data in Figure 3. This is because the introduction of a methyl ($\sigma_p = -0.17$)[24] or a methoxyl group ($\sigma_p = -0.27$),[24] each being an electron-donating group, into a benzene ring as substituent X increases or decreases, respectively, the $\Delta\Delta H^t$.

Effect of Polar Groups Introduced into Benzenes. Table I shows that the introduction of polar groups (methoxyl and nitro groups) into a benzene ring decreases the $\Delta\Delta H^t$; this observation would partly result from the presence of the dipole moment in **5f**,**g**. The replacement of hydrogen atoms by chlorine atoms in benzenes causes no appreciable changes in the $\Delta\Delta H^t$ (−1.3 kcal mol^{-1} for **4a** and **5e** and −1.2 kcal mol^{-1} for **5a** and **6b**); the replacement of hydrogen atoms by fluorine atoms in benzenes has turned out to increase the $\Delta\Delta H^t$ by ca. 0.3 kcal mol^{-1} (**4a** → **6f** and **5a** → **5i**) (Table I). The unusual effect of the halogenation remains to be elucidated.

Shape Specificity in Alkyl–Phenyl Interactions.[10a] The interactions between phenyl and alkyl groups appear to be responsible for physicochemical properties, molecular conformations, retention in HPLC, and enantiomer differentiation.[1] The specificity—for example, the geometrical shape specificity—of such weak interactions is, however, not yet clarified.

In order to examine the effect of three-dimensional shape of the alkyl group on its interaction with a phenyl group, the $\Delta\Delta H^t$ values were compared between alkane samples (Table II). Irrespective of the number of carbon atoms, the $\Delta\Delta H^t$ becomes more negative for cyclic alkanes (**7**) than for **3** by ca. 0.2–0.5 kcal mol^{-1}. For C_6 branched alkanes each having an isopropyl group (**8**), the $\Delta\Delta H^t$ has a tendency to be more negative than that for *n*-hexane. On the other hand, the $\Delta\Delta H^t$ for branched alkanes (**9**) each having at least one *tert*-butyl group tends to be larger than that for the straight-chain alkanes. Since the $\Delta\Delta H^t$ value for 2,2,4-trimethylpentane (**9b**) is more positive than that for *n*-octane, the repulsive interaction of a *tert*-butyl group seems to prevail over the attractive interaction of an isopropyl group.

On the basis of the experimental results given in Table II, we propose that the alkyl–phenyl interaction is specific for the three-dimensional shape of the alkyl group. The interaction of a phenyl group is more attractive with a cyclic alkyl group, and probably with a branched alkyl group having an isopropyl group, than with the corresponding straight-chain alkyl group.[25]

Watson[27] described the possibility of the presence of specific attractive interaction between phenylalanine and leucine side chains, each with a benzyl ($PhCH_2$) or isobutyl (*i*-Bu) group, in a polypeptide chain. X-ray analysis of the crystalline 1:1 complex[28] between a pair of acylurea derivatives [*p*-$NMe_2C_6H_4NHC(=O)NHC(=O)R^3$] and *p*-$NO_2C_6H_4C(=O)NHC(=O)NHR^4$] each having the $PhCH_2$ (R^3) or *i*-Bu group (R^4) revealed that

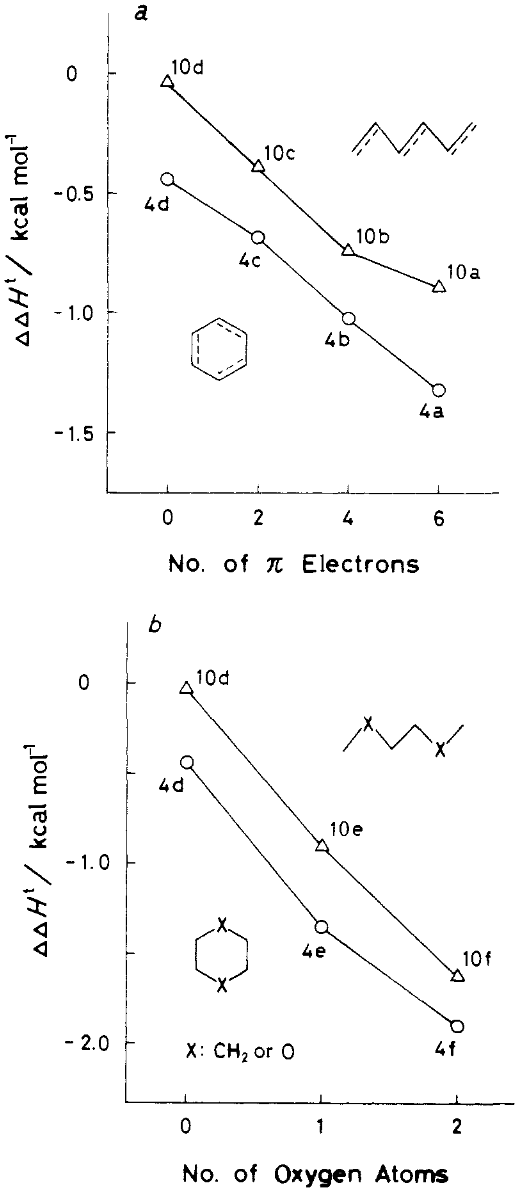

Figure 4. Dependence of $\Delta\Delta H^t$ for C_6 hydrocarbons and ethers on their number of π-electrons (a) and on their number of oxygen atoms (b).

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(24) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

(25) The shape-specific weak interactions mentioned here would stem, at least partly, from the dispersion interaction. The following situations make it very difficult to evaluate the energy of this interaction: (i) various modifications have been proposed of the equation predicting the interaction energy,[26] and (ii) the anisotropy in polarizability is difficult to estimate.

(26) Reference 22, pp 412–413.

(27) Watson, J. D. *Molecular Biology of the Gene*, 2nd ed.; Benjamin: New York, 1970; Chapter 4.

(28) Endo, T.; Miyazawa, K.; Endo, M.; Uchida, A.; Ohashi, Y.; Sasada, Y. *Chem. Lett.* **1982**, 1989. Uchida, A.; Ohashi, Y.; Sasada, Y.; Moriya, M.; Endo, T. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 120.

these two nonpolar groups are brought close together,[29] the same orientation[27] as postulated.

Shape Similarity Effect on the Weak Interactions.[10b] Weak interactions of a phenyl group are also assumed to exist with groups having unshared electrons. For example, a dipole–induced-dipole interaction between the 1,3-dioxane and phenyl rings affects the conformations of side chains of crown ether compounds.[2] Moreover, weak intramolecular interactions of a phenyl group with groups having π and/or unshared electrons were shown to play an important role in determining the conformations of molecules of biological interest.[5,30] These observations stimulated us to determine the $\Delta\Delta H^t$ for unsaturated hydrocarbons (**4a–c** and **10a–c**) and saturated ethers (**4e–g** and **10e,f**) (Table III).

Figure 4a plots the $\Delta\Delta H^t$ for cyclic (**4a–c**) and straight-chain unsaturated hydrocarbons (**10a–c**), together with those for cyclohexane (**4d**) and *n*-hexane (**10d**), against the number of π-electrons in the samples. The $\Delta\Delta H^t$ values are negative for all the samples studied and decrease with an increase in the number of π-electrons (ca. -0.3 kcal mol^{-1}/π-bond). This increase in strength of the interactions with increasing number of π-electrons in the samples would probably reflect the π-electron interactions. Additionally, the $\Delta\Delta H^t$ was investigated for various ethers (Figure 4b). In this case, the $\Delta\Delta H^t$ decreases with increasing number of oxygen atoms in the samples (ca. -0.7 kcal mol^{-1}/oxygen atom). This would come from multipole–induced-multipole interactions.

Of particular interest is the finding (Figure 4a and Table III) that when the samples **4** and **10** have the same number of π-electrons, $\Delta\Delta H^t$ values become more negative for cyclic hydrocarbons (**4a–c**) than for the corresponding straight-chain ones (**10a–c**) by ca. 0.3 kcal mol^{-1} (e.g., -0.68 kcal mol^{-1} for **4c** and -0.39 kcal mol^{-1} for **10c**). Further, the data in Figure 4b clearly indicate that when ethers **4** and **10** have the same number of oxygen atoms, the $\Delta\Delta H^t$ values are more negative for cyclic ethers (**4e,f**) than for the corresponding straight-chain ones (**10e,f**) by ca. 0.3 kcal mol^{-1}.[31]

Inspection of Corey–Pauling–Koltun (CPK) molecular models reveals that a phenyl group bears closer resemblance in three-dimensional shape to cyclic samples (**4**) than to straight-chain samples (**10**). The results and discussions in this section demonstrate that the weak interactions of a phenyl group become more attractive with a group that in three-dimensional shape is similar to a phenyl group.

Since the term "shape similarity" is obscure, we have recently developed a parameter (S_I)[32] for shape similarity between substituents, in light of the parameter A by Allinger,[33] as follows. A pair of substituents, each being represented by the three-dimensional coordinates of its atoms and their van der Waals radii, is so arranged as to give a maximal overlap. One investigates which of the points located with constant spacing (0.2 Å) are involved in each substituent. The S_I is defined as the ratio of the number of points involved in both of the substituents to that involved in either of them, the value ranging from 0 to 1. The S_I values obtained with a phenyl group as one of the pair are 0.48 and 0.79 for *n*-hexyl and cyclohexyl groups, respectively, indicating that a cyclohexyl group resembles a phenyl group in three-dimensional shape more closely than a *n*-hexyl group.[34]

Table IV. $\Delta\Delta H^t$ Values for Carbonyl Compounds[a]

sample	$\Delta\Delta H^t$/kcal mol^{-1}
2-pentanone (**11a**)	-1.51 ± 0.02
cyclopentanone (**11b**)	-1.96 ± 0.03
cyclohexanone (**11c**)	-1.93 ± 0.03
cyclohexyl methyl ketone (**11d**)	1.45 ± 0.05
acetophenone (**11e**)	-1.92 ± 0.03
ethyl acetate (**11f**)	1.43 ± 0.04
γ-butyrolactone (**11g**)	-2.67 ± 0.08
δ-valerolactone (**11h**)	-2.52 ± 0.06
N,*N*-dimethylacetamide (**11i**)[b]	2.37 ± 0.07

[a] Errors given are the standard deviations. [b] The $\Delta\Delta H^t$ value for isopropyldimethylamine (**11j**) is -0.77 ± 0.04 kcal mol^{-1}

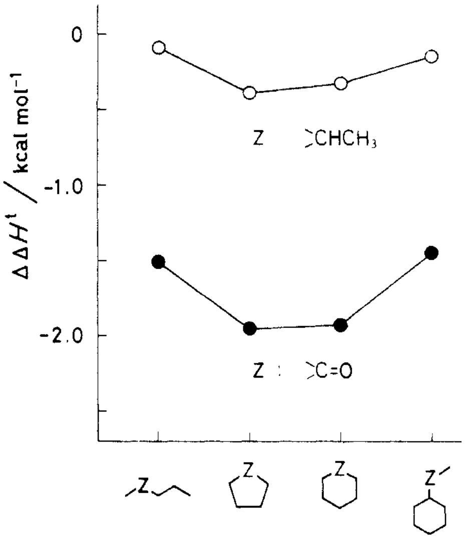

Figure 5. Dependence of $\Delta\Delta H^t$ for carbonyl compounds and the corresponding hydrocarbons.

Shape Specificity in Carbonyl–Phenyl Interactions. Energetically favorable interactions have recently been found to occur between aromatic rings of phenylalanine side chains and carbonyl oxygen atoms in proteins.[4] With this in mind, we determined the enthalpies of the interactions of a phenyl group with carbonyl compounds.

Table IV shows that (i) the interactions of a phenyl group are stronger with carbonyl compounds (**11a–d** and **11g–i**) by 1.3–1.6 kcal mol^{-1} than with the corresponding compounds (**4h,i**, **7a–c**, **8a**, and **11j**) where the CHCH$_3$ group is substituted for the carbonyl group and (ii) the interactions of a phenyl group become very strong with the lactones **11g,h** and amide **11i**.

A fascinating aspect of the data in Figure 5 is that cyclization markedly reduces the $\Delta\Delta H^t$ (**11a** → **11b** and **11f** → **11g**). This finding, taken together with those mentioned above, reveals that the "cyclization effect" on the weak interactions operates regardless of the nature of the samples [ca. -0.4 (alkanes), ca. -0.3 (alkenes), ca. -0.3 (ethers), -0.5 (ketones), and -1.2 kcal mol^{-1} (esters)]. Moreover, the $\Delta\Delta H^t$ values for ketones become more negative when a carbonyl group is a part of a six-membered ring (**11c**) than when a carbonyl group is attached to a cyclohexane ring (**11d**); this also indicates the shape similarity effect on the weak interactions.

Since 1960,[36] an aromatic CH group[4,37] has been suggested to act as a donor of the hydrogen bonding with a carbonyl oxygen atom, while acidic CH groups have generally been accepted as donors.[38] In view of the marked dependence of the $\Delta\Delta H^t$ on the

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[29] The two short intermolecular C--C distances between the PhCH$_2$ and *i*-Bu groups [3.602 (9) and 3.672 (9) Å] were observed.[28]

[30] Haslinger, E.; Kalchhauser, H.; Wolschann, P. *Monatsh. Chem.* **1982**, *113*, 633. Liwo, A.; Ciarkowski, J. *Tetrahedron Lett.* **1985**, *26*, 1873.

[31] In view of the finding by Stoddart et al.,[2] it is interesting to note that the interactions of a phenyl group are no less attractive with 1,3-dioxane (**4g**) ($\Delta\Delta H^t$ = -1.89 kcal mol^{-1}) than with its 1,4-isomer (**4f**) ($\Delta\Delta H^t$ = -1.84 kcal mol^{-1}) (Table III).

[32] Ito, M. M.; Kato, J.; Tsuyuki, M.; Endo, T. *Nippon Kagaku Kaishi* **1987**, 386.

[33] Allinger, N. L. *Pharmacol. Future Man, Proc. Int. Congr. Pharmacol., 5th* **1972**, *5*, 57.

[34] It has been found that the selectivity[32,35] in oxidation of a pair of associating thiols [HSCH$_2$C(=O)NHC(=O)NHR^5 and HSCH$_2$CH$_2$NHC(=O)NHC(=O)R^6] each with a nonpolar group (R^5 or R^6) has a correlation with the S_I for *n*-hexyl, isohexyl, and cyclohexyl groups (R^6) with a phenyl group (R^5) as one of the pair.

[35] Endo, T.; Tajima, K.; Yamashita, M.; Ito, M. M.; Nishida, J.; Ogikubo, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1561.

[36] The occurrence of "carbonyl–phenyl interaction" was already suggested between acetone and a substituted benzene by NMR spectroscopy in 1960: Schaefer, T.; Schneider, W. G. *J. Chem. Phys.* **1960**, *32*, 1218.

[37] Souhassou, M.; Aubry, A.; Boussard, G.; Marraud, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 447.

[38] Sutor, D. J. *Nature (London)* **1962**, *195*, 68; *J. Chem. Soc.* **1963**, 1105. Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063. Sarma, J. A. R. P.; Desiraju, G. R. *Acc. Chem. Res.* **1986**, *19*, 222.

shape of carbonyl compounds (Figure 5), it is uncertain whether or not the nature of the interactions of an aromatic CH group with them can be explained by the above CH--O hydrogen bond, since scarcely any reports have been published on the relationship between their shape and the strength of the CH--O hydrogen bonds with their oxygen atoms. A dipole-induced-dipole interaction would contribute to the carbonyl-phenyl interactions.

Conclusion

We have developed a novel and convenient method for evaluating the enthalpies of weak interactions between a phenyl group in a stationary liquid and a variety of molecules as samples with satisfactory accuracy by utilizing gas chromatography.

It has been found that the interactions of a phenyl group are (i) specific for the three-dimensional shape of molecules with which the phenyl group interacts and (ii) more attractive with cyclic molecules, which are similar in three-dimensional shape to the phenyl group, than with the corresponding acyclic molecules. The shape similarity effect holds for alkanes, alkenes, ethers, and carbonyl compounds.

The above effect on the weak interactions would underlie the "similarity recognition hypothesis"[39] that the three-dimensional shape similarity between groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved. Moreover, the *shape-specific weak interactions* between groups in reacting molecules have recently been shown to control chemical selectivity.[35]

This type of weak interactions would principally originate from the dispersion interaction or from the dispersion and dipole-induced-dipole interactions. Though such interactions depend on relative angular orientation between interacting groups (molecules), the present method is, of course, incapable of elucidating the orientation dependence of interaction enthalpies. The nature of the shape-specific weak interactions presented here will be better understood with the aid of quantum mechanical calculations.

Experimental Section

Materials. Commercially available silicone oils [OV-25 (**1**) and OV-101 (**2**), Gasukuro Kogyo] were used as received. They were coated on acid treated Celite 545 (Celite 545SK, Gasukuro Kogyo) in a weight ratio of 1 to 5. The stationary phases thus obtained were packed in stainless-steel tubes (3-mm internal diameter × 2-m length). The samples **4**–**11** (mostly >99% purity) were commercially available (Tokyo Kasei Kogyo) and distilled before use.

Gas Chromatography. Gas chromatographic measurements were made on a Hitachi 063 or 263-50 equipped with a FID detector and a data processor (SIC Chromatocorder 11). The carrier gas was nitrogen with a flow rate of 20 mL min^{-1}. Retention time was measured from the methane (99.9% purity, Nishio Kogyo) peak to correct for the free space in the system.

Enthalpy Calculations. Retention time measurements were practically made for the mixture of a given sample and an appropriate internal standard (IS) at various temperatures using a pair of stationary phases each with liquid **1** or **2**. An IS was so chosen that (i) the α' mentioned below does not exceed about 10 since larger α' values cause an increase in errors and (ii) its peak completely separates from that of a given sample. The measurements were made at least 6 times each at the six temperatures, whose range was about 50 °C, for **1** and **2** (Figure 1). The relative retention (α')[40] was determined for the sample-IS pair. The slope of the ln α'–T^{-1} plot for liquid **1** or **2**, which was evaluated by least-squares treatment based on eq 2, gave the $\Delta\Delta H^{t'}$ for the sample-IS pair.[41] The $\Delta\Delta H^{t'}$ was then converted to the $\Delta\Delta H^{t}$ for the sample-*n*-octane pair (Tables I–IV) by summing the $\Delta\Delta H^{t'}$ for the sample-IS pair and the $\Delta\Delta H^{t}$ for the IS-*n*-octane pair.

Acknowledgment. We thank Dr. Motohiro Nishio for encouragement throughout this work.

Registry No. 2, 9016-00-6; **3**, 111-65-9; **4a**, 71-43-2; **4b**, 592-57-4; **4c**, 110-83-8; **4d**, 110-82-7; **4e**, 142-68-7; **4f**, 123-91-1; **4g**, 505-22-6; **4h**, 96-47-9; **4i**, 10141-72-7; **5a**, 108-88-3; **5b**, 100-41-4; **5c**, 103-65-1; **5d**, 98-82-8; **5e**, 108-90-7; **5f**, 100-66-3; **5g**, 98-95-3; **5h**, 462-06-6; **5i**, 98-08-8; **5j**, 98-07-7; **6a**, 106-42-3; **6b**, 106-43-4; **6c**, 104-93-8; **6d**, 623-12-1; **6e**, 150-78-7; **6f**, 392-56-3; **7a**, 96-37-7; **7b**, 108-87-2; **7c**, 696-29-7; **7d**, 2207-01-4; **7e**, 6876-23-9; **7f**, 292-64-8; **8a**, 107-83-5; **8b**, 79-29-8; **9a**, 75-83-2; **9b**, 540-84-1; **9c**, 594-82-1; **10a**, 2235-12-3; **10b**, 592-48-3; **10c**, 592-41-6; **10d**, 110-54-3; **10e**, 628-28-4; **10f**, 110-71-4; **11a**, 107-87-9; **11b**, 120-92-3; **11c**, 108-94-1; **11d**, 823-76-7; **11e**, 98-86-2; **11f**, 141-78-6; **11g**, 96-48-0; **11h**, 542-28-9; **11i**, 127-19-5.

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[39] Endo, T.; Tasai, H.; Miyazawa, K.; Endo, M.; Kato, K.; Uchida, A.; Ohashi, Y.; Sasada, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 636. Endo, T. *Top. Curr. Chem.* **1985**, *128*, 91.

[40] The relative retention α mentioned above corresponds to the α' when *n*-octane is used as an IS.

[41] The $\Delta\Delta H^{t}$ corresponds to the $\Delta\Delta H^{t'}$ when an IS is *n*-octane.

Crystal Structures of Two Simple N-Substituted Dihydronicotinamides: Possible Implications for Stereoelectronic Arguments in Enzymology

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Abstract: Crystal structures of *N*-(methoxymethyl)-1,4-dihydropyridine-3-carboxamide (**1**) and *N*-propyl-1,4-dihydropyridine-3-carboxamide (**2**) have been determined and analyzed with a goal of detecting possible stereoelectronic interactions between the nitrogen lone pair and the antibonding orbital of the α–β bond in these molecules. In both molecules, the dihydropyridine ring skeleton is nearly planar. However, the N-substituent carbon atom in both molecules lies significantly (0.26 and 0.21 Å, respectively) out of the ring plane, and the α–β bond is nearly perpendicular to this plane. This suggests that the interaction between the nitrogen lone pair and the antibonding orbital of the α–β bond is larger in **1** than in **2**. Ultraviolet spectral data suggest an estimate of 1–3 kcal/mol as the energy difference associated with the n–σ^* interaction, an energy sufficiently large to be the target of natural selection in the evolution of dehydrogenases dependent on nicotinamide cofactors.

Much of the discussion about the chemical and biochemical reactivity of NADH has been based on the assumption that the 1,4-dihydropyridine ring occurs in a boat conformation.[1,2] The appealing feature of this model is that it places one hydrogen atom