

# Evaluation of enthalpies of cyclic alkene–benzene and ether–benzene interactions based on MO calculations

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**ABSTRACT:** Enthalpies of alkene–benzene and ether–benzene interactions were evaluated by semi-empirical MO (PM3) calculations of heats of formation for (i) alkenes and ethers (Y) and (ii) Y–benzene (PhH) pairs. In the case of the acyclic alkene–benzene systems, calculated enthalpies of the interactions ( $\Delta\Delta H_f$ ) had no close correlation with experimental values ( $\Delta\Delta H^t$ ) determined by GLPC. This was also true for the acyclic ether–benzene systems. The  $\Delta\Delta H_f$  values for cyclic alkenes and cyclic ethers were both more negative than the corresponding acyclic ones by 0.3–0.9 kcal mol<sup>-1</sup>, in essential agreement with the  $\Delta\Delta H^t$  for alkenes and ethers. With cyclic ethers and substituted benzenes, a close relationship exists between the theoretical ( $\Delta\Delta H_f$ ) and experimental interaction enthalpies ( $\Delta\Delta H^t$ ), the correlation coefficient ( $\rho$ ) for the  $\Delta\Delta H_f$ – $\Delta\Delta H^t$  plot being 0.95; using the correlation equation, the experimental enthalpies ( $\Delta\Delta H^t$ ) for cyclic ethers can be estimated from the theoretical enthalpies ( $\Delta\Delta H_f$ ) with an accuracy of  $\leq 0.1$  kcal mol<sup>-1</sup>. With all the cyclic systems so far examined (Y = cyclic alkenes, cyclic ethers and substituted benzenes), however, the correlation coefficient ( $\rho$ ) was reduced to 0.90. Copyright © 2000 John Wiley & Sons, Ltd.

**KEYWORDS:** intermolecular interaction; alkene–benzene; ether–benzene; MOPAC93; interaction enthalpies; semi-empirical MO calculations

## INTRODUCTION

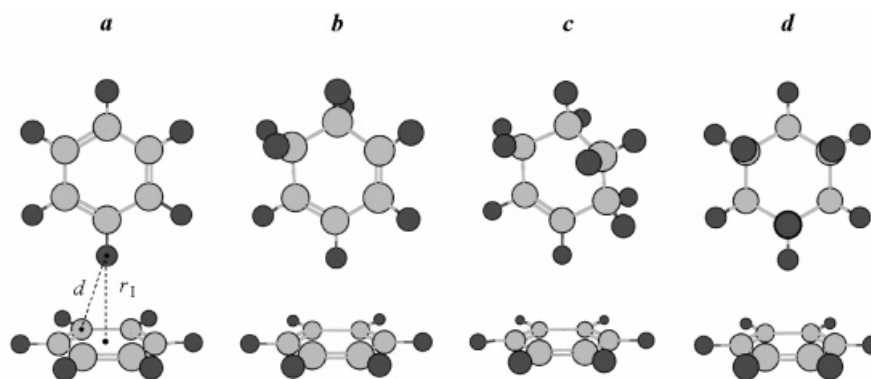
Precise molecular recognition is essential to living systems. For example, the following biological discrimination is well known: enzyme–substrate,<sup>1</sup> antigen–antibody,<sup>2</sup> nucleic acid–protein,<sup>3</sup> drug–receptor,<sup>4</sup> and hormone–receptor recognition.<sup>5</sup> In chemical systems, molecular recognition has been extensively studied using a variety of model compounds such as crown ethers,<sup>6</sup> cryptands,<sup>7</sup> calixarenes<sup>8</sup> and convergent cleft molecules.<sup>9</sup> It is now accepted that molecular recognition, whether biological or chemical,<sup>10</sup> is due to specific weak (non-covalent) interactions between interacting groups in the respective molecules.

Concerning weak interactions between groups, comparable in energy (or enthalpy) to van der Waals interactions, extensive experimental studies have been carried out. These include dipole–induced dipole interaction between the 1,3-dioxane and phenyl rings,<sup>11</sup> an alkyl–phenyl interaction,<sup>12</sup> an alkyl–alkyl interaction<sup>13</sup> including that between two *tert*-butyl groups,<sup>14</sup> etc. Further, theoretical studies have recently been made on aromatic–aromatic interactions,<sup>15–17</sup> for example.

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We have been studying factors controlling such precise molecular recognition as occurs in living systems, by use of a pair of acylurea derivatives (open-chain analogues of uracil and thymine) which can associate strongly with each other as well as with themselves.<sup>18</sup> As a result, it has been clarified that three-dimensional shape similarity between interacting groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved.<sup>19</sup>

These findings led us to investigate weak interactions between interacting groups. Using GLPC, it has been demonstrated that (i) enthalpies of weak interactions of a phenyl group ( $\Delta\Delta H^t$ ) with substituted benzenes,<sup>20</sup> alkanes,<sup>21</sup> alkenes,<sup>22</sup> ethers<sup>22</sup> and carbonyl compounds<sup>20</sup> range from  $-2.7$  to  $+0.1$  kcal mol<sup>-1</sup> (1 cal = 4.184 J) and (ii) the weak interactions of a phenyl group become more attractive with a cyclic group that is similar in three-dimensional shape to a phenyl group;<sup>20</sup>  $\Delta\Delta H^t$  is the enthalpy of the weak interaction of a PhX molecule with the phenyl group in the stationary liquid (practically a PhH molecule) relative to the enthalpy of that of an *n*-octane molecule with the phenyl group. Further examinations have revealed that the degree of recognition between molecules each having a non-polar group can be controlled by the strength of shape-specific weak interactions between non-polar groups in the respective molecules.<sup>23</sup>



**Figure 1.** Front views (a–d) of initial arrangements of cyclic alkene (Y)–benzene systems. The Y in the systems are benzene (PhH) (a), 1,3-cyclohexadiene (b), cyclohexene (c) and cyclohexane (d). These vertical arrangements were each chosen as a result of investigating various arrangements, including parallel ones. The symbols  $d$  and  $r_1$  are shown in the benzene–benzene system (a)

The above-mentioned experimental enthalpies of the interactions<sup>20</sup> can only be determined with a phenyl group as one component, because of the limitation of stationary liquids available in GLPC. Accordingly, some theoretical approaches to evaluate weak interactions between relatively non-polar molecules will help to elucidate an entire picture of the weak interactions including their shape specificity. This approach need not be very accurate and quantitative; it should, however, be (i) precise enough to bring about a good correlation with experimental results and (ii) convenient enough to make it possible to calculate the interaction energies between the phenyl group and a wide variety of groups within a realistic time.

*Ab initio* calculations seem not to be suitable for this purpose: (1) they require successive time and computer resources because of complicated calculations of configuration interactions (CI) using a large number of basis sets and (2) calculation methods are still a subject for theoretical chemists even for the intermolecular interaction of a methane dimer.<sup>24</sup> There appear to be no calculation methods available for electron correlation which allow calculations of interactions between benzene and various molecules to be precise enough within a realistic time.

On the other hand, for semi-empirical methods such as PM3 in MOPAC, CI calculations are not implemented explicitly, while the effect corresponding to electron correlation is supposed to be incorporated implicitly in the set of adjustable parameters, the use of which is characteristic of semi-empirical calculations. The latter view is consistent with the fact that heats of formation for various organic compounds can be evaluated with considerable accuracy by means of MOPAC.<sup>25</sup>

With this situation in mind, MOPAC was used to evaluate enthalpies of intermolecular interactions, and examinations were made of the effectiveness and limitations of the semi-empirical method. Recently, it has been demonstrated that the calculated enthalpies of weak interactions between benzene (PhH) and various

monosubstituted benzenes (PhX) have a close correlation with the corresponding experimental enthalpies determined by GLPC.<sup>26</sup> In this paper, we report that the calculated enthalpies of weak interactions of cyclic alkenes and ethers with benzene have a close correlation with the corresponding experimental enthalpies determined by GLPC.

## CALCULATION METHODS

All calculations were carried out with the MOPAC93 program<sup>27</sup> for Power Macintosh (Chem3D and MOPAC Pro, CambridgeSoft Corp.) on an Apple Power Macintosh 7200/120 computer. As alkenes (Y), 1-hexene, 1,3-hexadiene, 1,3,5-hexatriene, cyclohexane, cyclohexene, 1,3-cyclohexadiene and benzene (PhH) were used; as ethers (Y), 1-methoxybutane, 1,2-dimethoxyethane, tetrahydropyran and 1,4-dioxane were used.

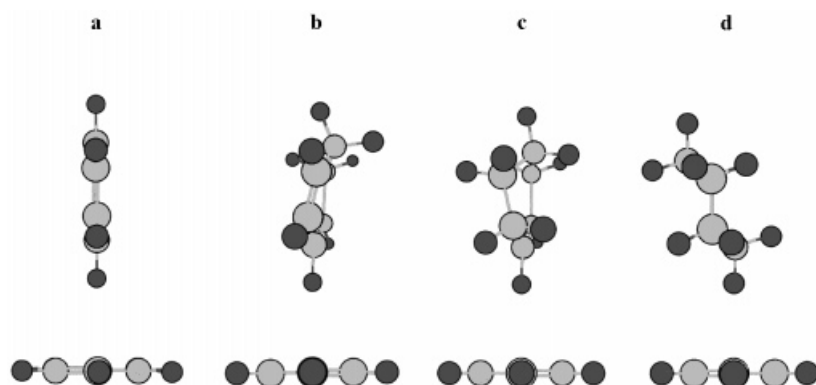
### Calculation method

Based on the results obtained with investigations on the monosubstituted benzene–benzene pairs (PhY–PhH systems),<sup>26</sup> theoretical interaction enthalpies ( $\Delta\Delta H_f$ ) were evaluated with the PM3 method.

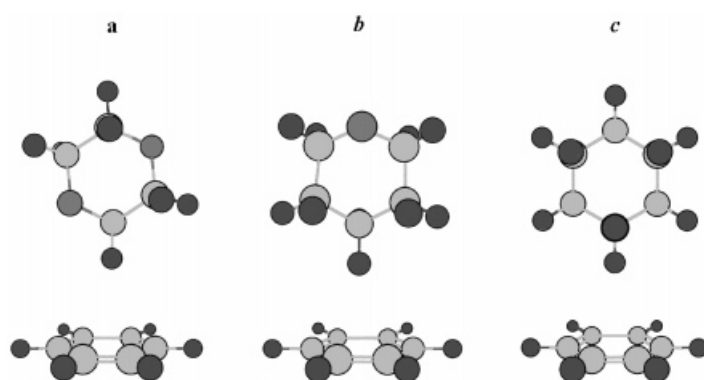
### Initial arrangement

Several arrangements were examined for all Y–PhH systems. On the basis of previous work,<sup>26</sup> vertical arrangements were mainly investigated as initial arrangements of a Y–PhH system (Figs 1–4). Unreasonable vertical arrangements, in which two H atoms facing each other (an H atom in PhH and the lowest H atom in Y) penetrate into each other within the van der Waals radius, are excluded as in the previous work.<sup>26</sup>

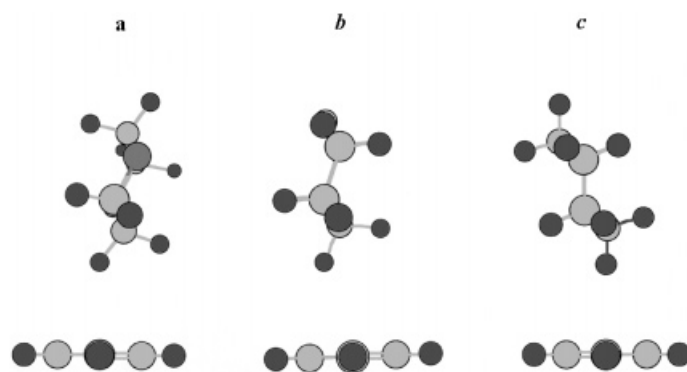
In the case of cyclic alkenes and ethers, the following



**Figure 2.** Side views (a–d) of initial arrangements of cyclic alkene (Y)–benzene systems. Symbols a–d for the systems as in Fig. 1



**Figure 3.** Front views (a–c) of initial arrangements of cyclic ether (Y)–benzene systems. The Y in the systems are 1,4-dioxane (a), tetrahydropyran (b) and cyclohexane (c). These vertical arrangements were similarly chosen as a result of investigating various arrangements



**Figure 4.** Side views (a–c) of initial arrangements of cyclic ether (Y)–benzene systems. Symbols a–c for the systems as in Fig. 3

examinations were made: (1) parallel stacked arrangements and (2) relative positions of C–C double bonds and O atoms, respectively, to the benzene ring. With straight-chain alkenes and ethers, the most stable (i.e. anti-periplanar form) and second most stable conformations were investigated.

### Intermolecular distance

The interatomic distance ( $d$ ) is defined as the distance

between the lowest H atom of Y, which is situated so as to be just above the centroid of the benzene ring and which is nearest to each C atom of PhH molecule, and the C atom of the PhH molecule [Fig. 1(a)]. An initial intermolecular distance ( $r_1$ ) is defined as the distance between the centroid of the benzene ring lying on a plane and the lowest H atom of the Y molecule located above the centroid of the benzene ring [Fig. 1(a)]. Setting up of  $d$  was performed using Chem3D (ver. 3.5) by geometrical calculation so that  $r_1$  may take the desired value (i.e. 2.7 Å).

## Energy minimization

Energy minimization (geometry optimization) was carried out in the following way both for a single molecule (Y or PhH) and for a pair of molecules (a Y-PhH system), thereby giving their heats of formation ( $\Delta H_f$ ): (1) in the case of single molecules, the structure preliminarily optimized by Chem3D was subject to geometry optimization with MOPAC calculation; (2) with Y-PhH systems, (i) initial arrangements (Figs 1–4) were set up, using the optimized structures of Y and PhH mentioned in (1), (ii)  $r_1$  was then set up and (iii) energy minimization was performed with MOPAC calculation.

## Enthalpy of interaction ( $\Delta\Delta H_f$ )

In general, the enthalpy of interaction ( $\Delta\Delta H_f$ ) between A and B molecules can be defined by Eqn. (1):

$$\Delta\Delta H_f = \Delta H_f(A-B) - \{\Delta H_f(A) + \Delta H_f(B)\} \quad (1)$$

where  $\Delta H_f(A-B)$  is heat of formation of co-existing A and B molecules,  $\Delta H_f(A)$  is that of molecule A, and  $\Delta H_f(B)$  is that of molecule B.

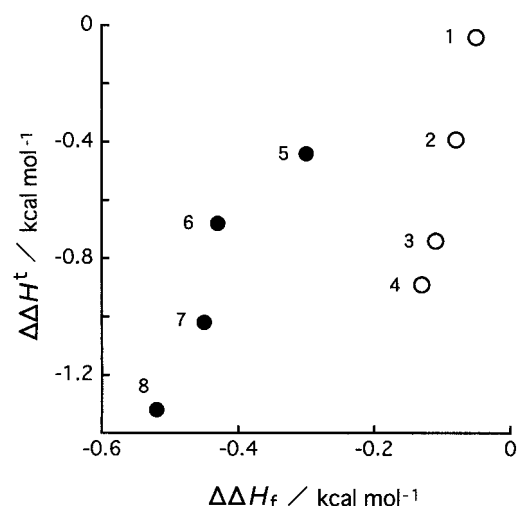
## RESULTS AND DISCUSSION

Semi-empirical MO calculations of heats of formation were performed for initial arrangements of the vertical type.

### Alkene-benzene systems

In the case of cyclic alkenes, arrangements after geometry optimization (optimized geometries) have been found to resemble the corresponding initial arrangements. The alkene-benzene interactions are all attractive. Optimized intermolecular distances ( $r_0$ ) change from 2.5 to 2.9 Å. The  $r_0$  values are slightly shorter than the sum of half the thickness of a benzene ring and the van der Waals radius of an H atom; this might come from the fact that the H atom in Y is located just above the centroid of the benzene ring. The  $\Delta\Delta H_f$  values for the cyclic alkenes decrease with the number of C—C double bonds, ranging from  $-0.30$  (cyclohexane) to  $-0.52$  kcal mol $^{-1}$  (benzene) (Fig. 5). The trend of the experimental enthalpies ( $\Delta\Delta H^t$ ) decreasing from cyclohexane ( $-0.44$  kcal mol $^{-1}$ ) to benzene ( $-1.32$  kcal mol $^{-1}$ ) with the number of double bonds by ca. 0.3 kcal mol $^{-1}$  was not observed in the  $\Delta\Delta H_f$  values.

With acyclic alkenes, the  $\Delta\Delta H_f$  values remained almost unchanged with the number of double bonds:  $-0.05$  (*n*-hexane),  $-0.08$  (1-hexene),  $-0.11$  (1,3-hexadiene), and  $-0.13$  kcal mol $^{-1}$  (1,3,5-hexatriene) (Fig. 5).



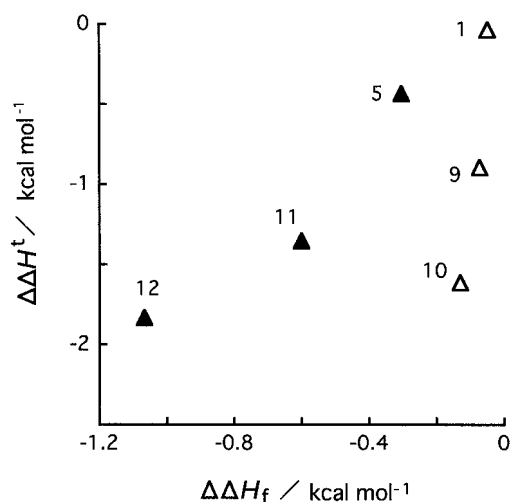
**Figure 5.** Plot of  $\Delta\Delta H_f$  for acyclic (○) and cyclic (●) alkene-benzene systems against the  $\Delta\Delta H^t$ . Alkenes Y used are as follows: 1, *n*-hexane; 2, 1-hexene; 3, 1,3-hexadiene; 4, 1,3,5-hexatriene; 5, cyclohexane; 6, cyclohexene; 7, 1,3-cyclohexadiene; 8, benzene (PhH)

The experimental enthalpies ( $\Delta\Delta H^t$ ) for acyclic alkenes<sup>20</sup> are  $-0.04$  (*n*-hexane),  $-0.39$  (1-hexene),  $-0.74$  (1,3-hexadiene) and  $-0.89$  kcal mol $^{-1}$  (1,3,5-hexatriene), clearly indicating the decrease in  $\Delta\Delta H^t$  with increasing number of C—C double bonds. Although the calculated enthalpies ( $\Delta\Delta H_f$ ) for acyclic alkenes appear to show a slight decrease with increasing number of C—C double bonds, they require closer examination before further discussion.

It is interesting that the  $\Delta\Delta H_f$  values for cyclic alkenes are more negative than those for the corresponding acyclic alkenes by 0.3–0.4 kcal mol $^{-1}$ , in essential agreement with the  $\Delta\Delta H^t$  for alkenes. Figure 5 displays a plot of  $\Delta\Delta H_f$  for cyclic and acyclic alkenes, each with the initial arrangement of vertical type (Figs 1 and 2), against the experimental enthalpies ( $\Delta\Delta H^t$ ). Although each system shows a positive gradient, there is no clear relationship between  $\Delta\Delta H_f$  and  $\Delta\Delta H^t$  in total.

### Ether-benzene systems

In the case of cyclic ethers, optimized geometries also resemble the corresponding initial arrangements. The  $r_0$  values range from 2.5 to 2.6 Å. The  $\Delta\Delta H_f$  values for Y = tetrahydropyran and 1,4-dioxane, each with the initial arrangement of vertical type (Figs 3 and 4), are  $-0.60$  and  $-1.07$  kcal mol $^{-1}$ , respectively (Fig. 6). The  $\Delta\Delta H^t$  values are reduced by ca. 0.5–0.9 kcal mol $^{-1}$  on introduction of an oxygen atom to cyclohexane [i.e.  $-0.44$  (cyclohexane),  $-1.35$  (tetrahydropyran),  $-1.84$  kcal mol $^{-1}$  (1,4-dioxane)] (Fig. 6). A fascinating aspect of the calculated results is that the  $\Delta\Delta H_f$  values



**Figure 6.** Plot of  $\Delta\Delta H_f$  for acyclic (△) and cyclic (▲) ether-benzene systems against  $\Delta\Delta H^t$ . Ethers Y used are as follows: 1, *n*-hexane; 9, 1-methoxybutane; 10, 1,2-dimethoxyethane; 5, cyclohexane; 11, tetrahydropyran; 12, 1,4-dioxane

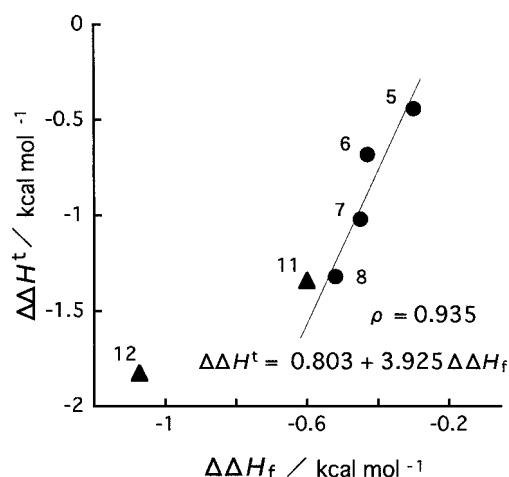
decrease from cyclohexane ( $-0.30$  kcal mol<sup>-1</sup>) to 1,4-dioxane ( $-1.07$  kcal mol<sup>-1</sup>) with the number of oxygen atoms by ca  $0.3$ – $0.5$  kcal mol<sup>-1</sup>.

The experimental enthalpies ( $\Delta\Delta H^t$ ) for acyclic ethers<sup>20</sup> alter markedly with increasing number of O atoms:  $-0.04$  (*n*-hexane),  $-0.90$  (1-methoxybutane),  $-1.62$  kcal mol<sup>-1</sup> (1,2-dimethoxyethane) (Fig. 6). The  $\Delta\Delta H_f$  values for acyclic ethers of more stable conformations hardly alter with the number of O atoms:  $-0.05$  (*n*-hexane),  $-0.07$  (1-methoxybutane),  $-0.13$  kcal mol<sup>-1</sup> (1,2-dimethoxyethane) (Fig. 6). It should be noted that the  $\Delta\Delta H_f$  values for cyclic ethers are also more negative than those for the corresponding acyclic ethers by  $0.5$ – $0.9$  kcal mol<sup>-1</sup>, in essential accordance with  $\Delta\Delta H^t$  for ethers. Although the calculated enthalpies ( $\Delta\Delta H_f$ ) for acyclic ethers appear to show a slight decrease with increasing number of O atoms, they require closer examination before further discussion.

#### Estimation of the experimental $\Delta\Delta H^t$ from the correlation equation for cyclic systems

The above results for alkenes and ethers suggest that the trend in correlation between calculated ( $\Delta\Delta H_f$ ) and experimental enthalpies ( $\Delta\Delta H^t$ ) differs with the shape of the molecules (i.e. cyclic or acyclic), rather than with the functional group in the molecules (double bond or ether linkage). Since the  $\Delta\Delta H_f$  values for acyclic systems scarcely change with the number of functional groups, the following discussion on the estimation of experimental  $\Delta\Delta H^t$  from the correlation equation is limited to cyclic systems.

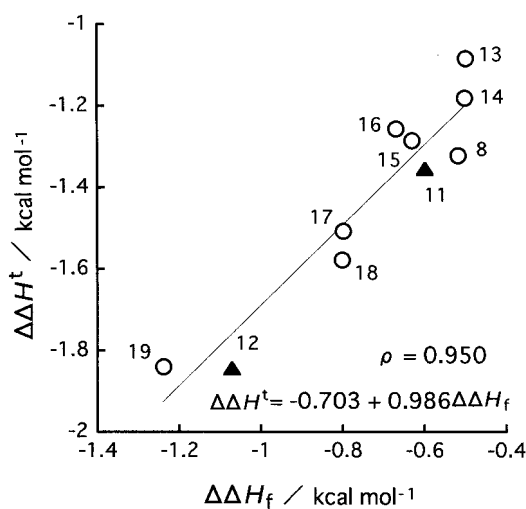
Figure 7 shows the  $\Delta\Delta H_f$ – $\Delta\Delta H^t$  plots for cyclic alkenes and ethers. The  $\rho$  for Y = cyclic alkenes and



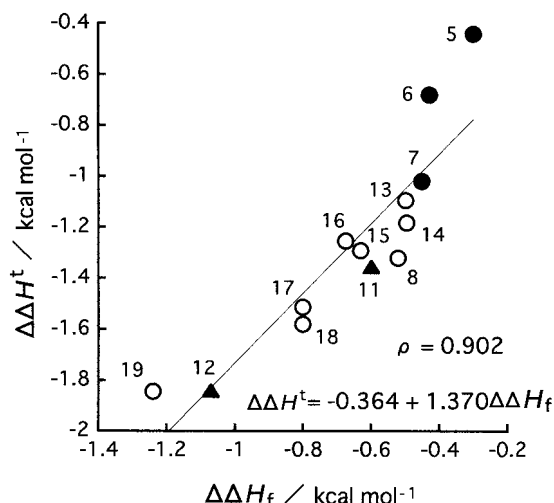
**Figure 7.** Plot of  $\Delta\Delta H_f$  for cyclic alkene (●) + cyclic ether (▲)–benzene systems against  $\Delta\Delta H^t$ . Numbering of cyclic alkenes and ethers as in Figs 5 and 6. The correlation equation and correlation coefficient ( $\rho$ ) are for cyclic alkenes

ethers is  $0.91$ , smaller than that for Y = cyclic alkenes alone ( $0.94$ ), suggesting that these two systems are better correlated independently.

The plots for cyclic ethers (tetrahydropyran and 1,4-dioxane) were then combined with those for the monosubstituted benzenes (PhX)<sup>26</sup> reported previously (Fig. 8). The  $\rho$  value for the  $\Delta\Delta H_f$ – $\Delta\Delta H^t$  correlation



**Figure 8.** Plot of  $\Delta\Delta H_f$  for cyclic ether (▲) + substituted benzene (○)–benzene systems against  $\Delta\Delta H^t$ . Numbering of cyclic ethers as in Fig. 6. Substituted benzenes Y used are as follows: 13, PhEt; 14, PhMe; 8, PhH; 15, PhCl; 16, PhF; 17, PhOMe; 18, PhNMe<sub>2</sub>; 19, PhNO<sub>2</sub>. Initial arrangements of substituted benzene–benzene systems are  $V_p$  or  $V_m$  arrangement where the lowest H atom at the *para* or *meta* position, respectively, to substituent X is located above the centroid of PhH.<sup>26</sup> Substituted benzenes belonging to  $V_p$  arrangement are PhMe, PhH, PhOMe and PhNMe<sub>2</sub> and the others belong to  $V_m$  arrangement<sup>26</sup>



**Figure 9.** Plot of  $\Delta\Delta H_f$  for cyclic alkene (●) + cyclic ether (▲) + substituted benzene (○) – benzene systems against  $\Delta\Delta H^t$ . Numbering of alkenes, ethers and substituted benzenes as in figs 7 and 8

reached 0.95. The differences between the experimental and ‘calculated’  $\Delta\Delta H^t$  values from the correlation equation in Fig. 8 are  $\leq 0.1 \text{ kcal mol}^{-1}$ , the correlation equation in Fig. 8 being nearly the same as that for the monosubstituted benzenes.<sup>26</sup>

Finally, when the plots for all the cyclic compounds so far studied (substituted benzenes,<sup>26</sup> cyclic alkenes and cyclic ethers) were combined with one another (Fig. 9), the  $\rho$  value for the  $\Delta\Delta H_f$ – $\Delta\Delta H^t$  correlation (0.90) was found to be smaller than that for Y = cyclic ethers and substituted benzenes (0.95). The differences between the experimental and ‘calculated’  $\Delta\Delta H^t$  values from the correlation equation in Fig. 9 are  $\leq 0.2 \text{ kcal mol}^{-1}$  except for Y = cyclohexane (0.34) and cyclohexene (0.27). This indicates that the cyclic alkenes are better estimated from a correlation equation independent of that for cyclic ethers and substituted benzenes. One apparent difference of cyclic alkenes from cyclic ethers and substituted benzenes is the absence of polar bonds (or partial charges) in the molecules. However, more extensive studies are required, in both experimental and computational fields, in order to determine whether the above difference causes the necessity for an independent correlation.

## CONCLUSIONS

The present work has clarified that enthalpies of weak interactions of alkenes and ethers (Y) with benzene (PhH) can be evaluated by the MOPAC93 semi-empirical MO method under the following calculation conditions: the use of (1) the PM3 method as a calculation method and (2) vertical arrangements as initial arrangements of Y–PhH systems, in each of which the lowest H atom of Y is

located just above the centroid of PhH. This is the second example in which theoretical enthalpies of the weak interactions related to a benzene molecule have a close correlation with the experimental enthalpies. There have probably been no reports on *ab initio* calculations of energies of intermolecular interactions of simple alkenes and ethers with benzene. The presence of the attractive weak interactions of benzene has, however, been shown with ethers<sup>11,28</sup> and alkenes.<sup>29</sup> The calculated  $\Delta\Delta H_f$  values by the semi-empirical calculation, although not in good agreement with the corresponding experimental  $\Delta\Delta H^t$  values, can be used to estimate  $\Delta\Delta H^t$  with appropriate correlation equations.

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