Molecular Recognition in Terms of a Dimensionless Index. 2. Thermodynamic Patterns of Intermolecular Interactions of PEG and Its Alcohol Substrates

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The systems containing poly(ethylene glycol) (PEG) receptor and its alcohol substrate (n-$C_nH_{2n+1}OH$, n = 1−5 and i-C_3H_7OH) were used to examine molecular exo-recognition between their constituent components in terms of the dimensionless index. On the basis of the hypothesis that all the local orientation-based fits of the common part of two alcohols on the same a receptor are subjected to the same a pattern of intermolecular interactions, two sorts of patterns of intermolecular orientation-based fitting between the PEG receptor and its alcohol substrate are believed to be responsible for the thermodynamic behavior accompanied by alcohol−PEG interactions on the two different kinds of PEG receptors. The interaction entropies estimated from these patterns are found to be in reasonable accordance with their experimental observations. The patterns of orientation-based fitting between PEG and alcohol are ascribed to the average patterns of PEG−alcohol exo-recognition on the thermodynamics time scale.

1. Introduction

Poly(ethylene glycol) (PEG), a type of noncyclic structure in which oxygen atoms and ethylene units are alternately linked together, is an important biocompatible material, much studied in both practical and essential research.[1,2] Unusual properties of this polymer have been intriguing and bedeviling scientists in many fields.[3,4] Despite its surprising amphiphilic balance as opposed to such analogues as poly(propylene oxide) and poly(methylene oxide), the flexibility of PEG's backbone may result in many complicated conformations in its structure. Furthermore, the conformational distribution toward the PEG receptor likely changes significantly with changing intermolecular substrate−receptor interactions.[5,6] For example, curled chains of PEG can construct many tiny "water pools" as well as many tiny "oil pools" to accommodate hydrophilic or hydrophobic substances[7,8] and form cationic complexes with alkali and alkaline-earth metal ions in the same manner as crown ethers.[9,10] However, both the kinetically labile noncovalent binding interactions and the large number of conformational states available to such a macromolecule−substrate system during the processes of molecular recognition make it difficult to identify structurally well-defined orientation-based fits occurring on the thermodynamics time scale, in particular when the macromolecule is incapable of molecular recognition of its small flexible substrate molecules in the same convergent manner as endo-recognition (where convergent molecular recognition takes place inside the intramolecular cavities which a receptor contains with its substrate).[11] Additionally, we found that induced fitting between the PEG receptor and its substrate was not strong enough to restrain the relative movements of them.[12] Recently, processes in which molecular recognition occurs between this kind of macromolecule without rigid protuberances and depressions on its external surface (called exo-receptor) and its organic substrate with a shortage of a sufficiently large contact area and a limited (or insufficient) number of interactions have been termed exo-recognition as opposed to endo-recognition.[11] Indeed, little is known about whether and how molecular exo-recognition occurs between constituent components. This knowledge gap is in part due to the lack of experimental physical methods to observe transient nonequilibrium conformations or patterns of intermolecular noncovalent binding interactions at high resolution.

We have previously proposed the dimensionless index (a dimensionless descriptor, calculated from the generally accessible thermodynamic data) to detect the average orientation-based fit which occurs in the interaction between the receptor and its substrate on the thermodynamics time scale,[12] and we used PEG as the model of a type of linear exo-receptor thanks to its simplicity in both topological structure and chemical composition and examined the thermodynamic behavior of intermolecular interactions of the gaseous substrate and the melted PEG liquid film (thus without the solvent effect) by means of gas−liquid chromatography (GLC). Orientation-based fits of two kinds of PEG receptors toward 26 types of organic small molecules were well classified into the three classes (A, B, and C) from their dimensionless indexes. We have found that the strong active site of the substrate, which is the acting site of the PEG receptor, correlates with its dimensionless index value to some extent. For example, alcohol substrates which contain an active site such as the electrophilic group OH possess negative indexes (Class B). Even so, some of those alcohol−PEG systems were in conflict with the classification and fell into the catalog in which substrates are detained through a combination of comparably significant intermolecular interactions associated with both ethylene groups and ether oxygen atoms in the PEG structure (Class C). Here, we make a further attempt to address the reason or structural basis underlying this conflict using the dimensionless index. The findings exhibit the inspiring simplicity behind complex PEG−alcohol interactions, suggesting that the dynamic property of patterns of intermolecular interactions should not be as omitted in the investigations of molecular exo-recognition as those in molecular recognition which takes place inside the intramolecular cavities which a receptor contains with its substrate (endo-recognition).

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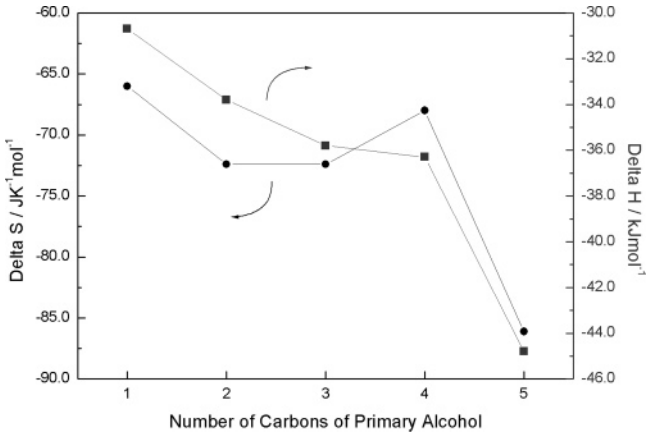


Figure 1. Plot of enthalpy−entropy relationship for the primary alcohol−PEG-6000 systems. The digitals 1 through 5 on the abscissa represent methanol, ethanol, *n*-propanol, *n*-butanol, and *n*-pentanol, respectively. 2-propanol is not labeled on this plot.

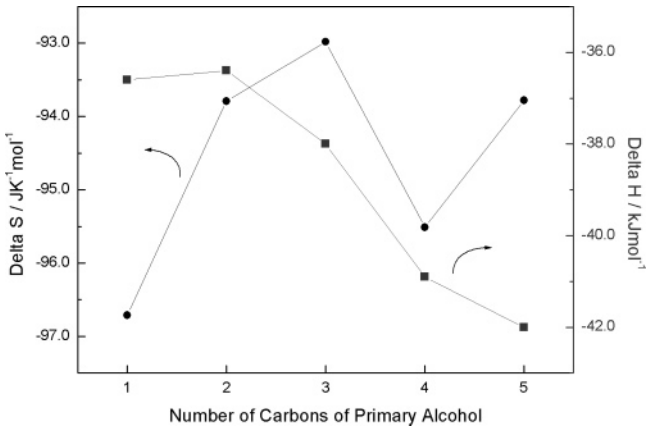


Figure 2. Plot of enthalpy−entropy relationship for the primary alcohol−PEG-1000 systems. The digitals 1 through 5 on the abscissa represent methanol, ethanol, *n*-propanol, *n*-butanol and *n*-pentanol, respectively. 2-Propanol is not labeled on this plot.

This paper contains three parts: (i) to extract patterns of alcohol−PEG interactions using the dimensionless index; (ii) structural basis behind the thermodynamic behavior of intermolecular interactions with systems; (iii) comparison between the calculated and the experimental thermodynamic changes with systems upon complexation.

2. Experimental Section

All the reagents used in the present experiments were purchased from Shanghai Chemical Company (Shanghai, China). The two kinds of poly(ethylene glycol) with GC purity are of the mean molecular weight 6000 (denoted by PEG-6000) and 1000 (denoted by PEG-1000), respectively. The two reagents were used as obtained. The alcohol series under consideration includes as follows: methanol, ethanol, *n*-propanol, 2-propanol, *n*-butanol, and *n*-pentanol. These reagents were chemically or analytically pure; among them the chemically pure reagents were further purified by fractional distillation or reduced pressure distillation. Then the alcohols were stored above 4 Å molecular sieves to remove the residual water.

The preparation of the melted PEG liquid film and the experimental details about the GLC method have been previously reported elsewhere.[12] With little difference between the inlet and the outlet pressure, under the present experimental conditions, the imperfect behavior of the carrier gas could be neglected.[12,27] The calculation process of dimensionless indexes was also given in the same literature.[12]

3. Results and Discussion

3.1. Thermodynamic Properties. In the first approximation, enthalpy changes for formation of association complexes are regarded as constant values independent of experimental temperature. The van't Hoff plots of ln(K) vs 1/T show quite good regression lines (The linear correlative coefficient for every substrate is larger than 0.995). It is not observed that experimental points on the van't Hoff plots are temperature dependent over the present experimental temperature interval, as observed for cyclodextrin complex formation.[13] Thus, the enthalpic and entropic changes can be derived from the van't Hoff equation. The individual thermodynamic quantities referring to primary alcohol substrates are schematically labeled in Figures 1 and 2. The enthalpy and entropy changes referring to the 2-propanol substrate are −32.0 kJ mol^{-1}, −67.9 JK^{-1}mol^{-1} on PEG-6000 and −35.8 kJ mol^{-1}, −92.6 JK^{-1}mol^{-1} on PEG-1000, respectively.[12] All the enthalpy and entropy changes possess negative values, indicating that the thermodynamic behavior of interaction of the substrates with PEG is enthalpically controlled over the present experimental temperature interval. Since the gas−liquid chromatographic method works without the use of solvent, thermodynamic behavior in dissolution can be completely regarded as a consequence of intermolecular interactions between PEG and its individual substrates.[12,14] Complexation of alcohol by the PEG receptor is responsible for the obtained thermodynamic quantities.

Alkyl groups of an organic substrate generally have an ability to interact with PEG's ether oxygen in an unconventional hydrogen bond[15,16,22] as well as to interact with PEG through van der Waals forces. It was reported that the interaction energy of $H_3CH\cdots OH_2$ was 0.3[15] to 0.5[17,18] kcal/mol (about 1.2−2.1 kJ/mol) and that the acidity of CH could cause a variation in energy of about 4.2 kJ/mol.[19] Frequency shifts produced by the unconventional H-bond were very small.[15,20] This interaction energy range correlates well with the data observed in the PEG−alcohol systems.

As seen in Figures 1 and 2, primary alcohols on the PEG receptors unexpectedly do not exhibit the linear enthalpy−entropy relationship. On PEG-6000, for example, as the chain of the alkyl group of primary alcohols grows, the enthalpy changes become more negative. Meanwhile, the corresponding entropy changes increase in a zigzag manner and display a plateau between ethanol and *n*-propanol ($\Delta S = -72.4$ and -72.4 JK^{-1} mol^{-1}, respectively). Additionally, intermolecular interactions of alcohol substrates with different PEG receptors (PEG-6000 and PEG-1000) exhibit distinct distributions of enthalpy−entropy pairs on the ΔH^o vs ΔS^o plots.

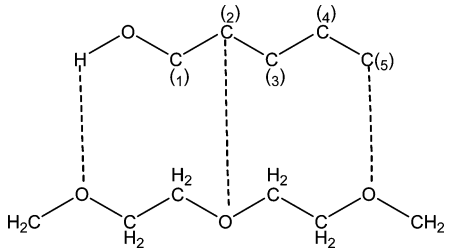
The discrepancy in the thermodynamic data between the same substrate on the two different PEG receptors is supposed to arise from the discrepancy in the mobility of chain segments of the receptors of different degrees of polymerization.[12] The influence of the receptors on intermolecular orientation-based fitting will be examined below in detail.

3.2. Patterns of Intermolecular Orientation-Based Fitting. The dimensionless index is capable of detecting the average orientation-based fit of constituent components. Its value of 100 represents no orientation-based fit available between constituent components. The smaller the index, the better the orientation-based fit. As listed in Table 1, the dimensionless indexes are also compared with their respective forward adjacent indexes in the same column. The results fluctuate up and down with

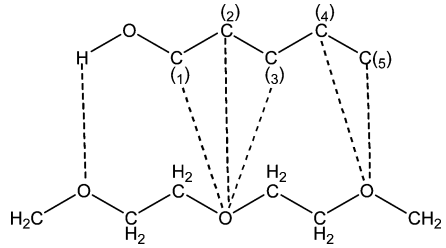
TABLE 1: Values of the Dimensionless Index for Orientation-Based Fits of the Alcohol Series to the Two PEG Receptors and Comparison between Adjacent Indexes in a Series

	dimensionless index			
substrate	PEG-6000		PEG-1000	
Methanol	−0.7		−2.8	
Ethanol	−3.8	less	0.3	greater
n-propanol	0.1	greater	1.3	greater
2-propanol	−0.9	less	1.5	greater
n-butanol	7.0	greater	−1.1	less
n-pentanol	−1.7	less	0.8	greater

SCHEME 1: Outline for Interaction Patterns of PEG-6000 with the Alcohol Series



SCHEME 2: Outline for Interaction Patterns of PEG-1000 with the Alcohol Series



the substrates shifting, exhibiting that the orientation-based fits between alcohol and PEG have dependence on the number of carbon atoms of alcohol substrate. This dependence represents a significant contribution of subsequently incremental or degressive structural units CH_2 in a substrate molecule to the orientation-based fits. The contribution is an averaging measure of entire events of molecular recognition which takes place in the receptor−substrate interactions because the dimensionless index is a phenomenological descriptor in nature. Suppose that all the local orientation-based fits of the common part of two alcohols on the same receptor are subjected to the same average pattern of intermolecular interactions; the orientation-based fit with the systems designated as "less" (Table 1) is thus a consequence of the local orientation-based fit which occurs between the increment of one CH_2 for the substrate and an oxygen atom of PEG. Two sorts of thermodynamic patterns of intermolecular orientation-based fitting between the alcohol substrates and their two different PEG receptors are schematically represented from their tabulated indexes in Schemes 1 and 2, respectively, where the dot lines indicate positions where sites participate in local orientation-based fits during complexation.

We add a comment to the patterns with the PEG-1000 receptor. According to the data in Table 1, the local orientation-based fits take place at the C(1) and C(4) positions, shifting close to the binding position of OH. But there is a smaller variance of the index for the substrates on PEG-1000 compared to that on PEG-6000, implying that there are some contributions from the local orientation-based fits occurring at C(2), C(3), and C(5) with PEG-1000.

The two sorts of thermodynamic patterns are responsible for the observed thermodynamic behaviors with the PEG and alcohol systems in complexation. They are discussed in detail below.

3.2.1. Alcohol−PEG-6000 Systems. Scheme 1 represents in a compact way the orientation-based fits occurring in the noncovalent binding of the PEG-6000 receptor to a series of the alcohol substrates and summarizes the average patterns of intermolecular interaction of the alcohol series and the PEG-6000 receptor on the thermodynamics time scale.

When electrophilic sites (methylene units) of the alkyl group of an alcohol substrate match ether oxygen atoms of PEG, its dimensionless index will become smaller; otherwise, its index value will be less negative because van der Waals forces act nondirectionally. The concomitant binding strength in the enthalpy term will then become weaker. As seen in Scheme 1, for example, the orientation-based fitting of *n*-pentanol to PEG (its index is −1.7) is contributed by its C(2), C(5), and hydroxyl units whereas the orientation-based fitting of *n*-butanol to PEG (its index is as high as 7.0) occurs through its C(2) and hydroxyl units. Therefore, the enthalpic change accompanied by the *n*-pentanol−PEG interaction (−44.8 kJ mol^{-1}) is more negative than that associated with the *n*-butanol−PEG interaction (−36.3 kJ mol^{-1}).

There are linkers available in a substrate molecule on its receptor that join two neighboring local fitting positions together. In a special case, one end of a linker, which meanwhile is one of the ends of a substrate molecule, does not participate in a local fit; a linker thus breaks open to partially detach from its receptor, which is called the pendent chain. It is of interest to note that *n*-ethanol, *n*-propanol, and *n*-butanol have zero, one, and two carbon atoms on their particular pendent chains, respectively (Scheme 1). It is observed that the entropic costs with these systems decrease as the lengths of the pendent chains of their substrates increase.

Paserba et al. measured the desorption kinetics of a series of poly(ethylene glycol) di-Me ethers ($CH_3(OCH_2CH_2)_nOCH_3$, $n = 1-22$) adsorbed on graphite to study the detachment of flexible linear heteropolymers from solid surfaces.[21] They found that the desorption barrier scales nonlinearly with the oligomer chain length and believed that for long oligomers, entropy favors conformations of the molecule that are partially detached from the surface at elevated temperatures and thus the average energy of the adsorbed state is quite different from that of the minimum energy configuration. On the contrary, here, partially detached conformations of the alcohol substrates are a consequence of orientation-based fits between alcohol and PEG and are enthalpically driven.

Compared to the ethanol−PEG-6000 interaction pattern, both the patterns of *n*-propanol−PEG-6000 and 2-propanol−PEG-6000 interactions contain a free CH_3 on their respective substrate molecules (Scheme 1). The corresponding entropic costs of the two systems are however not close to one another. Instead, the 2-propanol−PEG-6000 and the *n*-butanol−PEG-6000 systems exhibit essentially the same entropic changes upon complexation. We notice that both the free CH_3 of 2-propanol and of *n*-butanol are separated from their neighboring local fitting position C(2) by two C−C bonds. If we take into account the contribution of the entropic effect of the two identical CH_3 ends of 2-propanol to the entropic cost of the system, the resultant entropic gain is estimated to be 5.76 J mol^{-1} K^{-1}, which is slightly greater than the experimental difference (4.5 J mol^{-1} K^{-1}) in the entropic cost between the *n*-propanol−PEG-6000

TABLE 2: Classification of Weak Interactions of Alcohol with PEG as the Receptor Shifts to PEG-1000 from PEG-6000 (excerpted from the ref 11)[a]

category	class B	class C
I	methanol	*n*-butanol (B)
II	ethanol, *n*-propanol, 2-propanol, *n*-pentanol (C)	

[a] Shown are the classes of the alcohol−PEG-6000 systems. For systems that change their classes when the PEG weight shifts to 1000 from 6000, the classes are listed in parentheses immediately after the substrate's name.

and 2-propanol−PEG-6000 systems. This fact indicates that the pattern is reasonable with the 2-propanol−PEG-6000 system.

3.2.2. Alcohol−PEG-1000 Systems. Scheme 2 outlines the patterns of intermolecular orientation-based fits which operate between the PEG-1000 receptor and its respective alcohol substrates. As represented in Scheme 2, binding sites on the alkyl part of the alcohol substrate are arranged into two domains by their respective binding counterparts on PEG-1000: {C(1), C(2), C(3)}(Domain I) and {C(4), C(5)} (Domain II), indicating that substrate molecules are capable of offering one to three identical binding candidates to the same one oxygen atom of PEG-1000. In comparison with the aforementioned patterns operating on PEG-6000, we believe that the patterns operating on the PEG-1000 receptor have a one-carbon-atom tolerance around the positions that are responsible for local orientation-based fitting of the substrate to the PEG-6000 receptor. This tolerance is probably due to the insensitivity of C−H···O hydrogen bonds to its binding orientation[16,22] as well as thermal perturbations of chain segments of PEG-1000.

Thus, intermolecular interactions of PEG-1000 with its respective alcohol substrates in the enthalpy term are smoothed on the thermodynamics time scale by this tolerance, compared to those in the corresponding alcohol−PEG-6000 interaction patterns. Enthalpies for alcohol−PEG-1000 interactions vary smoothly with the number of carbons of the alcohol substrate. This is the reason why the entropic gain contributed from the two identical CH_3 ends of 2-propanol on the PEG receptor is hardly appreciable on the PEG-1000 receptor with respect to the entropic change of the *n*-propanol−PEG-1000 system, too.

On the other hand, the patterns represent PEG receptor selectivity to various patterns of intermolecular interactions of PEG and alcohol. Therefore, the term of receptor specificity can be naturally rationalized following from the principles of statistical thermodynamics. A slightly similar statistical physics view of this specificity can be found in the literature.[23]

3.2.3. Influences of the Pendent Chain and the Linker on the Patterns. The pendent chain and linker in a substrate molecule exist explicitly in their patterns associated with the PEG-6000 receptor and implicitly with the PEG-1000 receptor. As aforementioned, the pendent chains in a partially detached substrate can affect entropic changes with systems. Here, specific attention is paid to address the conflict in the classification of the twelve types of systems.

The classification of alcohol−PEG systems that we previously have performed[12] are excerpted and listed here in Table 2, where category I represents systems with dimensionless index values that decrease when the PEG molecular weight decreases from 6000 to 1000 but the category II represents systems where the index values increased. When the PEG receptor was shifted from PEG-6000 to PEG-1000, as seen in this table, the class of the butanol−PEG system changed from the exception class C back to the normal class B, whereas the class of the pentanol−PEG system was shifted from B to C. The discrepancies can be satisfactorily ascribed to a flip-flop between the pendent chain and the linker in the resultant supramolecular structures.

As aforementioned, the classification was performed from their dimensionless indexes for 26 types of systems. The more degrees of freedom of motion an orientation-based fit possesses, the greater its index value is. For the *n*-butanol−PEG system, comparing Scheme 1 with Scheme 2, we easily understand that out-of-order perturbation of the pendent chain of butanol partially detached on PEG-6000 is responsible for the butanol−PEG-6000 system falling into the exception class. This pendent chain is subsequently limited to some extent by the local fit occurring at its free end on the PEG-1000 receptor to form a linker with a decreased dimensionless index for this system, consequently moving this system back into class B.

On PEG-6000, in fact, except butanol of the two-carbon-atom pendent chain, all the substrates have the pendent chains of zero or a one-carbon-atom length. It is interesting to note that butanol belonged to class C whereas the other substrates fell into class B. This fact seems to mean that the partially detached butanol with the two-carbon-atom pendent chain can bring in a sufficient amount of degrees of freedom of motion in its orientation-based fit. It is indeed appreciable in the calculation of entropic costs below.

The *n*-pentanol−PEG system has a situation similar to that of the *n*-butanol−PEG system; the linker within pentanol on PEG-6000 can oscillate between the linker and the pendent statuses upon replacement of PEG-6000 with PEG-1000, thus giving the system more degrees of freedom of motion, with the dimensionless index of this system increasing beyond that of class B. The *n*-pentanol−PEG system indeed displays less enthalpy change than the other systems when the receptor shifts to PEG-1000 from PEG-6000. The *n*-pentanol−PEG-1000 system has enthalpic change close to that of the *n*-butanol−PEG-1000 system, evidently following from an estimate that the pattern of interactions of *n*-pentanol and PEG-1000 has a greater degree of freedom of motion than that of interactions of *n*-pentanol and PEG-6000. In conclusion, flip-flop between the pendent chain and the linker are in responsible for the conflicts of the classification with the 12 types of alcohol−PEG systems.

3.3. Estimation of Entropic Costs. Compared to the experimental error ranges, differences in the thermodynamic quantity between these different systems are not very great because of weak intermolecular interactions. Thus, although these patterns are well responsible for the thermodynamic behavior accompanied by the substrate−receptor interactions on the two kinds of PEG, it is necessary for us to quantitatively rationalize those thermodynamic changes caused by complexation of PEG with a series of alcohols based upon the above models of receptor−substrate interactions.

Considering that 2-propanol−PEG systems are simply featured by the entropic gain contributed from the interaction of the two identical CH_3 groups of 2-propanol with PEG, we focused on the calculation of entropies of interaction of PEG with the primary alcohol series.

We had not found the data about O−H···O hydrogen bonding between PEG and alcohol in literature. The hydrogen bond energy is 13.3−25.9 kJ mol^{-1} for the alcohol interaction, 18.8 kJ mol^{-1} for the alcohol−DMF interaction, and 14.2−24.2 kJ mol^{-1} for H_2O-H_2O, respectively.[24,25] If we use the O−H···O hydrogen bond energy of about 13.3 kJ mol^{-1} and the C−H···O unconventional hydrogen bond of 1.9 kJ mol^{-1}, the ratio (or Boltzmann probability) of the contribution of the single O−H···O hydrogen bonding to the contribution of the double

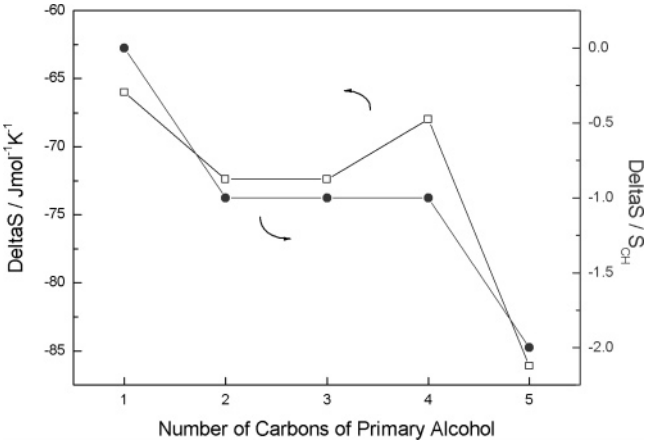


Figure 3. Comparison between the calculated (right) and the experimental (left) entropies for primary alcohol−PEG-6000 systems. On the abscissa, 1 represents methanol, 2 is for ethanol, 3 for *n*-propanol, 4 for *n*-butanol, and 5 for *n*-pentanol. The unit SCH designates the entropic cost caused by the orientation-based fit of a methyl or a methylene unit of alcohol to PEG's ether oxygen.

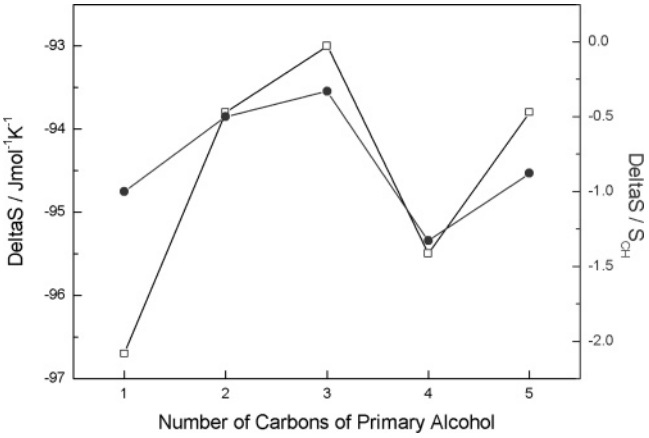


Figure 4. Comparison between the calculated (right) and the experimental (left) entropies for primary alcohol−PEG-1000 systems. On the abscissa, 1 represents methanol, 2 is for ethanol, 3 for *n*-propanol, 4 for *n*-butanol, and 5 for *n*-pentanol. The unit SCH designates the entropic cost caused by the orientation-based fit of a methyl or a methylene unit of alcohol to PEG's ether oxygen.

C−H···O hydrogen bonding is estimated to be as high as 23.3:1 at $T_{hm} = 362.85$ K. Therefore, the orientation-based fits in which no alcohol's OH takes part in hydrogen bonding with PEG are events of small probability. Although this evaluation based on the data is not very accurate, it is safe to estimate that the complexed alcohol substrate is first anchored on the PEG receptor by a hydrogen bonding interaction between its hydroxyl group and ether oxygen atoms of PEG, and then the alcohol's alkyl group is being positioned to fit toward their counterparts within the PEG receptor. Thus, we are able to calculate the entropic contribution from interactions between alcohol's alkyl groups and its receptor to estimate entropic changes with systems.

3.3.1. Complexation Entropies with the PEG-6000 Receptor. Since entropic costs are a consequence of the degrees of freedom of motion that are lost when two molecules are rigidly constrained with a weakly bound complex or by their intermolecular interactions,[12,26] we suppose that the entropic cost which results from fitting of a methyl or a methylene unit of alcohol to PEG's ether oxygen is approximately a constant value, designated as S_{CH}, and that the contribution of thermal perturbation to the entropy is zero; that is, the entropic contribution from the pendent chain and the linker is neglected. The entropic cost experienced by the methanol−PEG-6000 system is taken as a reference for entropic change calculation. Entropic costs then can be calculated from the obtained patterns with all of these systems.

The calculated results are schematically represented in Figure 3, along with the corresponding experimental entropies. There is a jump (about 4.4 J K^{-1} mol^{-1} high) available on the experimental curve with respect to the calculated curve. The jump is corresponding to the *n*-butanol−PEG system in which the substrate has a two-carbon-atom pendent chain. This is so because the calculated values exclude entropic contribution from the pendent chain of a substrate partially detached on PEG. Except for this point, as seen in this figure, the calculated entropic costs vary in agreement with the experimental curve.

3.3.2. Complexation Entropies with the PEG-1000 Receptor. In comparison with the alcohol−PEG-6000 systems, the alcohol substrates on the PEG-1000 receptor exhibit more complicated patterns of intermolecular interactions. The tolerance should be taken into account in the calculation of complexation entropies.

TABLE 3: Estimations of Entropic Costs Accompanied by the Orientation-Based Fits of the Particular Primary Alcohols to PEG-1000

substrate	fixed entropy, S_{CH}	perturbation factor	total entropy, S_{CH}
Methanol	−1	1	−1
Ethanol	−1	0.5	−0.5
n-propanol	−1	0.33	−0.33
n-butanol	−2	0.33, 1	−1.33
n-pentanol	−2	0.33, 0.5	−0.83

We use the perturbation factor for this tolerance. The factor is determined by the size of every fitting domains within a substrate. The procedure is listed step by step in Table 3. For *n*-pentanol on PEG-1000, for instance, there are two fitting domains, {C(1), C(2), C(3)} and {C(4), C(5)}, available on the alkyl group of *n*-pentanol. Thus, the perturbation factors are calculated of 1/3 for the former and 1/2 for the latter. Its entropy change equals $(-1 \times 0.33 + (-1 \times 0.5))S_{CH}$, where the possible correlation between the two perturbation factors is neglected. The comparison between the experimental and the calculated entropies is schematically represented in Figure 4. The calculated results are in reasonable coincidence with the experimental curve.

4. Conclusions

Investigations of molecular exo-recognition by macromolecules are a fundamental topic in material, drug design, chemistry, and life sciences. It is a pity that scientists hitherto have little knowledge about this problem. Here, using PEG as a noncavity macromolecule model receptor (model exo-receptor), we examine the patterns of intermolecular interactions between PEG and alcohol and influences of the PEG receptor of different degrees of polymerization on the patterns in terms of the dimensionless index.

The exposure of these patterns of intermolecular interactions where PEG acts as an exo-receptor seems to imply the inspiring simplicity behind complex macromolecule−small molecule interactions. On the basis of the hypothesis that all the local orientation-based fits of the common part of two alcohols on the same receptor are subjected to the same pattern of intermolecular interactions, two sorts of thermodynamic patterns of intermolecular orientation-based fitting between the alcohol substrates and their two different PEG receptors are responsible

for the thermodynamic behavior accompanied by the alcohol−PEG noncovalent binding interactions on the different receptors. The interaction entropies estimated from these patterns are found in reasonable accordance with their experimental observations.

Such investigations of thermodynamic patterns of intermolecular interactions are helpful for our understanding of molecular exo-recognition which is usually associated with nonequilibrium conformational structures. In addition to thermal perturbation of chain segments of PEG receptors, the flip-flop between the pendent chain and the linker in the resultant supremolecular structures have an influence on local orientation-based fits operating in the pattern. These factors make the molecular recognition patterns of alcohol and PEG complicated and illegible, in particular, while conversion between the pendent chain and the linker occurs on the PEG-1000 receptor. The dimensionless index provides an average (thermodynamic) insight into dynamic matching in exo-recognition on the thermodynamics time scale. Computer molecular simulations are helpful to extend our vision on a finer time scale (thus more details) to such dynamic thermodynamic patterns of intermolecular interactions. This aspect of the work will be presented elsewhere.

It should be noted that there is a distribution of molecular weights with chain macromolecules such as PEG. Probably, the weight interval between the PEG receptors that we used here is great enough. We have not found any hints of influences of the weight distribution. We estimate that the distribution simply affects populations of different receptor−substrate interaction patterns on the thermodynamics time scale.

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