STRUCTURAL FUNCTIONAL ANALYSIS
OF BIOPOLYMERS AND THEIR COMPLEXES

Evaluation of the Accuracy of Calculation of the Standard Binding Entropy of Molecules from their Average Mobility in Molecular Crystals

S. O. Garbuzynskiy and A. V. Finkelstein*

Institute of Protein Research, Russian Academy of Sciences, Pushchino, Moscow oblast, 142290 Russia
*e-mail: afinkel@vega.protres.ru

Abstract—One of the main problems in attempts to predict the binding constants of molecules (or free energies of their binding) is the correct evaluation of configurational binding entropy. This evaluation is possible by methods of molecular dynamics simulation, but these simulations require a lot of computational time. Earlier, we have developed an alternative approach which allows the fast calculation of the binding entropy from summarizing the available data on sublimation of crystals. Our method is based on evaluating the mean amplitude of the movements that are restricted in the bound molecule, e.g., in a crystal, but are not restricted in the free state, e.g., in vapor. In this work, it is shown that the standard entropy of binding of molecules by crystals under standard conditions (1 atm, 25°C) can be assessed rather accurately from geometric and physical parameters of the molecule and the average amplitude of the molecule motions in crystals estimated in our previous work.

INTRODUCTION

The prediction of the key parameters of molecular interactions is a very important area that has both fundamental and applied value, e.g., in the computer drug design. The dissociation constant of molecules, by definition related to binding free energy is the main such parameter. While some researchers focus on the enthalpy component of binding free energy [1–4], others suggest that the main obstacle to a satisfactory binding free-energy estimate is the difficulty in evaluation of its entropy component [5, 6].

Both components that make up the binding free energy (enthalpy and entropy) can in principle be estimated by methods of molecular dynamics [7, 8]. Enthalpy (or energy) can be estimated using various force fields (see, e.g., [9] and the literature quoted there). The entropy of binding can be assessed by tracing very long (until the establishment of thermodynamic equilibrium) molecular dynamics trajectory of motions of all atoms in the complex of bound molecules (e.g., in a protein-ligand complex), and then in these molecules taken separately [10].

In the models considering the solvent (water) by the explicit (atomic) view, this molecular-dynamics entropy takes into account both the configuration entropy of the molecules that form the complex and the entropy of the surrounding solvent [9]; in the models, where the solvent is presented in implicit form (as a medium), only the configuration entropy of the molecules that form the complex is considered, whereas the entropy of the solvent is included in the potentials of interatomic interactions, in particular hydrophobic and electrostatic ones (see [11–13] and the literature quoted there).

The configuration entropy, which is present in both model types, can also be estimated using other, approximate methods, based: on the variations in the side groups conformations (observed by X-ray and NMR in proteins [14–16] or obtained by optimizing these conformations using different force fields [17]), on an estimate of the molecule surface hidden from the water [18], or on the computation of either only elastic [19] or all [20] oscillation modes of a protein molecule and a ligand.

The main problem when using methods of molecular dynamics, along with an inaccuracy of the force fields used in the calculations, is the enormous computation time of the calculation. The enthalpy of an individual state (of a molecule or a complex) can be calculated rather quickly (using a given force field); in contrast, to calculate the entropy, it will be necessary to conduct a simulation up to the complete thermodynamic equilibrium of the entire ensemble of configu-
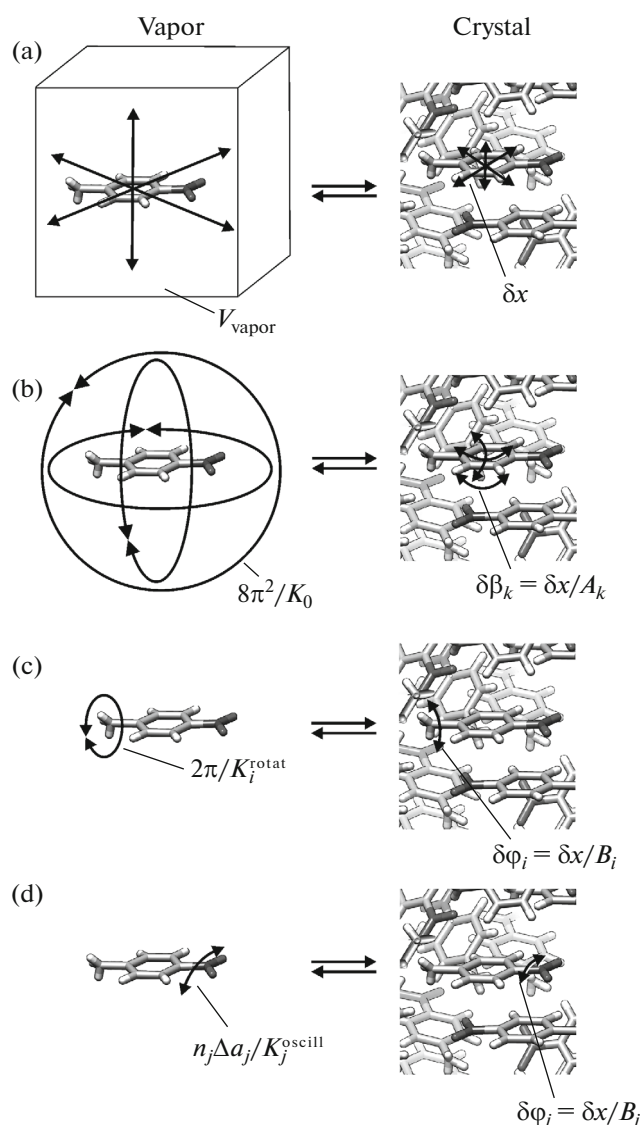
Fig. 1. Four types of molecular movements in vapor (left) and corresponding motions in a crystal, which are always oscillations restricted by neighboring molecules (right), considered in the sublimation entropy assessment. (a) Translational motions of the entire molecule in vapor and its corresponding movements (oscillations) in a crystal. (b) Rotational motions of the entire molecule in vapor and the corresponding oscillations in a crystal. (c) Free rotations around a covalent bond with a low potential barrier in vapor and the corresponding oscillations in a crystal. (d) Oscillations around a covalent bond with a high potential barrier in vapor and the corresponding oscillations in a crystal. V_{vapor} is the volume per molecule in vapor; δx is the molecule oscillation span in a crystal; the other expressions are explained in the description of formula (1).

rations, or at least a significant part of it (and of both complex and each molecule separately), which naturally requires a very large calculation time. The problem becomes even more complicated by the fact that the ligand and its binding site can be significantly deformed during the interaction process [5, 10, 21].

We have developed an alternative approach to the calculation of the molecule binding entropy or, more precisely, to the calculation of the configuration entropy of fixing a molecule in a complex (the solvent entropy, which plays an important role in force fields (see [3, 6, 9, 11−13]), is not the subject of this article). The approach is based on the consideration of those molecular motions which are allowed in the free state of the molecule, but are limited in its bound state (in a complex). Here, as in our previous work [22], we consider the reversible dissociation process of molecules from a crystal into vapor, i.e., the process of the sublimation of molecular crystals, as one of the simplest binding process variants.

In the previous works [22, 23], we calculated the average span (and amplitude of the molecule oscillations that correspond to this span) in the solid phase for a set of crystals of small organic molecules. In this paper, we use these average values along with the geometric characteristics of the molecules under consideration, as well as the values of the potential barriers for the rotation of atomic groups around the covalent bonds to calculate the sublimation entropy of crystals under the standard conditions (25°C, 1 atm). Earlier [22], we calculated the change in entropy of molecules for a set of 15 crystals under the conditions of the equilibrium transition from the crystal to the saturated vapor (thus, at saturated vapor pressure and not at atmospheric pressure); however, the additional experimental data on the vapor pressure at 25°C are needed for this calculation. These data are not required for calculation of the standard sublimation entropy, and it is possible to calculate it theoretically, then to compare the calculated values with the experimental data, assessing the accuracy of predictions, which yields the developed method.

RESULTS AND DISCUSSION

Theoretical Assessment of the Standard Binding Entropy

Since, by definition, the sublimation entropy (which is equal to the taken with the opposite sign entropy of binding of molecules by the crystal) is calculated as the difference in the entropy of the molecules in vapor and the same molecules in a crystal, we have assessed the molecular motions that are allowed for the free molecule but are restricted in the crystal by adjacent molecules and, therefore, are reduced to oscillations. These movements include [22, 23] the translational motions of the molecule as a whole (Fig. 1a), the rotation of the molecule as a whole (Fig. 1b), and two types of rotation around the covalent bonds (Figs. 1c, 1d), i.e., free or almost free rotations in the free molecule (Fig. 1c) and nonfree rotations, or rather oscillations in the free molecule (Fig. 1d).

The free or almost free rotation around a bond in the free molecule takes place in the case when the potential barrier of rotation around it in a free mole-

cule is less than $k_B T$ (being 0.6 kcal/mol at $T = 298$ K) [22]. The oscillations around a bond in a free molecule take place in the case of a high (greater than $k_B T$) potential barrier of rotation around it in a free molecule [22].

It should be noted that oscillations around the covalent bonds with very high barriers (>70 $k_B T$ [23]) may be not considered at all, since their magnitude, even in the free molecule, is so small that neighboring molecules in the crystal do not affect them, so they can be considered identical in the crystal and in the vapor and can be not taken into account in the calculation of the difference of entropies between the crystal and the vapor [22].

The same applies to the oscillations of the covalent bond lengths and valence angles: the magnitude of these oscillations is so small (less than the average amplitude of oscillations in crystals [22]) that the crystal does not affect them, and these movements can also be neglected in the calculation of the sublimation entropy [14, 22].

The binding entropy of a molecule by the crystal, equal to the sublimation entropy with the opposite sign, can be estimated as in [22] as shown below:

$$\Delta S_{\text{bind}} \equiv -\Delta S_{\text{subl}} \equiv S_{\text{crystal}} - S_{\text{vapor}}$$

$$= R \ln \left[\frac{\delta x_1 \delta x_2 \delta x_3}{V_{\text{vapor}} e} \right] + R \ln \left[\frac{\delta \beta_1 \delta \beta_2 \delta \beta_3}{\left(8 \pi^2 / K_0 \right)} \right] \quad (1)$$

$$+ R \sum_{i=1}^{n_{\text{rotat}}} \ln \left[\frac{\delta \varphi_i}{\left(2\pi / K_i^{\text{rotat}} \right)} \right] + R \sum_{j=1}^{n_{\text{oscill}}} \ln \left[\frac{\delta \varphi_j}{\left(n_j \Delta \alpha_j / K_j^{\text{oscill}} \right)} \right].$$

Here, R is the universal gas constant; the four summands correspond to the four types of considered movements in vapor, i.e., the translational motions of the whole molecule; the rotational motions of the whole molecule; the rotations around covalent bonds with barriers is less than $k_B T$; and the oscillations around covalent bonds with barriers greater than $k_B T$. The expressions that stand in the numerators refer to the crystal, and those that stand in the denominators refer to vapor.

The first term of Eq. (1) expresses a change in entropy of the translational motions of the molecule as a whole: δx_1, δx_2, and δx_3 are the spans of the motions for three translational degrees of freedom of the molecules in the crystal, that is, in the bound state (for simplicity, in the first approximation, we assume $\delta x_1 = \delta x_2 = \delta x_3 = \delta x$); the molecule in the crystal is limited by the volume of movement $V_{\text{crystal}} = \delta x_1 \delta x_2 \delta x_3$ and 1 mol of the molecules has entropy $R \ln(\delta x_1 \delta x_2 \delta x_3)$; $V_{\text{vapor}} = k_B T / P_{\text{vapor}}$ is the volume per molecule in vapor; under standard conditions (25°C, 1 atm), $T = T_0 = 298.15$ K, $P_{\text{vapor}} = P_0 = 101325$ Pa, and k_B is the Boltzmann constant (in the expression for vapor

entropy, $V_{\text{vapor}} e$ is used instead of V_{vapor} according to standard statistical physics; see also [22]).

The second term of Eq. (1) corresponds to the change in entropy of the rotations of the molecule as a whole, i.e., $\delta \beta_1$, $\delta \beta_2$, and $\delta \beta_3$ are the spans of oscillations of angles (in radians) during the rotation of the whole molecule in three rotational degrees of freedom in the crystal. It is reasonable to assume $\delta \beta_k = \delta x / A_k$, where A_1, A_2, and A_3 are three maximal radii of the studied molecule computed from its spatial structure; the result of multiplication $A_1 A_2 A_3$ is estimated as $A_1 A_2 A_3 = \max_i \{ |\mathbf{r}_i| \max_j (|\mathbf{r}_j \times \mathbf{r}_i|) \}$ [22], where the radius-vectors $\mathbf{r}$ of all atoms of the molecule are measured from its center of gravity and all i atoms of the molecule have unit weight. K_0 is the degeneracy (because of symmetry of the molecule) of rotation of the free molecule as a whole.

The third term in Eq. (1) corresponds to the losses of entropy of the rotation around the covalent bonds with low (less than $k_B T$) torsion barriers [22]: in this case, there is free or almost free rotation around this covalent bond in vapor. Here, n_{rotat} is the number of covalent bonds with the free or almost free rotation in the molecule, and $\delta \varphi_i$ is the spans of oscillations of angles (also in radians) in rotation around a covalent bond i, which is limited and becomes the oscillation in the crystal; it is reasonable to assume $\delta \varphi_i = \delta x / B_i$, where B_i is the maximal radius of the smallest (i.e., having the smallest maximal radius) of the groups rotating around the bond i; the maximal radius of each of the two groups connected by the valence bond is calculated as $B_i' = \max_m (|\mathbf{r}_m \times \mathbf{r}_i| / |\mathbf{r}_i|)$, where $\mathbf{r}_i$ is the vector of the valence bond i, and $\mathbf{r}_m$ are the radius vectors (calculated from this bond) of those atoms of this group, which are rigidly connected with the atom that forms the valence bond i); K_i^{rotat} is the degeneracy of the corresponding rotation around the bond i in a free molecule due to symmetry of the rotating groups.

The fourth term in Eq. (1) corresponds to the loss of entropy of the oscillation around the covalent bonds that have a high (more than $k_B T$) torsion barrier [22], and thus, free rotation around them is not allowed even in the free state of the molecule. Here,

n_{oscill} is the number of such covalent bonds in the molecule;

$\delta \varphi_j = \delta x / B_j$ is the spans of oscillations of angles (in radians) around a covalent bond j in the crystal, where B_j (similar to B_i, see above) is the maximal radius of the smallest of the groups which rotate around the bond j;

n_j is the number of energy minima for rotation around the bond j in a free molecule. Usually, $n_j = n_j^0$ (where n_j^0 is the multiplicity of the torsion potential

$E(\alpha) = \gamma_j\{1 - \cos[n_j^0(\alpha - \alpha_0)]\}$, which creates torsion barriers with the height of $2\gamma_j$); however, $n_j < n_j^0$ if the energy of some of the torsion potential minima (which correspond to $\alpha = \alpha_0$, $\alpha_0 + \dfrac{2\pi}{n_j^0}$, $\alpha_0 + 2\dfrac{2\pi}{n_j^0}$, $\alpha_0 + 3\dfrac{2\pi}{n_j^0}$, …) is increased by nonvalent interactions, like, e.g., in the case of the energy of peptide bond *cis*-rotamer. However, these cases are not noted among the molecules considered in this work;

K_j^{oscill} is the degeneracy (due to the symmetry) of the corresponding rotation around the bond j in a free molecule;

$\Delta\alpha_j$ is the movement span in each of the potential wells of the rotation around the bond j in a free molecule. Given the parabolic approximation for the shape of the energy well of the torsion potential, $E(\alpha) \approx \dfrac{\gamma_j(n_j^0)^2}{2}(\alpha - \alpha_0)^2$ in the region of energy minima, and standard formula for thermal oscillations in the well (see [24]),

$$\Delta\alpha_j \approx \sqrt{2\pi e\, RT \big/ [\gamma_j(n_j^0)^2]}, \qquad (2)$$

where the γ_j value is expressed in the same units as RT, i.e., in kcal/mol or kJ/mol.

Thus, the standard entropy ($T_0 = 298.15$ K, $P_0 = 101325$ Pa) of binding of a vapor molecule to a crystal can be calculated as

$$(\Delta S_{\mathrm{bind}}^0)_{\mathrm{calc}} = S_{\mathrm{crystal}} - S_{\mathrm{vapor}}^0$$

$$= R\ln\left[\frac{\delta x^3}{ek_B T_0/P_0}\right] + R\ln\left[\frac{\delta x^3/A_1 A_2 A_3}{8\pi^2/K_0}\right] \qquad (3)$$

$$+ R\sum_{i=1}^{n_{\mathrm{rotat}}}\ln\left[\frac{\delta x/B_i}{2\pi/K_i^{\mathrm{rotat}}}\right] + R\sum_{j=1}^{n_{\mathrm{oscil}}}\ln\left[\frac{\delta x/B_j}{n_j\Delta\alpha_j/K_j^{\mathrm{oscill}}}\right].$$

The δx value (the average span of 0.75 ± 0.14 Å, where $\sigma = 0.14$ Å is the standard deviation) of each movement of a molecule in the crystal, which exceeds the average amplitude of the oscillation of 0.18 ± 0.03 Å by $\sqrt{2\pi e} \approx 4.13$ times, was calculated in our previous work [22]; $\Delta\alpha_j$ is calculated according to formula (2), and all values needed for this and other calculations are taken from the geometric characteristics of a studied molecule as in [22, 23].

Experimental Assessment of the Standard Binding Entropy

We compared the calculated standard entropies of the vapor molecules binding by the crystals with the experimental data to assess the quality of the entropy calculations carried out by our method.

Our previously collected A2 database on small molecules [12, 13, 25, 26] contains the experimental data we need, including the enthalpy of sublimation and the saturated vapor pressure. The spatial structure of molecular crystals were taken from the Cambridge Structural Database, CSD [27], and the torsion potentials required for calculations were taken from the ENCAD force field [28].

We selected from the database A2 (see Table S1 in the supplementary material of [23]) containing 61 substances, those substances which crystals melt at temperature above +25°C, i.e. the substances which are crystals at the considered in this work standard conditions, and thus, extrapolations to +25°C are not needed (these extrapolations could lead to significant errors). 34 substances match this requirement (see Table 1), but six of them were excluded from our further calculations because very large differences were found in the experimental data for these substances obtained from different but equally reputable sources (see Table 1 and [23]).

Eventually, 28 crystals of small organic molecules were selected for the work. It should be noted that almost all of these molecules contain cycles (see Table 2) and, therefore, represent rather rigid structures; whereas crystals of flexible molecules, such as alkanes, were culled since they melt at temperatures well below 0°C (see Table S1 in the supplementary material of [23]), and thus, the extrapolation of their experimentally derived thermodynamic parameters to a standard temperature of +25°C entails significant uncertainties, and therefore, for these substances, we cannot properly evaluate the quality of our predictions.

Table 1 summarizes the experimental data on the sublimation enthalpies of these crystals (ΔH_{subl}) at 25°C in order to obtain the entropy of sublimation of the crystal $\Delta S_{\mathrm{subl}} = \Delta H_{\mathrm{subl}}/T$ at 25°C and pressure P_{vapor} (also given in Table 1) of the saturated vapor, which is in thermodynamic equilibrium with the crystal.

Assuming that gas is close to ideal at low vapor pressure (see Table 1), we can obtain the standard (that is, at the temperature $T_0 = 298.15$ K (+25°C) and pressure $P_0 = 101325$ Pa (1 atm)) entropy of binding molecules by the crystal $(\Delta S_{\mathrm{bind}}^0)_{\mathrm{experim}}$ from the experimental values according to

$$(\Delta S_{\mathrm{bind}}^0)_{\mathrm{experim}} = -\Delta H_{\mathrm{sublim}}/T + R\ln\left(P_0/P_{\mathrm{vapor}}\right). \qquad (4)$$

Comparison of Calculations with the Experimental Data

Thus, we have calculated the theoretical standard entropy of binding $(\Delta S_{\mathrm{bind}}^0)_{\mathrm{calc}}$ based on formula (3) and compared the results of these calculations with the experimental standard entropy of binding $(\Delta S_{\mathrm{bind}}^0)_{\mathrm{experim}}$ defined by formula (4) for 28 crystals. The data used to

Table 1. Thermodynamic data for the sublimation of crystals melting at temperature above 25°C

#	T_{melt}	$\langle \Delta H \rangle = \Delta H_{subl}$	ΔH_{min}	ΔH_{max}	$\pm\delta\Delta H/RT$	$\langle P \rangle_{geom} = P_{vapor}$	P_{min}	P_{max}	$\pm\delta\ln(P)$	$\dfrac{-(\Delta S^0_{bind})_{experim}}{R}$
7	60.3	56.0	55.6	56.6	1.1	1731.5	1730	1733	0.001	18.56
9	119.0	80.7	80.7	80.7	0.64	1.39	0.20	4.02	1.37	21.41
11	54.4	75.2	74.6	75.8	0.36	147	79.59	210.0	0.44	23.85
18	115.7	65.2	62.8	68.6	1.0	16.1	13.3	19.58	0.44	17.60
20	44.8	72.8	72.3	73.3	0.25	14.17	13.33	15.06	0.06	20.54
22	40.9	68.9	68.6	69.7	0.25	45.77	44.7	46.83	0.02	20.14
23	172.3	97.1	94.1	103.8	1.6	0.00818	0.0024	0.089	1.69	*
24	71.2	89.0	88.3	89.7	0.28	0.21	0.12	0.36	0.55	22.87
25	114.0	96.8	96.0	98.0	0.31	0.017	0.0031	0.123	1.52	23.49
26	146.0	101.0	100.0	102.0	0.4	0.015	0.00043	0.43	2.83	*
28	69.2	88.5	87.3	89.8	0.50	0.25	—	—	—	22.86
31	171.0	99.1	94.3	102.2	1.84	0.0101	—	—	—	23.92
32	148.0	91.6	87.7	97.1	1.22	0.55	0.197	1.54	0.6	24.89
33	51.6	78.0	74.8	79.1	1.09	5.2	2.09	21.86	1.09	21.64
35	29.8	75.4	73.7	76.0	0.39	39.95	39.9	40.0	0.001	22.63
36	35.5	73.7	73.1	73.9	0.36	14.6	—	—	—	20.93
40	72.8	84.0	84.0	84.0	0.28	6.42	3.49	11.86	0.61	24.27
41	74.8	84.8	84.6	85.0	0.11	9.02	3.93	20.8	0.83	24.94
42	45.7	75.4	75.1	75.6	0.10	29.4	23.62	36.5	0.22	22.34
43	60.8	85.4	85.0	85.8	0.14	2.96	1.84	4.78	0.48	24.06
45	26.5	77.1	73.8	80.4	1.3	7.49	6.06	9.25	0.21	21.65
47	80.2	72.0	70.4	73.0	0.8	11.1	10.9	11.3	0.02	19.97
49	83.0	81.0	76.5	84.4	1.2	0.88	0.33	2.33	0.98	21.07
50	98.5	91.5	85.1	97.5	1.8	0.0086	0.00273	0.0273	0.97	*
51	246.2	101.0	97.7	103.2	1.07	0.00255	0.000183	0.0355	2.63	*
52	185.0	104.0	86.0	114.5	3.6	0.00041	0.00012	0.00140	1.07	*
53	93.4	85.0	83.4	86.0	0.49	0.316	0.3	0.3333	0.05	21.67
54	69.0	81.3	77.9	82.9	0.81	1.26	1.19	1.333	0.06	21.55
55	114.8	84.6	80.2	87.6	1.3	0.136	0.043	0.432	1.1	20.66
56	215.0	97.9	84.0	104.5	2.9	0.0083	0.00087	0.08	2.26	*
57	99.2	90.3	86.6	92.5	0.98	0.038	0.0161	0.091	0.87	21.69
58	123.0	100.5	98.0	102.0	1.9	0.1173	—	—	—	26.94
59	107.8	100.1	99.2	102.0	0.73	0.00115	0.001084	0.001229	0.06	22.15
60	151.2	101.0	98.5	104.5	1.30	0.0006	—	—	—	21.86

See [25, 26] for list of references. Here, # denotes the substance number in our complete database [25, 26]; T_{melt} is the melting temperature, °C; ΔH is sublimation enthalpy (in kJ/mol, at 25°C): $\langle \Delta H \rangle$ is the arithmetic mean, ΔH_{min} and ΔH_{max} are the minimal and maximal ΔH values, respectively, according to the literature data; the dimensionless quantity $\pm\delta\Delta H/RT$ is the average ΔH error expressed in units of RT at $T = 298.15$ K (25°C); P is the saturated vapor pressure (in Pa at 25°C); $\langle P \rangle_{geom}$ is the geometric mean; P_{min} and P_{max} are the minimal and maximal P values, respectively, according to the literature data; the dimensionless quantity $\pm\delta\ln(P)$ is the average $\ln(P)$ error; and $(\Delta S^0_{bind})_{experim}$ is the standard sublimation entropy obtained from the experimental data by formula (4). * The substances for which very large differences between the observed experimental values ($|\delta\Delta H/RT| + |\delta\ln(P)| > 2.5$)) are presented for the same substance in different authoritative sources are shaded in gray.

Table 2. Geometric and energetic parameters associated with the free rotation of entire molecules and their individual groups
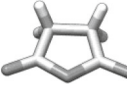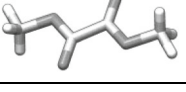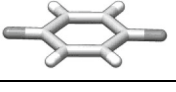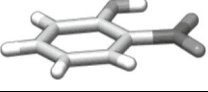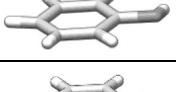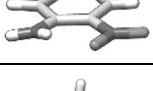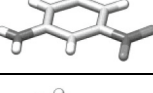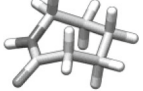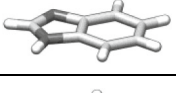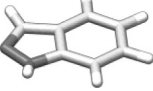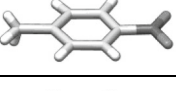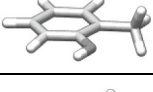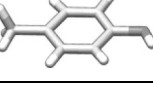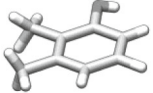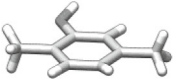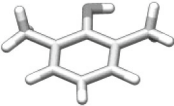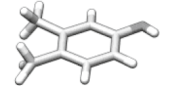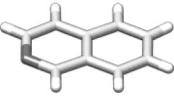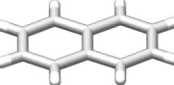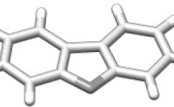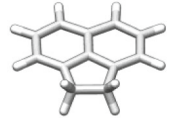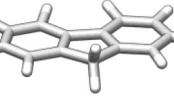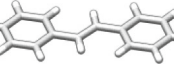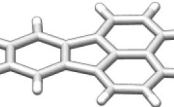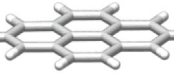
No.	Name of the compound	Molecular structure	CSD code [27]	K_0	$A_1A_2A_3$, Å^3	n_{rotat}	γ_i, kcal/mol [28]	B_i, Å	K_i^{rotat}
7	Trioxane		TROXAN11	12	11.57	0	–	–	–
9	Succinic anhydride		SUCANH13	2	14.58	0	–	–	–
11	Dimethyloxalate		DMEOXA01	2	24.42	0	–	–	–
18	p-Benzoquinone		BNZQUI03	4	14.69	0	–	–	–
20	2-Nitrophenol		ONITPH	1	24.16	0	–	–	–
22	Phenol		PHENOL03	2	18.07	0	–	–	–
24	o-Nitroaniline		ONITAN	1	29.97	0	–	–	–
25	m-Pitroaniline		MNIANL03	1	33.46	0	–	–	–
28	Caprolactam		CAPLAC	2	23.30	0	–	–	–
31	1h-Benzimidazole		BZDMAZ02	2	30.06	0	–	–	–
32	1h-Indazol		INDAZL	1	26.46	0	–	–	–
33	p-Nitrotoluene		NITOLU	2	34.38	1	0.1	1.03	3
35	o-Cresol		OCRSOL	1	30.16	1	0.1	1.03	3
36	p-Cresol		CRESOL01	1	35.56	1	0.1	1.03	3
40	2,3-Xylenol		DIMPHE12	1	34.73	2	0.1	1.03	3

Table 2. (Contd.)

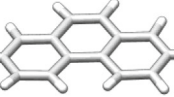| No.	Name of the compound	Molecular structure	CSD code [27]	K_0	$A_1A_2A_3$, Å³	n_{rotat}	γ_i, kcal/mol [28]	B_i, Å	K_i^{rotat}
41	2,5-Xylenol		DMPHOL11	1	37.33	2	0.1	1.03	3
42	2,6-Xylenol		DMEPOL10	2	33.83	2	0.1	1.03	3
43	3,4-Xylenol		DPHNOL10	1	41.20	2	0.1	1.03	3
45	Isoquinoline		BERXOL	1	37.04	0	–	–	–
47	Naphthalene		NAPHTA10	4	30.88	0	–	–	–
49	Dibenzofuran		DBZFUR11	2	55.25	0	–	–	–
53	Acenaphthene		ACENAP03	2	50.32	0	–	–	–
54	Biphenyl		BIPHEN04	4	55.75	0	–	–	–
55	Fluorene		FLUREN01	2	63.32	0	–	–	–
57	Phenanthrene		PHENAN08	2	65.14	0	–	–	–
58	Trans-stilbene		TSTILB10	2	93.89	0	–	–	–
59	Fluoranthene		FLUANT02	2	83.17	0	–	–	–
60	Pyrene		PYRENE02	2	71.16	0	–	–	–

Table 3. Geometric and energetic parameters associated with the oscillations of individual groups in the molecules

| No.	Type-1 bond in the molecule					Type-2 bond in the molecule					Type-3 bond in the molecule				
	n_{oscill}	γ_i, kcal/mol [28]	B_j, Å	n_j	K_j^{oscill}	n_{oscill}	γ_i, kcal/mol [28]	B_j, Å	n_j	K_j^{oscill}	n_{oscill}	γ_i, kcal/mol [28]	B_j, Å	n_j	K_j^{oscill}
7	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
9	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
11	2	0.6	1.03	3	3	2	1.8	1.35	2	1	1	10	1.35	2	2
18	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
20	1	10	1.06	2	2	1	1.65	0.94	2	1	0	–	–	–	–
22	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
24	1	10	1.06	2	2	1	10	0.87	2	2	0	–	–	–	–
25	1	10	1.06	2	2	1	10	0.87	2	2	0	–	–	–	–
28	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
31	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
32	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
33	1	10	1.07	2	2	0	–	–	–	–	0	–	–	–	–
35	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
36	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
40	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
41	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
42	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
43	1	1.65	0.94	2	1	0	–	–	–	–	0	–	–	–	–
45	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
47	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
49	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
53	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
54	1	20	2.15	2	2	0	–	–	–	–	0	–	–	–	–
55	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
57	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
58	2	10	2.15	2	2	1	10	5.26	2	1	0	–	–	–	–
59	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
60	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–

calculate $(\Delta S_{\text{bind}}^0)_{\text{calc}}$ are in Tables 2 and 3, and the experimental data for $(\Delta S_{\text{bind}}^0)_{\text{experim}}$ are in Table 1.

A comparison of the predicted values with the experimental values is shown in Fig. 2.

The correlation coefficient of the predicted and experimental values is 65%. It is not very high, but we must bear in mind that this correlation coefficient refers to relatively small differences in the standard entropy of sublimation of different molecules, while the average standard entropy of sublimation for all of these molecules is estimated with a very high accuracy. Indeed, the average theoretically estimated value of $\left\langle -(\Delta S_{\text{bind}}^0)_{\text{calc}}/R \right\rangle = 21.7$ (and the standard deviation

of the $-(\Delta S_{\text{bind}}^0)_{\text{calc}}/R$ value from the average is $\sigma = \pm 1.9$ so that the average $\left\langle -(\Delta S_{\text{bind}}^0)_{\text{calc}}/R \right\rangle$ is determined with an accuracy of ± 0.4, which is calculated as usual as $\sigma/\sqrt{n}$, where $n = 28$ is the size of our sample. The average experimental value is $\left\langle -(\Delta S_{\text{bind}}^0)_{\text{experim}}/R \right\rangle = 22.1$; the standard deviation is ± 2.0, so the value $\left\langle -(\Delta S_{\text{bind}}^0)_{\text{experim}}/R \right\rangle$ is determined with an accuracy of ± 0.4). Therefore, there is no systematic error in our calculation. The average discrepancy between the calculated and experimental values is $\left\langle \left| (\Delta S_{\text{bind}}^0)_{\text{calc}}/R - (\Delta S_{\text{bind}}^0)_{\text{experim}}/R \right| \right\rangle = 1.3$, and the
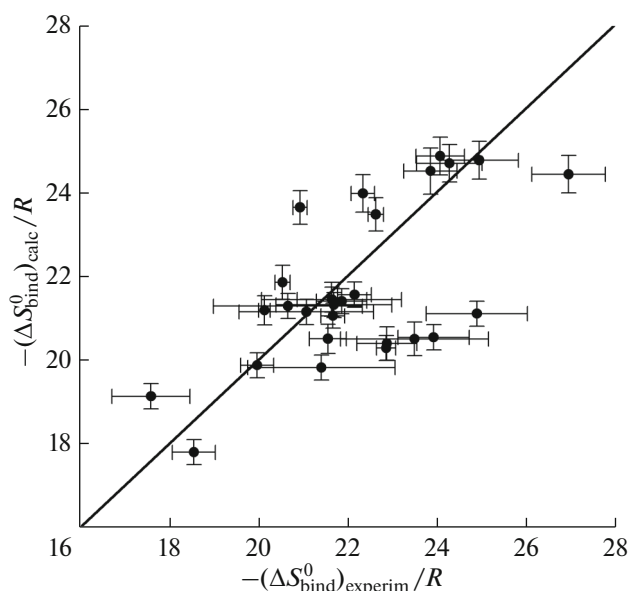
Fig. 2. Comparison of calculated $(\Delta S^0_{bind})_{calc}$ and experimental $(\Delta S^0_{bind})_{experim}$ standard entropy of binding of a vapor molecule by a crystal. Diagonal corresponds to $(\Delta S^0_{bind})_{calc} = (\Delta S^0_{bind})_{experim}$, i.e., to the ideal prediction.

discrepancy normalized to the experimental value is $\left\langle \left(\left| (\Delta S^0_{bind})_{calc} - (\Delta S^0_{bind})_{experim} \right| \right) / (\Delta S^0_{bind})_{experim} \right\rangle =$ 0.056. Thus, the average relative error of our standard binding entropy calculations is only 5.6%.

In contrast to the equilibrium sublimation entropy considered in our previous works [22, 23], the standard entropy of binding (the same as taken with the opposite sign sublimation entropy at standard conditions: 25°C and 1 atm), depends only on the mobility restriction of molecules in crystals, but does not depend on the density of saturated vapor of these molecules.

Therefore, the standard entropy of binding considered here reflects the physics of binding molecules in a crystal more accurately; however, it correlates with the experimental data notably worse than the equilibrium sublimation entropy does (the correlation of the calculations with experiment for the same set of molecules is 65% in the case of the standard sublimation entropy and 94% in the case of equilibrium sublimation entropy [23]). This difference can be because a large experimental value of the vapor pressure logarithm is already included in the calculation of the equilibrium sublimation entropy [22, 23], which correlates with the equilibrium sublimation entropy at a level of 90% *per se*.

We can conclude that the developed method allows doing successful calculations of both the standard configuration entropy of small organic molecule binding in crystals and, in particular, the equilibrium

entropy of their binding which is directly included in the binding constant of a molecule with a crystal [23].

This is the basis for hopes that the proposed fast method can be applied to interesting biological phenomena, e.g., to calculating the configuration entropy of ligand binding with proteins. For a quick evaluation of the contribution of the enthalpy of all interactions and the contribution of the solvent's entropy to the free energy of binding of molecules (and, therefore, their contribution to the binding constant), one can use, e.g., the previously developed force field PFFsol1.1, which enables a fast calculation of the molecular interactions in an implicitly specified water environment [13].

ACKNOWLEDGMENTS

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