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Hydrophobic Indexes for Various Monosaccharides

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The hydrophobic and the hydrophilic surface areas of seven kinds of monosaccharide molecules were calculated by using Hermann's method. The hydrophobic indexes (Index A and Index B) which are defined as the ratio of the hydrophobic and the hydrophilic surface areas of the molecule are clearly correlated with the partition coefficient of monosaccharide between polystyrene gel and water, and the free energy change of transfer of monosaccharide from water to 1-butanol, indicating that the fraction of the hydrophobic surface area plays an important role in the interaction of monosaccharides and hydrophobic solutes in water.

Sugar has so far been regarded as a typical hydrophilic nonelectrolyte like urea. Generally sugars have nearly the same numbers of CH groups as OH groups in a molecule, and the hydration behavior of monosaccharide has been discussed in terms of the orientation of OH groups of hexopyranose ring.[1]

Recently several evidences have been revealed on the hydrophobic character of saccharides. Various saccharides are partitioned to polystyrene gel from aqueous phase.[2–4] The partition coefficients obtained from the gel chromatography using polystyrene gel as a stationary phase are different from each other irrespective of the same molecular formula and the same configuration (Cl), *i.e.* D-glucose, D-galactose, and D-mannose. The partition coefficients increase with the concentration of structure making salts such as NaCl, and decrease with increase of the concentration of structure breaking salt, NaSCN.[3] Inversely, cyclohexane is adsorbed by Sephadex gel, which is the polymer of D-glucose.[5]

On the other hand, the condensed ring compounds of D-glucose, such as cyclodextrins, include the hydrophobic solute in their cavities and the inner wall of the cavity has been regarded as hydrophobic.[6]

These experimental results seem to indicate that the saccharide molecule has the hydrophobic character even if it is considerably weak, because the interactions mentioned above may be hydrophobic.

In order to confirm that the nature of interactions mentioned above are hydrophobic, we investigated the correlation between the partition coefficients[3] and the surface area ratio of hydrophobic and hydrophilic groups for various monosaccharides molecules. For the partitioning of saccharide to polystyrene gel phase from aqueous phase may be mainly based on the adsorption of saccharide molecules onto the phenyl groups of polystyrene through hydrophobic interaction and the hydrophobic character of saccharides may possibly originate from the hydrophobic surface formed by the CH and CH_2 groups of monosaccharide molecules.[3,4] From these viewpoints, we calculated the hydrophobic and hydrophilic surface areas of seven kinds of monosaccharide molecules, on the assumption that the hydrophobic surface area is the area occupied by CH and CH_2 groups at a distance of 1.4 Å above the atom surface. Combining this area with the total surface area, the hydrophilic surface area is also obtained. Good correlations between the surface area ratio of hydrophobic and hydrophilic groups and the partition coefficients or the free energy of transfer were obtained.

Experimental

Calculation of Surface Area: Surface area of monosaccharides was calculated basically by the computer program QCPE 225 MOLAREA developed by Hermann.[7] The atomic coordinates mainly obtained from the X-ray data except for ribofuranose were used in the calculation. For the furanose-type saccharides, furanose ring was assumed to be planar and the atomic coordinates were obtained from usual bond lengths and bond angles. The van der Waals radii were used as the radii of the atoms. The surface area at a distance of 1.4 Å above the spherical atom surface was calculated on the assumption that the radius of water molecule is 1.4 Å. Since the OH groups of monosaccharide molecule rotate around the C–O axis, the OH group was approximated to the sphere with the radius of 1.72 Å.

Definition of Hydrophobic Area: Total hydrophobic surface area was defined as the area occupied by CH and CH_2 groups of monosaccharide. The hydrophilic surface area is the area occupied by OH and -O- groups and corresponds to the difference between total surface area and hydrophobic surface area.

Monosaccharide molecule is approximated to a disk which has two surfaces. The two surfaces of monosaccharide molecule are in general not equivalent in their hydrophobic areas, the one is richer in CH and CH_2 groups than the other.

For the calculation of the hydrophobic surface area of CH-rich surface (specified hydrophobic surface area), we first selected the CH and CH_2-rich surface from the molecular model and specified hydrophobic surface area occupied by the specified carbon and hydrogen atoms was calculated under the following conditions.

1) For the β-axial CH and CH_2 groups, the specified hydrophobic surface area is equal to the calculated area.

2) For the α-axial and α-equatorial CH and CH_2 groups, the specified hydrophobic surface area is zero.

3) For β-equatorial CH and CH_2 groups, the specified hydrophobic surface area is half the calculated area.

4) The specified hydrophobic surface area of monosaccharide molecule is the sum of the area obtained from 1) and 3).

For the calculation of the surface area of ribofuranose, we assumed that the five membered ring of furanose is planar. Therefore, every OH group attached to furanose ring belongs to either α- or β- type. In this case, the specified hydrophobic surface area of β-CH or CH_2 group was assumed to be the calculated area and that of α-CH or CH_2 group zero. The same criterion was applied to the calculation of the specified hydrophobic surface area of 2-deoxy-D-ribofuranose. Definition of the hydrophobic index: As an expression of hydrophobicity of a compound, the value of hydrophile-lipophile balance(HLB) is frequently used in the physical chemistry of surfactants. HLB value is originally the mass ratio of the hydrophilic and the lipophilic groups. In the similar manner, we defined the hydrophobic index (Index) as the surface area ratio instead of the mass ratio, because aldohexopyranoses, *i.e.* glucose, galactose and mannose, have the same mass ratio of hydrophobic and hydrophilic groups in this treatment.

The hydrophobicity of α- and β-anomers of monosaccharide A, index A_α and A_β, are defined by Eqs. 1 and 2, respectively. The index of monosaccharide A is the sum of indexes of each anomer.

$$\text{Index } A_\alpha = \frac{\text{Total hydrophobic surface area } (\alpha)}{\text{Total hydrophilic surface area } (\alpha)} \times \alpha\text{-anomer } \% \tag{1}$$

$$\text{Index } A_\beta = \frac{\text{Total hydrophobic surface area } (\beta)}{\text{Total hydrophilic surface area } (\beta)} \times \beta\text{-anomer } \% \tag{2}$$

$$\text{Index A} = \text{Index } A_\alpha + \text{Index } A_\beta \tag{3}$$

Since D-ribose and 2-D-deoxyribose have six and four isomers, respectively, indexes of these saccharides were calculated by the extention of the above treatment.

The indexes B_α and B_β were calculated by the similar equations to those of index A_α and A_β using the specified hydrophobic surface area instead of total hydrophobic surface area. Index B was defined as the sum of index B_α and B_β.

Results and Discussion

The results are shown in Tables 1 and 2. Funasaki *et al.*[8] correlated the hydrophobic surface area with hydrophobic interaction for oligoethylene glycol diethers and diesters. First we investigated the correlation between the average total hydrophobic surface area ($=\Sigma$ hydrophobic surface area$\times$anomer fraction) and the partition coefficients of monosaccharides (K_{av}) obtained from the polystyrene gel-water chromatography by Janado.[3] The magnitude of K_{av} increases in the order galactose<glucose<mannose<arabinose<xylose<ribose<deoxyribose. However the magnitude of the average total hydrophobic surface area calculated from the data of Table 1 lies in the order xylose<arabinose<glucose<mannose<galactose<ribose<deoxyribose, which is quite different from the order of magnitude of K_{av}.

On the other hand, the mangitude of average specified hydrophobic surface area ($=\Sigma$ specified hydrophobic surface area$\times$anomer fraction) lies in the order arabinose<xylose<mannose<galactose<glucose<ribose<deoxyribose. This order is also different from that of K_{av}. These results would be reasonable, because the hydrophobicity of the molecule depends on both the sizes of hydrophobic and the hydrophilic groups of the molecule as seen in the HLB values of the surfactants. It is reasonable to assume as a first approximation that the strength of hydrophobicity and hydrophilicity of a saccharide molecule depends on the dimensions of the surface area of hydrophobic and hydrophilic groups, respectively, because the hydrophilic groups are mainly OH groups except an ether oxygen group and hydrophobic groups are aliphatic CH or CH_2 groups.

Based on this idea, we calculated the hydrophobic index A (Index A) as shown in Table 1. From the definition of index, the larger the index is the stronger the hydrophobicity. Therefore, the order of hydrophobicity lies in the order, glucose<galactose<mannose<xylose<arabinose<ribose<deoxyribose. The reversing of the order is observed at glucose-galactose and arabinose-xylose as compared with the order of K_{av}. The dependences of K_{av} and log K_{av} on index A are shown in Figs. 1 and 2, respectively. Almost a linear relation is observed between index A and K_{av}. But a nonlinear relation is obtained between index A and log K_{av}. However index A increases with K_{av}. The relation between index A and the relative free energy of transfer of monosaccharide from water to 1-butanol, ΔG^{tr}[4] (galactose as a standard), is shown in Fig. 3. The negative value of ΔG^{tr} increases nonlinearly with index A. From Figs. 2 and 3, free energy of interaction of monosaccharide with hydrophobic compound is correlated nonlinearly with index A, because $RT \log K_{av}$ (R: the gas constant, T: absolute temperature) gives the energy dimension.

Based on the idea that the CH-rich surface interacts with hydrophobic solute, we calculated the index B by using the specified hydrophobic surface area instead of the total hydrophobic surface area. Therefore the index B refers to the preferential interaction of the CH-rich surface and hydrophobic solute. As seen in Table 2, index B lies in the order galactose<glucose<arabinose<mannose<xylose<ribose<deoxyribose. As compared with the order of K_{av}, the position of mannose is replaced by arabinose.

Table 1. Indexes A of various monosaccharides

Compounds	Conformation	Position of OH 12345	Anomer %	Total hydrophobic area (A^2)	Total hydrophilic area (A^2)	Index A
α-D-Glucose	C1 (G-G)	aeeee	36	97.1	243.3	38.7
β-D-Glucose	C1 (G-G)	eeeee	64	95.1	250.5	
α-D-Galactose	C1 (G-T)	aeeae	36	100.6	238.8	40.6
β-D-Galactose	C1 (G-T)	eeeae	64	98.1	247.0	
α-D-Mannose	C1 (G-G)	aaeee	68	97.1	231.4	42.0
β-D-Mannose	C1 (G-G)	eaeee	32	101.1	240.8	
α-D-Arabinose	1C	eeaa	63	100.7	193.4	48.1
β-D-Arabinose	1C	aeaa	34	93.3	206.9	
α-D-Xylose	C1	aeee	33	94.8	206.3	44.1
β-D-Xylose	C1	eeee	67	92.8	213.5	
α-D-Ribopyranose	1C	eaea	20	101.9	193.6	51.9
α-D-Ribopyranose	C1	aeae		105.2	189.9	
β-D-Ribopyranose	1C	aaea	56	94.5	207.2	
β-D-Ribopyranose	C1	eeae		109.2	189.3	
α-D-Ribofuranose	Plane	ααα*β*	6	105.8	203.0	
β-D-Ribofuranose	Plane	βααβ	18	95.2	215.3	
2-Deoxy-α-D-ribopyranose	1C	e ea	70	130.7	152.0	75.7
2-Deoxy-β-D-ribopyranose	1C	a ea		119.8	170.2	
2-Deoxy-α-D-ribofuranose	Plane	α αβ	30	123.9	176.3	
2-Deoxy-β-D-ribofuranose	Plane	β αβ		122.6	176.3	

G: Gauch, T: Trans, a: axial, e: equatorial.

Table 2. Indexes B of various monosaccharides

Compounds	Specified hydrocarbon atoms	Specified hydrophobic area (A^2)	Index B
α-D-Glucose	3*, 5, (1/2·6)	46.3	20.9
β-D-Glucose	1, 3, 5, (1/2·6)	57.3	
α-D-Galactose	3, (1/2·4), 5, (1/4·6)	36.2	20.2
β-D-Galactose	1, 3, (1/2·4), 5, (1/4·6)	56.6	
α-D-Mannose	(1/2·2), 3, 5, (1/2·6)	44.0	21.8
β-D-Mannose	1, (1/2·2), 3, 5, (1/2·6)	67.5	
α-D-Arabinose	1, (1/2·4), (1/2·5)	46.2	21.7
β-D-Arabinose	(1/2·1), 2, (1/2·3), (1/4·5)	39.4	
α-D-Xylose	(1/2·1), 2, 4, (1/4·5)	48.5	22.3
β-D-Xylose	1, 3, (1/2·5)	45.7	
α-D-Ribopyranose (1C)	1, (1/2·2), 3, (1/2·4), (1/2·5)	69.4	26.7
α-D-Ribopyranose (C1)	(1/2·1), 2, (1/2·3), 4, (1/4·5)	59.9	
β-D-Ribopyranose (1C)	(1/2·2), 3, (1/2·4), (1/2·5)	48.8	
β-D-Ribopyranose (C1)	2, (1/2·3), 4, (1/4·5)	43.2	
α-D-Ribofuranose	1, 2, 3, (1/2·5)	68.8	
β-D-Ribofuranose	2, 3, (1/2·5)	52.7	
2-Deoxy-α-D-ribopyranose	1, (1/4·2), 3, (1/2·4), (1/2·5)	77.1	38.3
2-Deoxy-β-D-ribopyranose	(1/4·2), 3, (1/2·4), (1/2·5)	53.43	
2-Deoxy-α-D-ribofuranose	1, (1/2·2), 3, (1/2·5)	67.1	
2-Deoxy-β-D-ribofuranose	(1/2·2), 3, (1/2·5)	45.5	

*: Integer means the position of carbon atom.

As shown in Fig. 4, an almost linear relation is obtained between index B and K_{av}. The order of K_{av} is better correlated to that of index B than that of index A. As shown in Figs. 5 and 6, index B is nonlinearly correlated with log K_{av} and ΔG^{tr}.

We cannot judge from the above results which index is more closely correlated to the thermodynamic data. Judging from the fact that monosaccharide molecule rotates at considerably fast rate in aqueous solution, index A may be more plausible than index B.

The partition coefficients of monosaccharides between active charcoal and water[9] were not correlated to these indexes, indicating that the negatively charged surface of active charcoal may

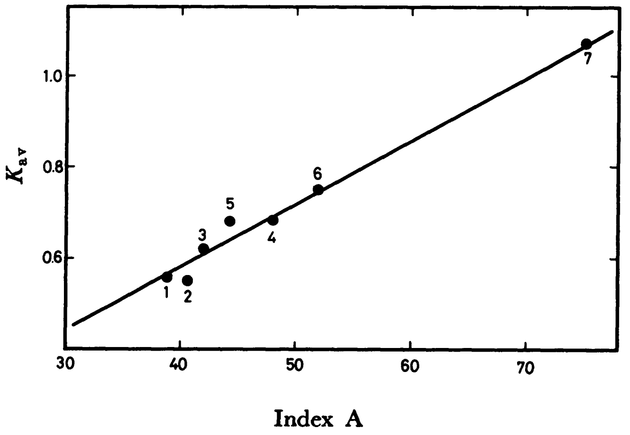

Fig. 1. Relation between Index A and K_{av}.
1: glucose, 2: galactose, 3: mannose, 4:arabinose, 5: xylose, 6: ribose, 7: deoxyribose.

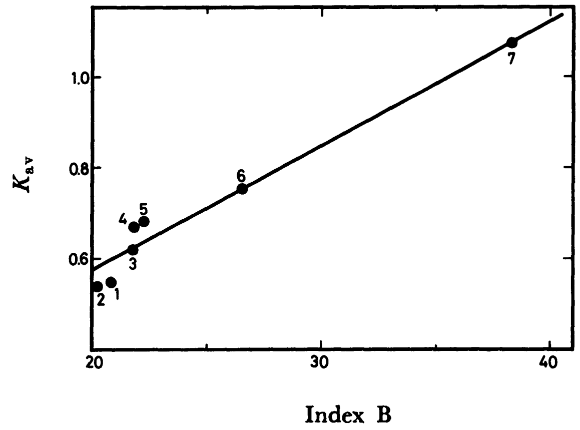

Fig. 4. Relation between Index B and K_{av}.
Symbols: see Fig. 1.

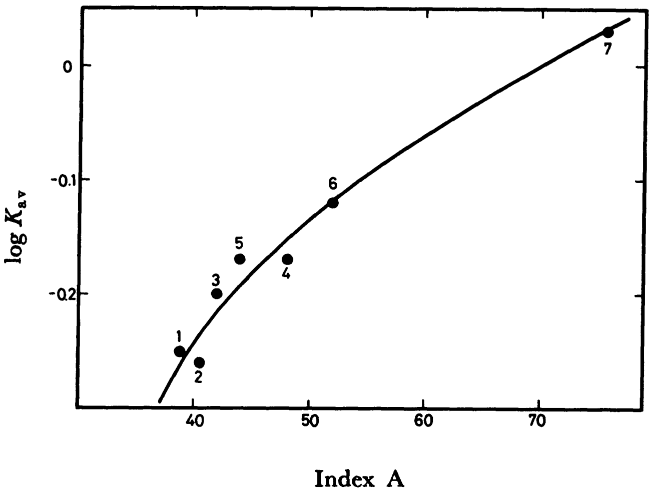

Fig. 2. Relation between Index A and log K_{av}.
Symbols: see Fig. 1.

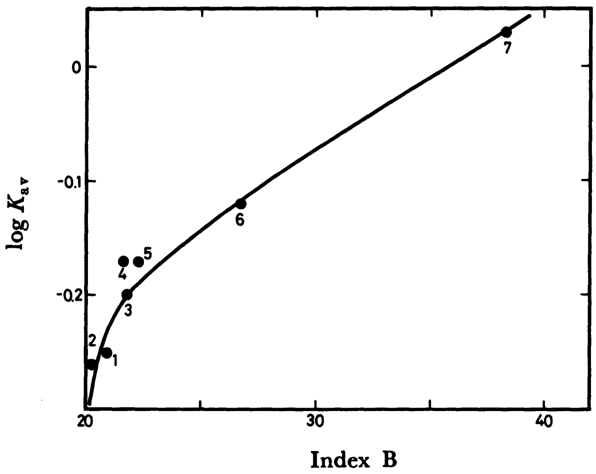

Fig. 5. Relation between Index B and log K_{av}.
Symbols: see Fig. 1.

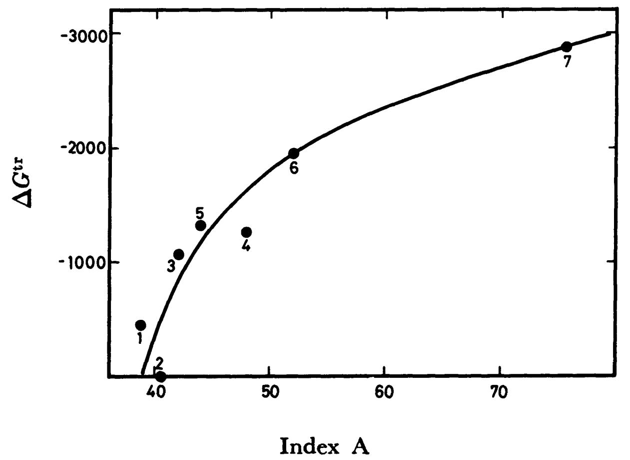

Fig. 3. Relation between Index A and ΔG^{tr} (cal/mole) (1 cal =4.184J).
Symbols: see Fig. 1.

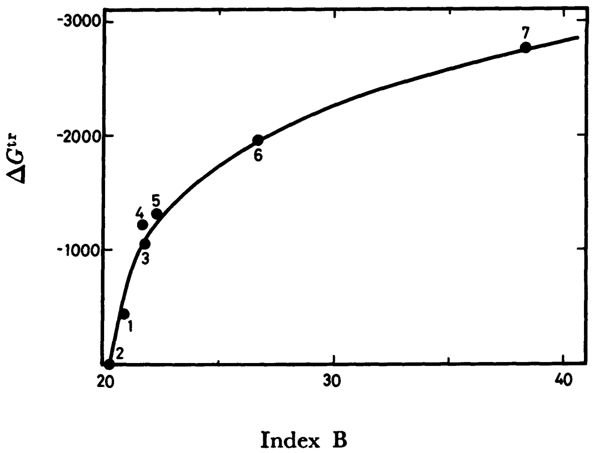

Fig. 6. Relation between Index B and ΔG^{tr} (cal/mole).
Symbols: see Fig. 1.

influence the interaction of monosaccharide molecule with charcoal surface.

An important problem of this treatment is related to the evaluation of hydrophilicity of the monosaccharide molecule, that is, the validity of the relation of hydrophilicity and the hydrophilic surface area. The hydrophilic character of saccharide molecule comes from the hydrogen bonding of OH groups with water molecules, which is stabilized by the suitable orientation of OH group of monosaccharide molecule. Water molecules form tridymite-like structure in liquid state.[1] Based on the special hydration model originally proposed by Kabayama and Patterson,[10] an equatorial OH group of pyranose ring is more favorable than an axial OH group on the formation of hydrogen bonding with water molecule in aqueous solution. In this calculation, the hydrophilic surface area occupied by equatorial OH group is larger than that of axial OH group at anomer carbon atom. But this relation does not always hold at another carbon atoms. Therefore, we cannot comment whether the difference of orientation of OH group reflects the surface area of hydrophilic group of monosaccharide at the present stage. We did not take into account the presence of monosaccharide of straight chain form throughout the discussion, because of its low amount in aqueous solution of equilibrium state.

In conclusion, it was revealed that the fraction of hydrophobic surface area is primarily important factor on the interaction of monosaccharides with hydrophobic compounds in water.

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