Supramolecular Rare Sugar

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Abstract. We introduce rare sugars including their derivatives and supramolecular rare sugars, that have been actively researched at Kagawa University, Japan. Although the rare sugars are special sugars which hardly exist in nature, we has succeeded in mass synthesis of the rare sugars by utilizing biological enzyme isomerization reaction. In addition, the rare sugars have various functions such as blood sugar level suppressing function, cancer cell growth suppressing function, and antibacterial action. In addition, since rare sugars have a large number of hydroxyl groups, they have a possibility for using as devices for expressing various functions by employing them as ligands of transition metal complexes. In recent years, it is successful that we have synthesized the supramolecular rare sugars (SRSs) from the different types of rare sugars, that is not as simple mixtures but as single crystals having supralattice structure, that can be freely controlled optical rotation. It has been found that the crystal structures of these SRSs mostly follow the Wallach rule, but do not satisfy the Wallach rule especially in the case of D,L-psicose. Therefore, we have investigated the single crystal X-ray structural analyses of SRSs, obtaining the detailed crystal structure data, and analyzed the intermolecular interaction between their sugar molecules in the crystal by means of the DV-Xα molecular orbital calculation. According to our detailed analysis of the research, calculating the intermolecular interaction revealed that the stability of the intermolecular interaction in the crystal can not be explained only by following the simple Wallach rule. Specifically, for example in the case of D,L-psicose, the total energy in a crystal can be stabilized by aligning the polarization vectors of the molecules, and as a result, we have clarified that the SRSs crystal structure can be stabilized, even if it does not follow the simple Wallach rule.

1. Introduction

There are two types of monosaccharides, which are classified into natural sugars that exist in large quantities in nature, and rare sugars that rarely exist in nature. Typical examples of the natural sugars are D-glucose and D-fructose and so on. On the other hand, typical examples of the rare sugars are D-psicose and D-allose, and there are many other types of rare sugars. Since the rare sugars rarely exist in nature, little research has been done up to now. The price of the rare sugar as a reagent is extremely expensive. For example, the price of the natural sugar beta-D-glucose is about 0.001 USD, that is
equal to about 14 Indonesian Rupiah per a gram. On the other hand, the price of the rare sugar beta-D-
allose is about 1,000 USD, that is equal to about 14 million Indonesian Rupiah per a gram. Therefore, 
the price of the rare sugar is about 1 million times more expensive than that of the natural sugar. But 
the difference of the molecular structure between them is quite small, as shown in Figure 1.

![Figure 1](image1.png)

**Figure 1.** Comparison of the molecular structures between the natural sugar beta-D-glucose (left) and 
the rare sugar beta-D-Allose (right).

In Kagawa University, Japan, professor Ken Izumori has found the enzyme named “D-tagatose-3-
epimerase (DTE)”. By using the enzime DTE, it is very easy to obtain the rare sugar by enzymatic 
isomerization of the natural sugar. As a result, the strategic way for synthesizing the rare sugar has 
been presented as a map named “Izumoring”, as shown in Figure 2.

![Figure 2](image2.png)

**Figure 2.** Izumoring, that is the strategic map through the new way and new path for producing the 
rare sugars.

The purpose of this study is to newly synthesize the supramolecular rare sugars composed of multiple 
kinds of rare sugars located on the strategic Izumoring map, as shown in Figure 3.

![Figure 3](image3.png)

**Figure 3.** Supramolecular rare sugar is synthesized by the plural kinds of rare sugar molecules located 
on the Izumoring map, which is used as a parts list of the building blocks of the supramolecule

Each sugar molecule has a specific optical rotation phenomenon. Therefore, if a supralattice structure 
can be created by freely combining multiple types of the rare sugar molecules having the different 
kinds of optical rotations, the supramolecular rare sugar can be expected for the application to an 
optical device that can freely be controlled of the optical rotation.
2. Experimental and Result

We have already succeed to synthesize a several kinds of the supramolecular rare sugars, for example, D-psicose : D-glucose = 1 : 9, D-psicose : D-allose = 1 : 1, and D-psicose : D-fructose = 1 : 3. Unfortunately, these three kinds of the suplameolecular rare sugars are obtained only as a powder crystal with a low quality of the crystallinity. On the other hand, we have also succeed to synthesize the single crystals with a high quality of the crystallinity as a D,L-racemic supramolecule, as following, D-fructose : L-fructose = 1 : 1 (P-1),
D-psicose : L-psicose = 1 : 1 (Pna2₁),
D-sorbose : L-sorbose = 1 : 1 (P2₁/c),
D-allose : L-allose = 1 : 1 (P2₁/c),
D-arabinose : L-arabinose = 1 : 1 (P2₁/c).

![Scheme. Supralattice structure of the supramolecular rare sugar D,L-allose.](image)

3. Discussion

The results of the single-crystal X-ray structural analysis of the chiral monosaccharides D-psicose, D-allose and D-fructose are summarized in Table 1.

**Table 1. Results of the X-ray single crystal structural analyses of chiral D-psicose, D-allose and D-fructose, as well as the corresponding racemic supramolecular rare sugars D,L-psicose, D,L- allose and D,L-fructose.**

|                | D-psicose | D,L-psicose | D-allose | D,L-allose | D-fructose | D,L-fructose |
|----------------|-----------|-------------|----------|------------|------------|--------------|
| Formula        | C₆H₁₂O₆   | C₆H₁₂O₆     | C₆H₁₂O₆ | C₆H₁₂O₆   | C₆H₁₂O₆   | C₆H₁₂O₆      |
| Crystal System | orthorhombic | orthorhombic | orthorhombic | monoclinic | orthorhombic | triclinic     |
| Space Group    | P₂₁₂₁     | Pna2₁       | P₂₁₂₁    | P₂₁/c     | P₂₁₂₁     | P-1          |
| a [Å]          | 7.727     | 11.263      | 4.918    | 4.98211   | 9.191     | 5.43124      |
| b [Å]          | 8.672     | 5.355       | 11.925   | 12.5624   | 10.046    | 7.2727       |
| c [Å]          | 11.123    | 12.654      | 12.805   | 11.8156   | 8.095     | 10.1342      |
| alpha [°]      | 90        | 90          | 90       | 90         | 90        | 69.120       |

The space groups of the chiral compounds were all orthorhombic P₂₁₂₁ and Z = 4. The unit cell volume was about 750 Å³, and there are no significant difference among these three types of chiral sugar molecules. In addition, the results of the single-crystal X-ray structural analysis of the supramolecular rare sugars composed of racemic D,L-enantiomers of these chiral compounds are also summarized in Table 1. Among these three supramolecular rare sugars, the space groups, symmetry, and their Z-values are varied from each other. In the supramolecular rare sugar D,L-psicose, the space group remained an orthorhombic, but the symmetry was changed into Pna2₁. This symmetry means that the racemic D,L-enantiomers are existed in the unit cell. On the other hand in the case of the supramolecular rare sugar D,L-allose, the space group was monoclinic and the symmetry was reduced. The space group is P₂₁/c, which means that the mirror symmetry exists along to the c-axis direction. As a result, the D-allose and L-allose coexist in the unit cell. Furthermore, in the case of the
supramolecular rare sugar D,L-fructose, the space group was reduced to be triclinic, and the symmetry to be P-1, which is having an inversion center in the unit cell. In the supramolecular rare sugar D,L-fructose, it was found that the Z-value is to be 2, the unit cell volume was halved, and \( V = 366 \text{ Å}^3 \). In all those chiral and racemic forms, the chemical composition per one sugar molecule is \( \text{C}_{6}\text{H}_{12}\text{O}_6 \), and the molecular weight is equal. Therefore, if the Z-value is the same, it means that the larger the unit cell volume, the smaller the crystal density. Comparing the unit cell volume between the chiral and supramolecular rare sugars in the case of psicose, it can be seen that the increases from 745 Å³ in the chiral one to 763 Å³ in the supramolecular rare sugar. In contrast, in the case of the allose, it can be seen that the cell volume is reduced from 751 Å³ in the chiral one to 739 Å³ of supramolecular rare sugar. Furthermore, even in the case of fructose, it can be seen that the cell volume is decreased from 747 Å³ of the chiral one to supramolecular rare sugar 732 Å³ (= 366.088 Å³ × 2). In general, the racemic crystals with optical isomers are denser and more stably packed than chiral crystals, according to the Wallach’s rule. The changing of the density after racemization of these materials are summarized in Table 2.

### Table 2. Changing of the crystal density before (chiral) and after (racemic) racemization.

|        | racemic (g/cm³) | chiral (g/cm³) | difference |
|--------|----------------|---------------|------------|
| psicose| 1.568          | 1.600         | –0.032     |
| fructose| 1.634        | 1.606         | 0.028      |
| allose | 1.618          | 1.593         | 0.025      |
| arabinose| 1.655      | 1.627         | 0.028      |
| fucose | 1.520          | 1.486         | 0.034      |
| mannitol| 1.504        | 1.484         | 0.020      |

In almost of all materials, the density of the supramolecular racemic rare sugar is larger that that of the chiral one. So, the tendency only in the case of the psicose is unusual. Such an unusual trend has been come from the existence of the intramolecular hydrogen bonding between two OH groups among the 3,5-diaxial structural situation. The hydrogen bonding network in the case of chiral D-psicose, the homochiral bonding network such as 5(D) -> 3(D) -> 5(D) -> 3(D)… can be observed among the D-psicose molecules. On the other hand, the hydrogen bonding network is weakened by the heterochiral intermolecular interaction such as 5(D) -> 3(D) -> 1(L) -> 5(D) -> 3(D) -> 1(L) ->… between two enantiomer sugar molecules.

![Figure 4](image)

**Figure 4.** Hydrogen bonding networks in chiral D-psicose (left) and supramolecular rare sugar D,L-psicose (right).

To discuss the crystal stability and their packing, we must discuss not only the hydrogen bonding but also the direction of the molecular packing in the crystal. Concerning to the molecular orientation in the chiral D-psicose, the 6 membered ring is stacked along to the e-axis in a unit cell. On the other hand in the case of the supramolecular rare sugar D,L-psicose, the hexagonal molecular packing can be included among the heterochiral molecules. As a result, the stacking of the 6 membered ring are directly along not to the e-axis but to the b-axis. According to the calculation of the molecular orientation and the dipole moment of these materials, it is revealed that there is quite large dipole moment between the intramolecular hydrogen bonding. In the case of the chiral D-psicose, all these dipole moments have been cancelled into zero due to the antiparallel situation in the P2₁2₁2₁ space group.
On the other hand in the supramolecular rare sugar D,L-psicose, the dipole moment has not be cancelled because of the modified space group Pna21. As a result, there is quite large amount of the total dipole moment can be obtained in the crystal of the supramolecular rare sugar D,L-psicose. The hydrogen bonding among these heterochiral molecules are weakened by the large dipole moment.

4. Conclusion
We can succeed to obtain the new category of the rare sugar “supramolecular rare sugar” in many kinds of the combinations between plural rare sugar molecules located on the strategy map “Izumoring”. Change of the unit cell volume in a single crystal of the supramolecular rare sugar can be explained according to the Wallach’s rule, except only in the case of the D,L-psicoes. The specificity of the psicose have been realized by the intramolecular hydrogen bonding and the dipole moment observed in the single crystal of the supramolecular rare sugar D,L-psicose.

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