The crystal structure of 

meso-tetrasulfonatophenylporphyrin complexed with concanavalin A (ConA) was determined at 1.9 Å resolution. Comparison of this structure with that of ConA bound to methyl α-d-mannopyranoside provided direct structural evidence of molecular mimicry in the context of ligand receptor binding. The sulfonatophenyl group of meso-tetrasulfonatophenylporphyrin occupies the same binding site on ConA as that of methyl α-d-mannopyranoside, a natural ligand. A pair of stacked porphyrin molecules stabilizes the crystal structure by end-to-end cross-linking with ConA resulting in a network similar to that observed upon agglutination of cells by lectins. The porphyrin binds to ConA predominantly through hydrogen bonds and water-mediated interactions. The sandwiched water molecules in the complex play a cementing role, facilitating favorable binding of porphyrin. Seven of the eight hydrophilic interactions of the monosaccharide moiety. The porphyrin, being a symmetric molecule, also shows multivalency in terms of structural as well as functional mimicry of sugars but were found to bind at a site adjacent to the well characterized monosaccharide-binding site on ConA (10, 11). The conserved Tyr-Pro-Tyr region of the peptides shares excellent similarity with the trimannose moiety in terms of structural superimposition and their surface hydrophobicity profiles. Both the peptide and the trimannose moiety showed similarity in the energetics of binding when docked into the reciprocal sites on ConA (12). Recently ConA and a few other lectins were shown to bind to certain porphyrin derivatives (17–19). The prominent hydrophobic character of the porphyrin molecules had been invoked to explain their binding to these lectins, including ConA.

In the present study, meso-tetrasulfonatophenylporphyrin (H2TPPS), which binds to ConA with an association constant ($K_a$) of $1.22 \times 10^4 \text{ M}^{-1}$, was co-crystallized with this lectin, and the structure of the complex was determined by x-ray crystallography. H2TPPS is a free base porphyrin having four aryl side groups attached to a closed tetrapyrrole ring known as the porphine core. Each aryl side group bears a sulfonate group at the para position. It was observed that the porphyrin binds to the monosaccharide-binding site on ConA mimicking the interactions of the monosaccharide moiety. The porphyrin, being a symmetric molecule, also shows multivalency in terms of con- canavalin A binding and results in cross-linking similar to that observed in the agglutination of cells. Thus, we demonstrate here that two completely unrelated molecules, obviously having independent chemical properties, bind at a common site on a receptor and exhibit similar functions.

**Materials and Methods**

Preparation of ConA•H2TPPS Complex Crystals—8 mg/ml ConA (Sigma) was co-crystallized with H2TPPS (Alfa Inorganics) using the hanging drop method. The reservoir solution contained 1.25 M (NH₄)₂SO₄, 0.75 M NaCl, and 1 mM Mn²⁺ and 1 mM Ca²⁺ ions in 10 mM Tris buffer (pH 7.4). The crystals appeared after about 3 weeks.

X-ray Diffraction Data Collection and Refinement—The x-ray intensity data were collected on an image plate detector (Marresearch, Nor- derstedt, Germany) installed on a rotating anode x-ray source (Rigaku, Tokyo, Japan) operated at 40 kV and 70 mA (CuKα radiation). The crystal to detector distance was 110 mm, and 1° oscillation frames were collected.

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The atomic coordinates and structure factors (code 1JN2) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

¶ To whom correspondence should be addressed. Tel.: 91-11-616-7623 (ext. 234); Fax: 91-11-616-2125; E-mail: dinakar@nii.res.in.

Concanavalin A (ConA), a lectin from Canavalia ensiformis, has been exploited for addressing the structural basis of molecular mimicry (10–13). The mannose-containing carbohydrates on the cell surface have been characterized to be the specific ligands of ConA (14). In addition to the carbohydrate ligands, ConA was also shown to bind a number of peptides sharing a common sequence motif Tyr-Pro-Tyr derived from phage display library (15, 16). These peptides exhibit structural as well as functional mimicry of sugars but were found to bind at a site adjacent to the well characterized monosaccharide-binding site on ConA (10, 11). The conserved Tyr-Pro-Tyr region of the peptides shares excellent similarity with the trimannose moiety in terms of structural superimposition and their surface hydrophobicity profiles. Both the peptide and the trimannose moiety showed similarity in the energetics of binding when docked into the reciprocal sites on ConA (12). Recently ConA and a few other lectins were shown to bind to certain porphyrin derivatives (17–19). The prominent hydrophobic character of the porphyrin molecules had been invoked to explain their binding to these lectins, including ConA.

Functional Equality in the Absence of Structural Similarity

**An Added Dimension to Molecular Mimicry**

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Manisha Goel‡, Deepti Jain‡, Kanwal J. Kaur‡, Roopa Kenoth§, Bhaskar G. Maiya§, Musti J. Swamy§, and Dinakar M. Salunke¶

From the ‡Structural Biology Unit, National Institute of Immunology, New Delhi 110067, India and the §School of Chemistry, University of Hyderabad, Hyderabad 500046, India

Concanavalin A (ConA), a lectin from Canavalia ensiformis, has been exploited for addressing the structural basis of molecular mimicry (10–13). The mannose-containing carbohydrates on the cell surface have been characterized to be the specific ligands of ConA (14). In addition to the carbohydrate ligands, ConA was also shown to bind a number of peptides sharing a common sequence motif Tyr-Pro-Tyr derived from phage display library (15, 16). These peptides exhibit structural as well as functional mimicry of sugars but were found to bind at a site adjacent to the well characterized monosaccharide-binding site on ConA (10, 11). The conserved Tyr-Pro-Tyr region of the peptides shares excellent similarity with the trimannose moiety in terms of structural superimposition and their surface hydrophobicity profiles. Both the peptide and the trimannose moiety showed similarity in the energetics of binding when docked into the reciprocal sites on ConA (12). Recently ConA and a few other lectins were shown to bind to certain porphyrin derivatives (17–19). The prominent hydrophobic character of the porphyrin molecules had been invoked to explain their binding to these lectins, including ConA.

Specificity is a key aspect of molecular recognition. In molecular mimicry, however, the specificity is obviously violated by completely unrelated molecules exhibiting functional equivalence. The functional mimicry involving unrelated molecules is often used as an effective control during various regulatory mechanisms (1, 2). However, sometimes the accidental structural similarities lead to aberrations such as autoimmune disorders (3, 4). Molecular mimicry has wide applications in rational drug design as well (5, 6). Extensive experimental as well as computational studies have been carried out to analyze and exploit functional mimicry associated with chemically dissimilar molecules (7–9). It is generally believed that the molecular mimicry occurs when the topological features associated with two chemically independent molecules exhibit obvious resemblance. However, the precise structural basis of molecular mimicry remains a puzzle.
Functional Equality in the Absence of Structural Similarity

Table I

| Parameter | Value |
|-----------|-------|
| r.m.s., root mean square. | |
| Cell constants (Å) | 106.0, 117.3, 126.0 |
| Space group | F2222 |
| Maximum resolution (Å) | 1.9 |
| Completeness (%) | 94 |
| No. of observed reflections | 97,008 |
| No. of independent reflections | 31,014 |
| Multiplicity | 3.0 |
| Average (I/σI) | 7.6 |
| Completeness in last shell (1.97–1.90 Å) (%) | 88.4 |
| Rmerge (%) | 8.9 |
| No. of solvent atoms | 51 |
| Solvent content (%) | 66 |
| r.m.s. deviation bond length (Å) | 0.02 |
| r.m.s. deviation bond angle (°) | 2.00 |
| Rcryst (%) | 19.5 |
| Rfree (%) | 23.2 |

RESULTS AND DISCUSSION

Overall Structure of the ConA-Porphyrin Complex—The molecular packing in the unit cell of ConA-porphyrin complex is shown as viewed along the a (Fig. 1A) and b (Fig. 1B) axes, respectively. All four ConA monomers interacting with a pair of stacked porphyrins are part of different tetramers. This leads to the cross-linking of ConA by porphyrin molecules through the noncovalent interactions (Fig. 1) similar to those observed in the complexes of biantennary oligosaccharides with different lectins (26–31). The cross-linking of any lectin with a ligand other than carbohydrates or glycopeptides has been observed for the first time in this crystal structure. If porphine is considered as a cell surface and the protruding sulfonatophenyl group as the sugar moieties perched on it, then the interaction of H2TPPS with ConA in crystals mimics the cross-linking of cells by ConA, resulting in their agglutination.

The H2TPPS molecule could be unambiguously defined in the electron density map as shown in Fig. 2A. The porphyrin molecule is located on a crystallographic 2-fold axis occupying a special position. Thus, only one-half of the H2TPPS molecule, consisting of one full pyrrole ring with the halves of two other pyrrole rings that are adjacent to it and two sulfonatophenyl side groups, is part of the asymmetric unit. The phenyl rings of H2TPPS are not coplanar with the pyrrole rings of the porphine core as seen from Fig. 2B. The rotation of the phenyl rings with respect to the plane of the porphine ring is evident in the electron density map (Fig. 2A). The asymmetric unit of the crystals of ConA-H2TPPS complex also contains a monomer of ConA comprising of 237 residues and two metal ions (Mn2+ and Ca2+). It is evident that the binding of porphyrin does not affect the structure of ConA.

One H2TPPS molecule interacts with two monomers of ConA via two of its side groups (Fig. 3). In other words, the two stacked H2TPPS molecules interact with four ConA monomers such that ConA molecules surround them on all sides. The other two side groups do not show equivalent interactions with ConA. The symmetry-related porphyrin molecules stack over each other in a slightly staggered fashion (about 27°) to prevent steric clashes between the side groups. The pair of stacked porphyrin macrocycles maintains a distance of about 3.6 Å with respect to each other. The porphyrins are well known to have an inherent propensity to undergo π–π stacking (23). However, the self-stacking arrangement has not been observed in any of the crystal structures of proteins containing porphyrins. The closest examples of such stacking seen in porphyrins could be the 18 overlapping Bchl a molecules forming a complete ring in the light-harvesting complex from Rhodopseudomonas acidophila (24) or the bacteriochlorophylls forming a primary electron donor “special pair” that partially stack upon each other (25). Neither of these stacking arrangements appears to be as extensive and exclusive as observed in the present crystal structure.

Specific Interactions of Porphyrin with ConA—Porphyrin interacts with only six amino acid residues of each monomer of
ConA (Fig. 3). The porphine core shows no direct contacts with ConA in the crystal structure of H$_2$TPPS-ConA complex unlike in the case of porphyrins bound to other proteins. The only exception, however, is the hydrogen bond involving nitrogen of one of the pyrrole rings (N4B) with a water molecule, W-5.

Furthermore, this water molecule forms a hydrogen bond with W-29 that, in turn, interacts with Tyr-12 of ConA. The core porphine moiety contributes to binding predominantly through hydrophobic interactions in other protein-porphyrin complexes (32). Apart from binding to proteins, porphyrins are also known to bind to DNA primarily by intercalation (33). However, the nature of interactions in the present case is unique in the sense that the porphine core provides only a support base for specific interactions involving the sulfonatophenyl groups.

The sulfonate group attached at the end of the phenyl ring of H$_2$TPPS occupies the known monosaccharide-binding site on ConA (Fig. 4A). The oxygen atoms of this sulfonate group are involved in water-mediated and direct hydrogen bonding interactions with ConA (Fig. 4B). The direct hydrogen bonding of porphyrin with ConA is through O-13 of the porphyrin and backbone amide of Arg-228 of ConA. Another hydrogen bond is mediated by W-15 bridging Thr-226:OG1 of ConA and O-11 of porphyrin. Similarly W-12, which is also networked with W-7, forms a bridge between O-13 of porphyrin and the side chains of Asp-208 and Asn-14. The role of water-mediated interactions in cementing the empty spaces between the receptor and the ligand has long been appreciated (34, 35). Carbohydrate-binding proteins modulate their substrate specificity and affinity with the help of bound water molecules (36–38). The multiple ligand specificity of periplasmic lysine-, arginine- and ornithine-binding protein for various amino acids is also optimized by relocation of protein-bound water molecules (39). These observations corroborate the role of water in defining the mode of interaction of H$_2$TPPS in its binding to ConA.

H$_2$TPPS and Methyl a-D-Mannopyranoside as Molecular Mimics—The ConA-porphyrin and ConA-sugar crystal structures were superimposed in the ligand-binding region (Fig. 4A). It was observed that H$_2$TPPS shows only partial complementarity with the binding site. On the other hand, the mannopyranoside shows a much more snug fit within the binding site on ConA. However, in the interaction of H$_2$TPPS, the water-mediated hydrogen bonds create a network similar to that observed in the case of methyl a-D-mannopyranoside binding to ConA. The interaction of methyl a-D-mannopyranoside with ConA involves eight hydrogen bonds. The binding of the sulfonatophenyl group of porphyrin mimics seven among them. The geometrical relationship of the hydrogen bonding networks of the porphyrin-ConA and monosaccharide-ConA complexes is depicted in Fig. 4B. The hydrogen bonds involving the O-4 atom of the sugar are in this case taken over by the water, W-12. Similarly the interactions of the O-6 atom of the sugar are replaced by another water molecule, W-7. These two water molecules together account for five hydrogen bonds. The O-13 of porphyrin takes over the hydrogen bonding function of O-3 of the sugar ligand. The hydrogen bond of O-11 of the porphyrin to residue Thr-226 of ConA through W-15 corresponds to the hydrogen bond in the case of methyl a-D-mannopyranoside-ConA complex, where a water molecule (W-56 in 5CNA) bridges the hydrogen bond between O-2 of the sugar and residue 226 of ConA. Thus, O-11 of H$_2$TPPS acts as the mimicking counterpart of the O-2 atom of the monosaccharide. The hydrogen bond involving O-5 of the sugar and the backbone amide of Leu-99 of ConA is the only interaction, which does not have a counterpart in the ConA-H$_2$TPPS complex. The equivalence of the hydrogen bonds in the ConA-sugar structure and the ConA-H$_2$TPPS structure is described in Table II. The porphyrin-ConA complex also takes advantage of the external bound water W-15 in a fashion similar to the binding of methyl a-D-mannopyranoside to ConA where W-15 has a counterpart in W-56. Similarity of hydrogen bonding has been suggested to be
involved in molecular mimicry in the case of anti-hen egg white lysozyme antibody (D1.3) complexed with an anti-idiotypic antibody and lysozyme binding to D1.3. However, only 6 of 14 protein-protein hydrogen bonds are conserved in this case (40). On the other hand, the mimicry between a trimannose moiety and a peptide ligand of ConA is predominantly modulated by hydrophobic features (12). The present case is particularly interesting because almost all the hydrogen bonds, except one, are being mimicked by the porphyrin. The surface areas of the ligand and the receptor that become inaccessible to solvent and the intermolecular interaction energies are expected to be similar when the two different ligands behave as mimics of the same receptor. The buried surface area of porphyrin ligand increases from 137.9 to 224.4 Å² in the presence of W-7 and W-12 and is closer to the buried surface area of monosaccharide ligand, which is 228.7 Å². The buried surface area of ConA, however, does not show any substantial difference, increasing from 102.2 to 125.9 Å² on inclusion of water molecules and being intermediate (119.5 Å²) in the case of monosaccharide ligand. The incorporation of the two water molecules as part of the porphyrin ligand increases the strength of interaction in terms of total energy from −22.6 to −48.8 kcal/mol. The total energy of interaction of the monosaccharide ligand is about −34.3 kcal/mol. The major contribution of the water molecules is to the electrostatic energy, which increases from −0.6 to −24.9 kcal/mol in their presence. The van der Waals interaction energy is very similar in all cases, −21.1 kcal/mol for monosaccharide, −22.0 kcal/mol for porphyrin, and −23.9 kcal/mol for porphyrin in the presence of water molecules. Thus, it appears that the complementarity of porphyrin binding to ConA, in terms of buried surface area and interaction energy, enhances on incorporation of two bound water molecules.

In conclusion, the accommodation of different but related ligands at the common receptor-binding site using the extraordinary cementing ability of water molecules has often been

**FIG. 4.** Sugar (green) and porphyrin (blue) share a common binding site on ConA. A, superimposition of ConA-porphyrin and ConA-sugar crystal structures in the ligand-binding region. Molecular surface of ConA is decorated with color to indicate charge distribution (red for negative and blue for positive). It is evident that porphyrin binds to ConA through the sulfonatophenyl group in a groove in which methyl α-D-mannopyranoside is known to bind. B, stereo view of the hydrogen bonding interactions of ConA with both sugar and porphyrin ligands. The hydrogen bonds are shown as thin lines in the color of their respective ligands. The residues of ConA (brown) involved in hydrogen bonding are highlighted. The bound water molecules involved in the interactions with ConA and the ligands are also shown. This figure was generated by GRASP (42).

**TABLE II**

| Distance | Sugar | Water<sup>a</sup> | ConA | Water<sup>a</sup> | Porphyrin | Distance |
|----------|-------|-------------------|------|-------------------|-----------|----------|
| A        |       |                   |      |                   |           |  Å       |
| 3.03     | O-5   | W-56              | Leu-99:N | W-15              | O-11      | 2.65     |
| 2.82     | O-2   | W-56              | Thr-226:OG1 | W-15              | O-13      | 2.62     |
| 2.72     | O-5   | W-56              | Arg-228:N | W-15              | O-13      | 2.66     |
| 2.63     | O-4   | W-56              | Asp-208:OD2 | W-12              | W-7      | 3.09     |
| 2.99     | O-4   | W-56              | Asn-14:ND2 | W-12              | W-7      | 2.64     |
| 2.88     | O-6   | W-56              | Asp-208:OD1 | W-7               | W-7      | 2.94     |
| 2.97     | O-6   | W-56              | Tyr-100:N | W-7               | W-7      | 3.13     |
| 3.06     | O-6   | W-56              | Leu-99:N | W-7               | W-7      | 3.13     |

<sup>a</sup> Bound waters in monosaccharide-ConA complex (5CNA).

<sup>b</sup> Bound waters in porphyrin-ConA complex.

<sup>c</sup> W corresponds to the bound water molecule.
observed (38–41). However, the present study provides an attractive example of equivalence between completely unrelated ligands. It is evident that both the ligands bind to the same site on ConA using similar interactions. The binding of H$_2$TPPS to ConA resembles that of the monosaccharide by virtue of it being able to mimic the interactions of the sugar with the help of bound water molecules. This is contrary to the sugar-mimicking peptides, which bind to ConA mimicking the hydrophobic features of the carbohydrate ligands (11–12). The symmetrical nature and multivalency of porphyrin lead to end-to-end cross-linking akin to that observed in cell-cell agglutination by ConA. Therefore, H$_2$TPPS binding to ConA would be considered functionally equivalent to that of the natural carbohydrate ligands of ConA.

The similarity of sugar and porphyrin observed here has direct implications to the structural basis of molecular mimicry. Molecular mimicry is understood and interpreted in many diverse ways. It covers an entire gamut of quasi-equivalences from sequence similarity in proteins to the similarity as seen by the immune response to chemically different ligands. The sulfotetraphenyl group of the porphyrin and the sugar are two different ligands that do not share any obvious shape similarity yet bind at a common site on ConA through a remarkable correspondence of hydrogen bonding interactions. This is facilitated by the bound water molecules. However, it does not mean that any functional group can adopt a particular topology of specific binding through water of hydration. The incorporation of bound water molecules relates to the structural properties of the concerned molecules. In fact, the water of hydration, like flexibility as in induced fit, has often been suggested to be responsible for modulation of affinity (38–39). In the present case, such a cementing role of water is reflected in terms of mimicry.

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