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The Binding of the Lewis b Blood Group Determinant by the Lectin 4 of *Griffonia simplicifolia*

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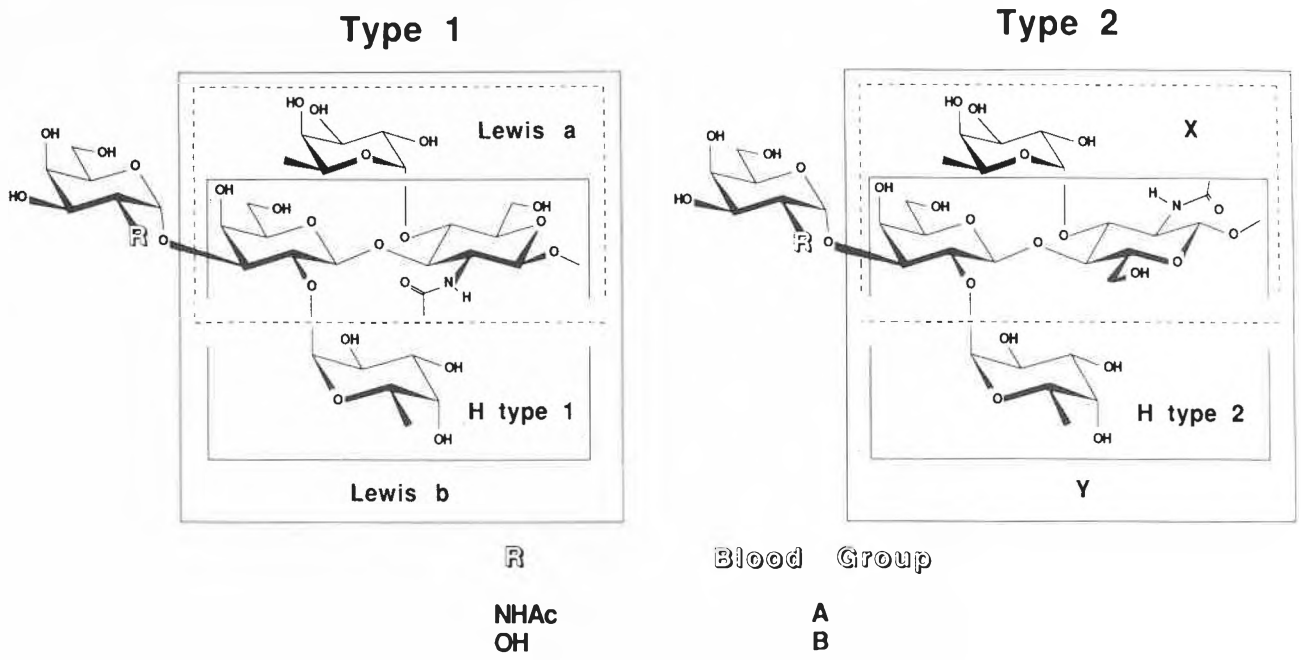
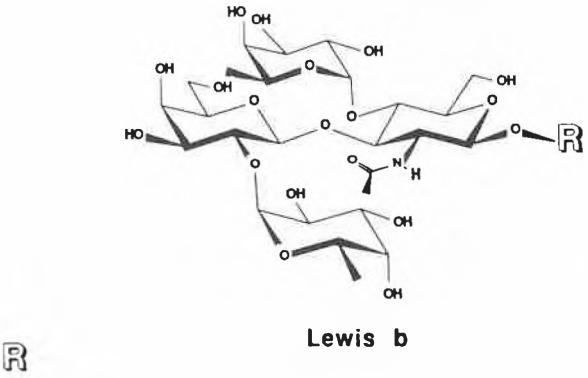
The focus of recent investigations is on how and why monoclonal antibodies and lectins rapidly and reversibly bind complex carbohydrates by way of highly specific non-covalent interactions[1, 2]. Our approach is based on studies using a wide variety of oligosaccharides in the form of synthethic inhibitors, artificial antigens, and immunoadsorbents[3]. The binding of the Lewis b (Le^b) human blood group determinant by the fourth lectin isolated from the seeds of *Griffonia simplicifolia* was given special attention since the protein was known[4] to also bind the structurally similar Y determinant. Conformational studies based in NMR data showed the two tetrasaccharides to possess substantial topographies in common and, in fact, the binding studies have now established that these are the surfaces recognized.

Scheme 1: ABH Human Blood Groups



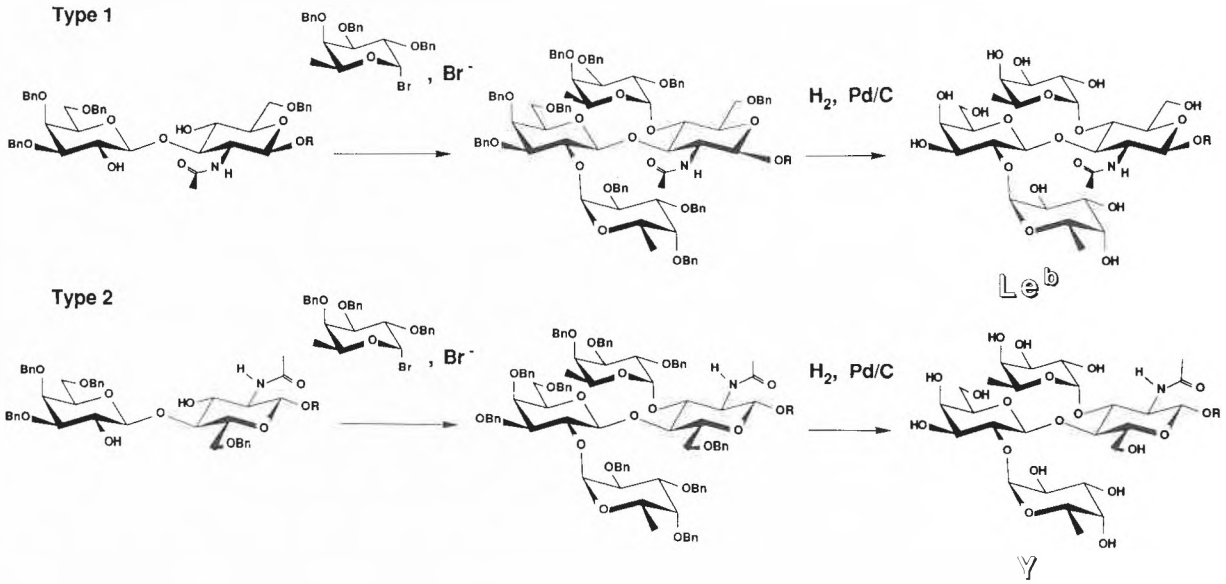
Scheme 2: Inhibitors, Artificial Antigens, and Immunoadsorbents



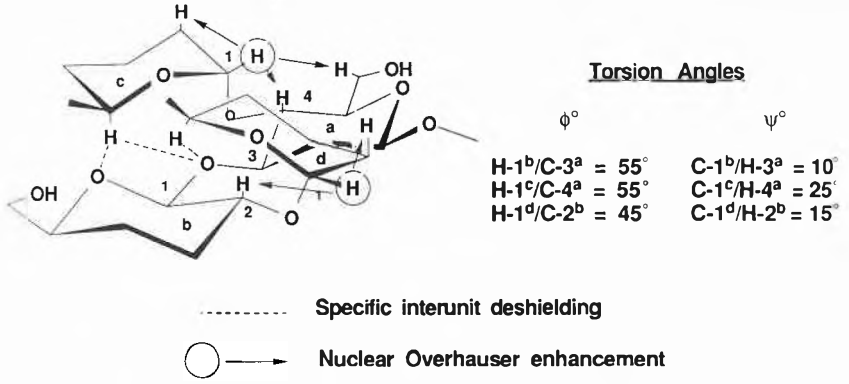
The lectin crystallized readily and, indeed, crystals were also grown for the complexes with the Le^b-OMe, Y-OMe, 6a-iodo-Le^b-OMe, and several deoxy- and *nor*-derivatives of Le^b-OMe[5]. These crystals, near 50% aqueous, appear isomorphous and to diffract to at least 2.5 Å.

The binding of the Le^b-OMe idiotype and its derivatives was examined using a radioimmunoassay and by following changes in ultraviolet absorption[6]. The cluster formed by OH-3b and OH-4b of the βDGal unit and OH-4c of the αLFuc(1→4) unit, was found to provide the key polar interaction[2, 6]. Whether or not this interaction contributes importantly to the driving force remains an open question. Alterations of the Le^b-OMe structure in other ways had a wide range of effects on binding both in terms of changes in enthalpy and entropy. Thus, for example, the *nor*-derivative of the αLFuc(1→4) is bound more weakly largely because of a

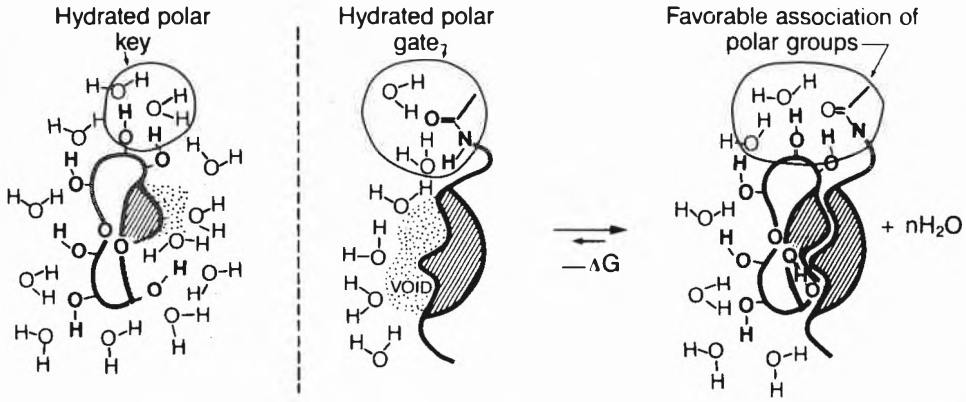
Scheme 3: Synthesis of the Le^b and Y Human Blood Group Determinants



Scheme 4: Conformational Preference of Le^b Determinant



Scheme 5: Schematic Representation of Specific Complex Formation



lesser decrease in enthalpy. In contrast, the replacement of the OH-6b had little effect on binding but causes near 4.5 kcal/mol lesser decreases in both ΔH^0 and $T\Delta S^0$ (298 K). Replacement of the 6b-hydroxymethyl group by hydrogen provided an inactive compound. It is proposed that OH-6b is accepted into an hydrophobic environment by becoming intramolecularly hydrogen-bonded to O-5b. The involvements of the hydroxy groups at positions 2c, 3c, 2d, 3d, and 4d remain uncertain. The changes in the thermodynamic parameters which occur when these are replaced suggest continuing interaction with water when in the combining site. The hydroxy groups of the d-αLFuc unit do not appear involved in polar interactions with the complex since the replacement of the whole unit by the simple methoxymethyl group causes little in the thermodynamic parameters. This is not the case for OH-2c and OH-3c of the other αLFuc unit. Perhaps these hydroxy groups remain bonded to water molecules that have become «structured» through immobilization within the complex. The location of the water molecules in the various crystalline complexes should allow conclusions to be reached in these regards.

It is suggested that these non-covalent binding reactions occur, in general, mainly because the interfacing of complementary amphiphilic surfaces leads to energetically more favorable arrangements for the bulk water. An attempt to better appreciate the effect of structure on the hydration of amphiphilic molecules such as αLFucOMe by theoretical calculation will be briefly presented.

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[2] R.U. Lemieux, *Proc. VIIth Int. Symp. Med. Chem., Uppsala*, Vol. *1*, (1984), p. 329–351.
[3] R.U. Lemieux, *Chem. Soc. Rev.* 7 (1978) 423.
[4] S. Shibata, I.J. Goldstein, D.A. Baker, *J. Biol. Chem. 25* (1982) 9324.
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[6] U. Spohr, O. Hindsgaul, R.U. Lemieux, *Can. J. Chem. 63* (1985) 2644.