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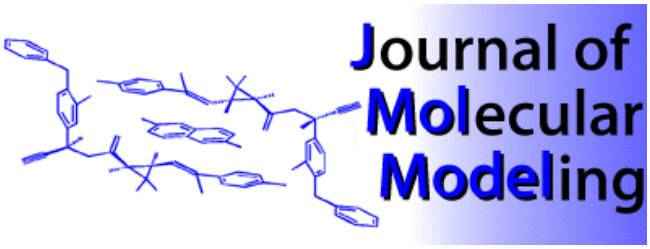

FULL PAPER

W3-SWEET: Carbohydrate Modeling By Internet

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Abstract The software tool SWEET accessible through Internet is described which rapidly converts the commonly used sequence information of complex carbohydrates directly into a preliminary but reliable 3D model. The basic idea is to link preconstructed 3D molecular templates of monosaccharides in a specific way of binding as defined in the sequence information. In a subsequent step a fast routine to explore the conformational space for each glycosidic linkage has been implemented. Systematic rotations around the glycosidic linkages are performed, calculating the van der Waals interactions for each step of rotation. The user interaction is supported by an input spreadsheet consisting of a grid of sugar symbol and connection type cells. Several ways to visualise and to output the generated structures and related information are implemented. Since interactivity is an absolute prerequisite for each WWW application, the limitations of the approach are discussed in detail. SWEET will open modelling techniques to a broader range of users, especially for those who do not have access to the required hard- and software equipment.

Keywords Carbohydrate modeling, WWW-interface, Software development, Conformational search, Monosaccharide library

Introduction

Carbohydrates possess a potential of information content that is several orders of magnitude higher in a short sequence than in any other biological macromolecule [1, 2]. The diversity of carbohydrate structures is a consequence of the broad range of monomers of which they are composed and of the different ways in which the monomers are joined. Even a small number of monosaccharides can create a large number of different oligosaccharides, including many with branching structures. The number of all possible linear and branched isomers of a hexasaccharide was calculated to exceed 10^{12} [3, 4]. Not surprisingly, carbohydrates exhibit remarkable biological specificity both as modifiers of proteins and as ligands.

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A few data collections exist where the sequence of complex carbohydrates is stored. The CarbBank, provided by the Complex Carbohydrate Research Centre of the University of Georgia (http://www.ccrc.uga.edu), contains sequences and bibliographic data of all types of saccharides. It is estimated that 15.000-20.000 records will be published each year, which is about four times as many as were published in 1991. CarbBank is certainly the most elaborated attempt to establish a specific data collection for molecules of this kind. A WWW-based interface is accessible at (http://www.boc.chem.ruu.nl/sugabase/carbbank.html). SugaBase [5] (http://www.boc.chem.ruu.nl/sugabase/databases.html), developed at the Bijvoet Center for Biomolecular Research at the University of Utrecht (http://www.boc.chem.ruu.nl), combines 1D carbohydrate structures and bibliographic data with ^{1}H-NMR and ^{13}C-NMR chemical shifts.

There is a strong dichotomy between the numerous and plentiful oligosaccharide class of biopolymers and the relatively small number of available experimental 3D structures. The current release of the Cambridge Structural Database [6] (http://www.ccdc.com.ac.uk) has approximately one thousand entries of 3D structures for mono- and oligopyranoses. The Brookhaven Protein Database [7] (http://www.pdb.bnl.gov) contains less than twenty unique carbohydrates, but the number of entries representing protein-carbohydrate complexes exceeds one hundred.

Unlike proteins, carbohydrates cannot yet be described in terms of their three-dimensional or secondary structural motifs. Therefore, currently no knowledge-based methods can be applied to model 3D structures of oligosaccharides.

Nevertheless - as a first approximation - one can make the assumption that each glycosidic linkage shows conformational behaviour which is independent from the structural features of the rest of the molecule. Imberty et al. [8,9] claim that any occurrence of interactions between different residues can only result in a reduction of the available conformational space found for disaccharides. It is highly improbable that a new linkage conformation which has not been detected by a careful conformational analysis of disaccharides will occur in complex oligosaccharides.

The aim of this research was to create a software tool which rapidly converts the commonly used sequence information of complex carbohydrates directly into a preliminary but reliable 3D model (see Figure 1). This 3D model can then be used as a starting structure for additional refinements combining computational and experimental results. Recently a similar molecular builder for complex carbohydrates and polysaccharides has been described [10]. We found that con-

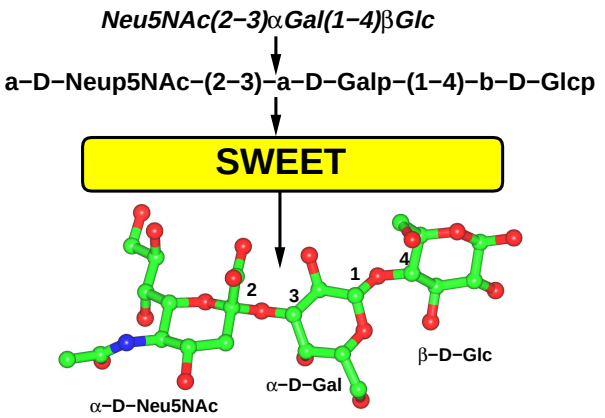

Figure 1 *Graphical illustration of the purpose of SWEET: it converts the commonly used sequence information of carbohydrates directly into a preliminary but reliable 3D structure. For systematic reasons all structural features like D- and L- and pyranose (p) or furanose (f) ring form of the sugar units have to be explicitly given in the sequence*

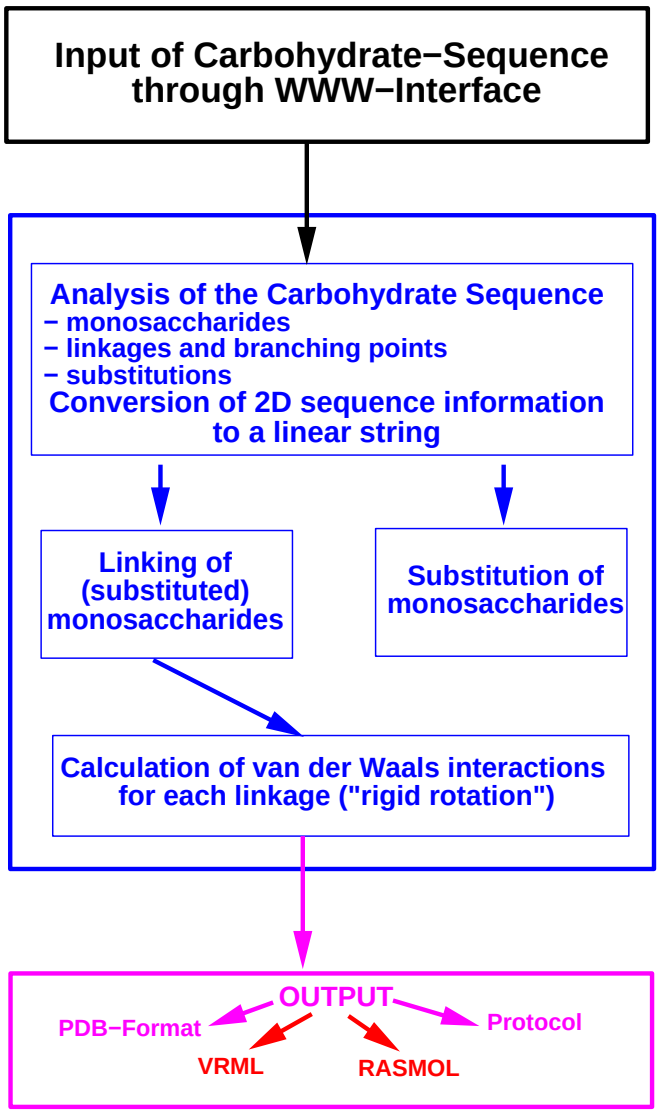

Figure 2 *Schematic representation of how the different components of the W3-SWEET approach are linked together*

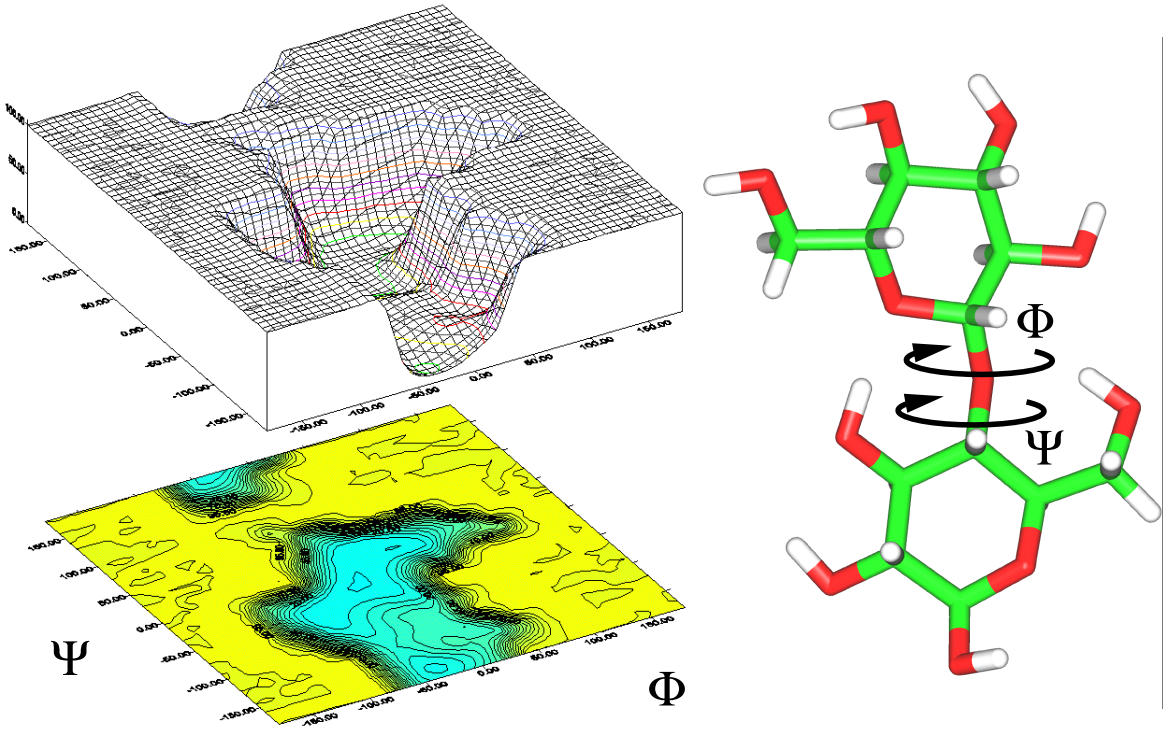

Figure 3 *Graphical illustration of the rigid rotation approach. Only the conformational space of the Φ, Ψ torsion angles of the glycosidic bonds are evaluated systematically. The van der Waals-interaction energies are calculated for all grid points from -180° to 180° with an increment of 20° (top left). Grid points with high energies are neglected. The conformational map is calculated from the generated energy hyper-surface by projecting iso-energy contours around the minima found into the Φ, Ψ plane (bottom left)*

struction of reasonable geometry of oligo- and polysaccharides using commercially available general purpose molecular modelling software is often laborious. A normal hexose contains five stereocenters each of which has to be assigned correctly. Additional knowledge about the conformational preferences of specific glycosidic linkages is needed to obtain a good starting geometry for subsequent refinements.

The rapid development of WWW techniques and the availability of new public-domain tools to handle, visualise and manipulate graphical and/or structure-oriented data [11-13] as well as the increase of information offered in the web has dramatically changed the way of scientific communication during the last few years. Nowadays several large data collections such as the Brookhaven Data Base can easily be accessed and searched by WWW-based interfaces [7]. Even quite complex modelling procedures such as conversion of 2D chemical formula to 3D spatial structures [14-16] (http://schiele.organik.uni-erlangen.de/corina/corina.html [a]) or knowledge-based modelling of proteins by homology [17] (http://www.expasy.ch/swissmod/SWISS-MODEL.html) can be realised using WWW facilities. This development will open modelling techniques to a broader range of users, especially for those who do not have access to the required hard- and software equipment. During the last few years some activities have been started to develop the virtual resources in glycosciences [18]. (see e.g. the glycoscience network page: http://www.vei.co.uk/TGN/welcome.htm) However, compared to the broad range of databases of protein and DNA sequences and the availability of software tools to look up and to analyse these sources of information via WWW [19], the development of adequate data bases and software tools in glycosciences is still at its infancy.

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[a] The WWW interface of CORINA works with SMILES strings as input. Unfortunately these strings become quite complicated for oligosaccharides, since each atom and each stereocenter have to be assigned correctly. A valid SMILES string for α-D-Glcp(1-4)β-D-Glc is: O[C@@H]1[C@@H](O)[C@@H](O)[C@@H](CO)O[C@H]1O[C@@H]2[C@@H](CO)O[C@@H](O)[C@H] (O)[C@H]2O
A valid SMILES string for α-D-Neup5NAc(2-3)β-D-Galp is: C1[C@H](O)[C@@H](NC(=O)C)[C@H]([C@H](O)[C@H](O)CO)O[C@@]1(C(=O)(=O))O[C@@H]2[C@@H](O)[C@@H](CO)O[C@@H](O)[C@@H]2O It is obvious that already for disaccharides a lot of experience is necessary to be able to input a valid and correct SMILES string.

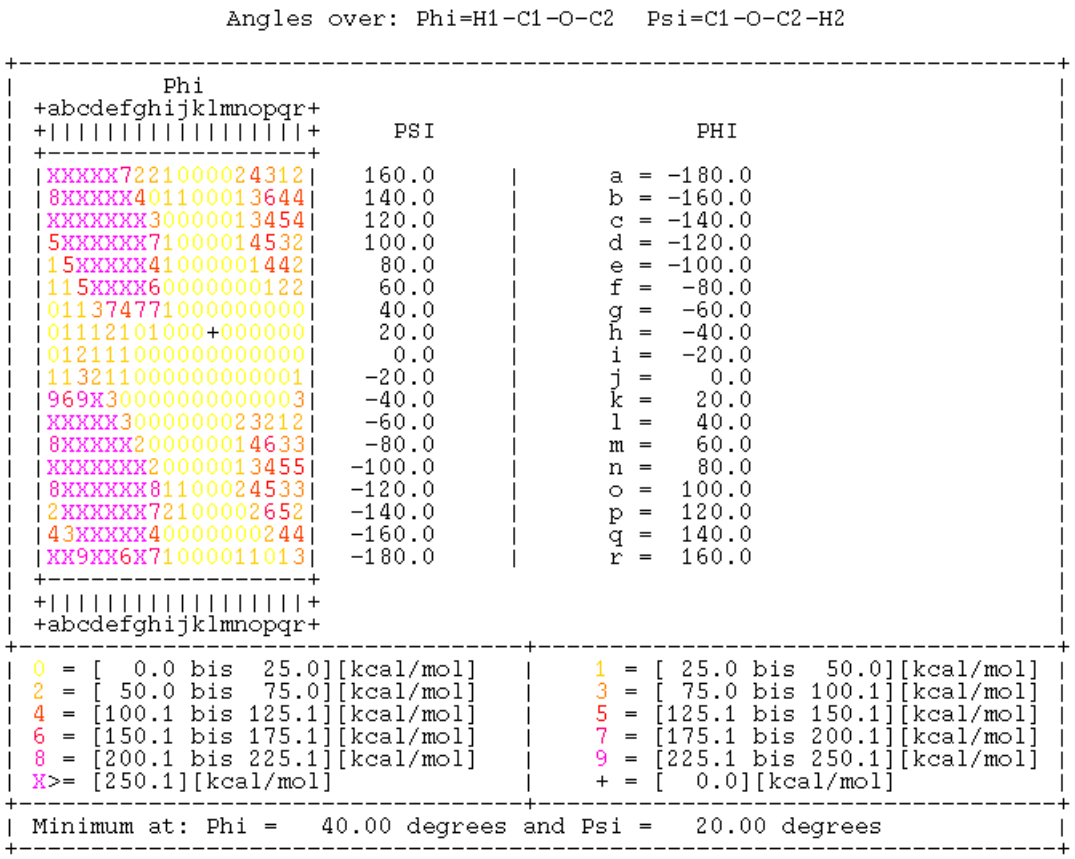

Figure 4a *Global conformational map of Galβ(1-2)Galβ based on the rigid rotation approach. Using a grid size of 20° the interaction energies between the two sugar moieties of the 324 grid points are calculated and visualized using a Ramachandran-like representation. The energies are divided into 10 intervals between 0 and 250 kcal/mol which are indicated by numbers and colors as given in the legend of the plot. The absolute minimum of the grid that was found is indicated by a cross and its values are given at the bottom of the legend. For a comparison with a conformational map where all exocyclic groups have been relaxed and optimized see Siebert et. al. [33]*

Method and materials

General philosophy of SWEET

SWEET [20,21] is an interactive tool to convert the sequence information of saccharides into reliable proposals of 3D structure (conformation). The basic idea of our approach is to link pre-constructed 3D molecular templates of monosaccharides in a specific way of binding as defined in the sequence information. In a subsequent step a fast routine to explore the conformational space for each glycosidic linkage has been implemented. Systematic rotations around the glycosidic linkages are performed, calculating the van der Waals interactions for each step of rotation. The obtained energy profiles define the allowed and forbidden conformational regions for each disaccharide. Figure 2 displays a schematic representation how the different components of the W3-SWEET approach, which will be discussed subsequently, are linked together.

Linkage of Monosaccharides

SWEET can handle linear as well as branched structures and can detect cyclic structural paths. 2D sequence information is converted to a linear string representing branches by increasing nesting levels using a context-free grammar. The linear notation is used as serial information for construction of the 3D structure. Linear notation consists of sugar symbols, linkage information and, implicitly, branching information. Therefore, further processing of the linear notation requires some additional sources of information as follows:

Structure templates. Each sugar symbol represents a 3D sugar structure which must be available for generating the 3D structure of the macromolecule. Correctness and completeness of the macromolecule require availability of all the template structures which are present in the 2D sequence. Of course, practical needs such as fast performance and storage considerations will not allow to maintain a library of tem-

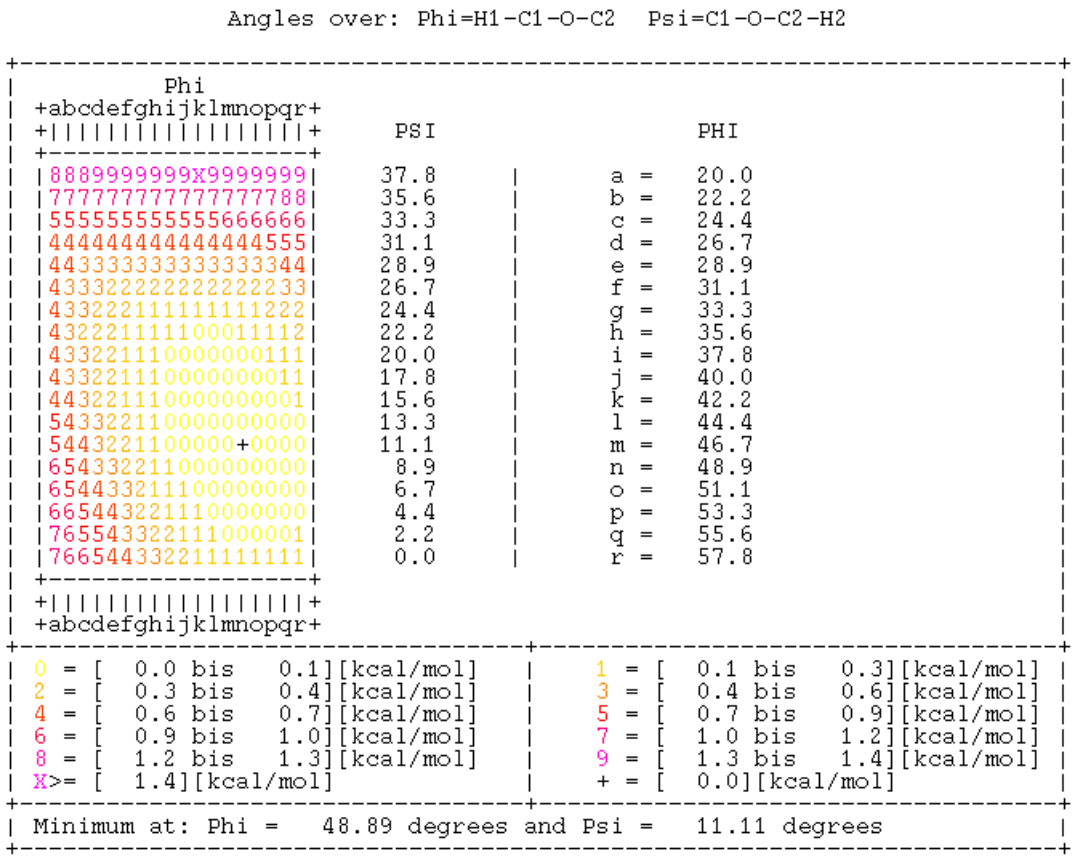

Figure 4b *Fine conformational map of Galβ(1-2)Galβ around the global minimum (see Figure 4a). For 324 grid points around the global minimum (grid size = 1.8°) the interaction energies between the two sugar moieties are calculated. The energies are divided into 10 intervals between minimal and maximal energy value indicated by numbers and colors as given in the legend. The absolute minimum energy of the grid that was found is indicated by a cross and values of its torsion angles are given at the bottom of the legend*

plates of all sugars and functional groups found in Nature. Compromise approach has been chosen by creating a template library of approximately 300 basic structures of monosaccharides and functional groups, in accordance with the content of SugaBase [5]. Satisfactory conversion rate of 98% of SugaBase entries has been achieved within the benchmark test of the approach. Additional needs, however, could be met by building a 'self-learning' system which adds any new-constructed nonstandard monosaccharide into the template library.

Bond information. Positions of ring atoms which are involved in a certain glycosidic linkage are indicated in the sequence information. Connecting 3D residues requires parameters for bond angles and bond lengths which are taken from appropriate lists. Information about bond mechanisms is required for correct processing of bond formation, i. e., omitting atoms during condensation etc.. Several common bond mechanisms are implemented (condensation, substitution, and elimination). Bookkeeping of atom numbering is made for residues and for macromolecules. Original numbering must be kept for identification of atoms within residues, whereas a consistent numbering of the macromolecule must be created during formation. Single template structures are stored in the libraries in minimised form.

Exploring the conformational space for each glycosidic linkage. It is generally accepted that carbohydrates are flexible molecules [22] containing several bonds which can freely rotate. Thus they represent a particularly challenging class of molecules for conformational analysis, that is, for experimental methods as well as for theoretical approaches [23]. The determination of conformational preferences of oligosaccharides is best approached by describing their preferred conformations on potential energy surfaces as a function of the glycosidic linkage Φ, Ψ torsional angles [24]. A comprehensive conformational search for larger oligosaccharides including all possible degrees of freedom takes even with state-of-the-art computational power several CPU hours to days [25]. Therefore, to fulfil the requirement of an interactive program, two principle different possibilities can be considered to obtain the appropriate Φ, Ψ values.

(i) A database of possible values for the torsional angles Φ, Ψ can be created using more elaborated techniques to explore the conformational space of oligosaccharides. Data from

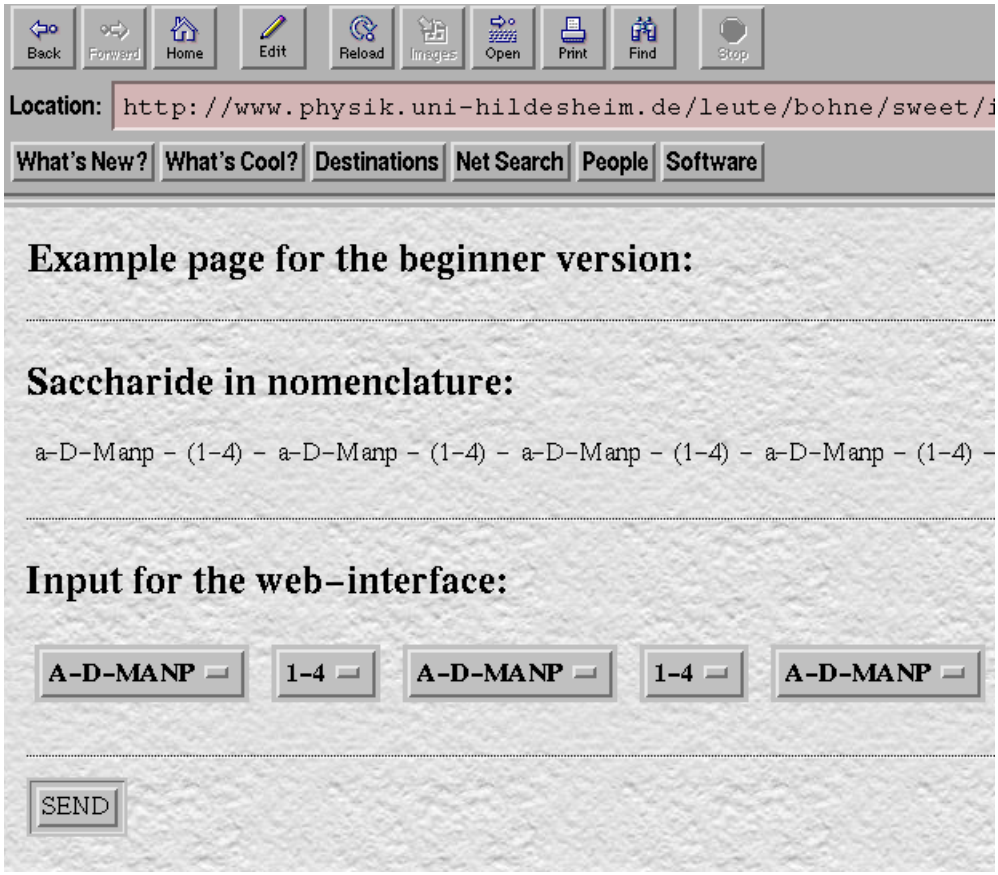

Figure 5 *Beginners' input mode guides the novice how to input correctly a carbohydrate sequence. A CarbBank representation of a linear carbohydrate has been displayed at the top to illustrate the way how the normal carbohydrate sequence has to be filled into the spreadsheet. The name of the carbohydrate templates and their linkage positions have to be input into separate boxes. For the beginners' version a restricted number of frequently occurring monosaccharides and linkages can be selected from a pop-up menu. Playing with this mode, it becomes immediately obvious how to input carbohydrate sequences correctly*

the literature [8,9] could also be used for this purpose. When joining the 3D templates of monosaccharides according to the sequence information, the appropriate Φ, Ψ values for each linkage have to be looked up and applied to the structure.

(ii) Creating interactively two-dimensional Ramachandran-type energy profiles evaluating only the non-bonded interactions during a systematic rotation of the torsion angles of the glycosidic bond for each disaccharide and use the minima on these maps for the buildup protocol.

The most simplifying and fast approximation is to estimate the 3D structure of oligo- and polysaccharides from the knowledge of the Φ, Ψ glycosidic torsional angles by determining only the conformational freedom around these angles. The sugar rings themselves and the exocyclic groups are kept fixed in their appropriate conformation. The COC bond angle of the glycosidic linkage is fixed to a value of 117°. This procedure is often call rigid rotation approach (Figure 3).

It has been found that the non-bonded interactions, especially van der Waals interactions, have a dominating influence on the conformations of many oligosaccharides. It is well-known that it is relatively easy to rank conformations in their order of increasing or decreasing van der Waals repulsion [26].

In the current implementation of SWEET, the non-bonded energy profiles are obtained from the rigid rotation approach for each disaccharide in two steps. At first, for a complete rotation from –180° to 180° with 20° increment, the van der Waals-interaction energies, based on the MM2 (87)-parametrisation [27, 28] are calculated (Figure 4a). In the case of a 1-6 linkage, the ω torsion angle is also systematically evaluated. A simple protocol has been implemented to find all minima on the calculated energy hypersurface. A given grid point on the map is assigned to be a minimum if all adjacent energy grid points exhibit higher energy.

At second, a 'fine' conformational map with 18×18=324 grid points around the minimum of global map using a step size of 1.8° is calculated (Figure 4b). The refined Φ, Ψ values of the global minimum are subsequently used in the buildup protocol of the oligosaccharide 3D structure (conformation).

This procedure selects only one conformation out of a manifold, although it is well known that oligosaccharides normally exhibit several conformations in solution. The interactive version of SWEET has an option to select per glycosidic linkage which of the minima found on the global map shall be evaluated in more detail. The reason not to enable this option in W3-SWEET was to keep the WWW interface as simple as possible so that it can be used without any additional explanation.

Figure 6 *The expert mode allows to generate easily any carbohydrate sequence by typing the desired template names and their linkage positions into the corresponding boxes. A CarbBank representation of a complex carbohydrate has been displayed at the top to illustrate the way how the normal carbohydrate sequence has to be filled into the spreadsheet*

Input

The interactive version of SWEET (which will be made available soon, see http://www.dkfz-heidelberg.de/stzglyco/) offers several ways to input sequence information. Here only the W3-SWEET interface will be discussed. Interaction is supported by an input spreadsheet consisting of a grid of sugar symbol and connection type cells (see Figure 5 and Figure 6). We have created a beginners' version (Figure 5) to guide potential users how to use the expert version (Figure 6). The beginners' version offers a restricted number of frequently occurring monosaccharides and linkages which can be selected from a list. For the expert version the systematic name and the linkage have to be typed as text. Additionally, an example of a branched hexasaccharide can be activated that illustrates the correct way how the different structural features of carbohydrates have to be filled into the spreadsheet. The nomenclature of the structures and linkages follows the

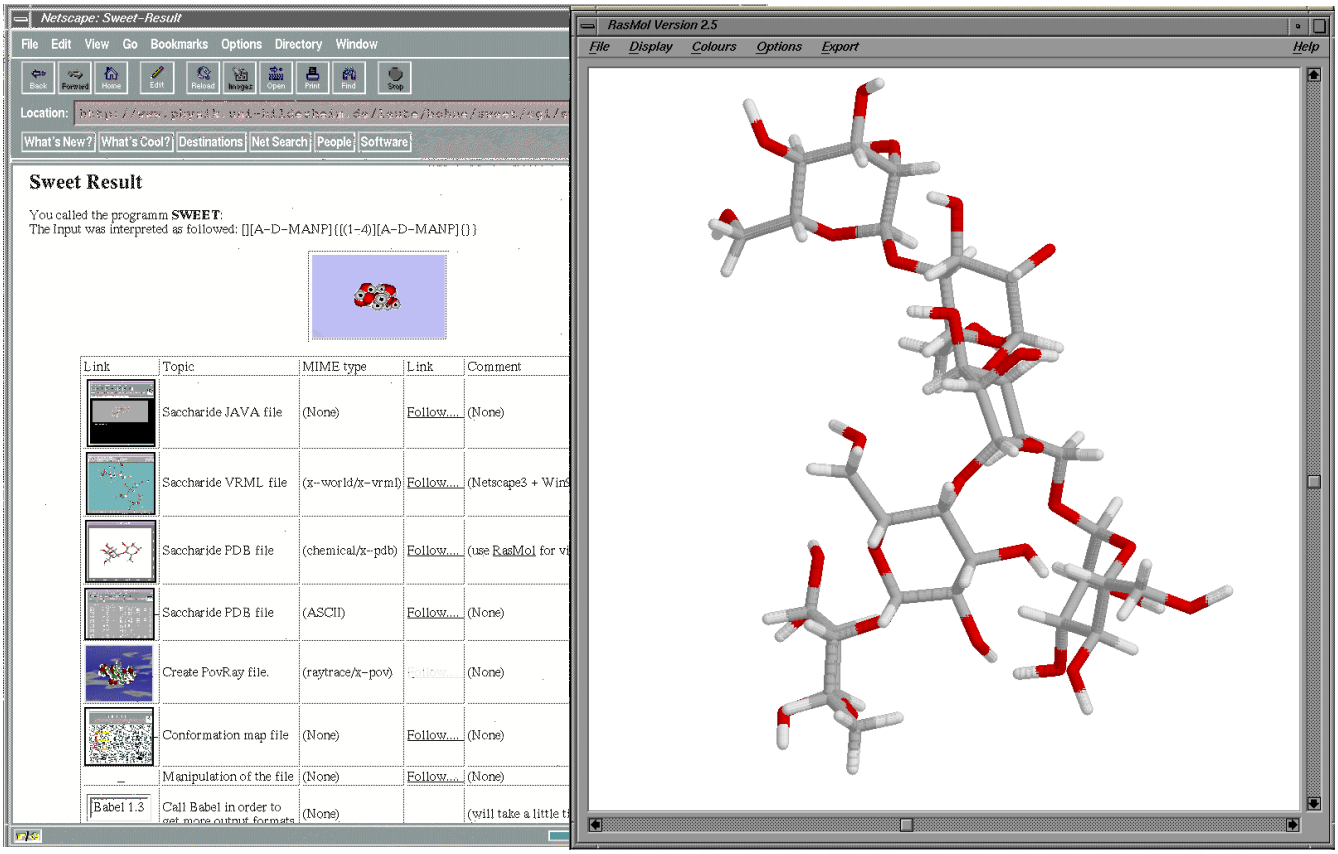

Figure 7 *Typical screen view of a SWEET session. The various output modes offered by SWEET are indicated by small icons on the left side. The 3D structure of the carbohydrate sequence, which has been input through the expert mode of SWEET (Figure 5), is shown on the right. The generated coordinates are transferred back from the server and are immediately visualized using the favorite 3D-browser (RASMOL in this case) which has to be assigned using the mailcap definitions. The 3D-browser is running on the local machine*

definitions as used for CarbBank and SugaBase. Therefore all structural features like D- and L-isomers and pyranose (p) or furanose (f) rings, which are often omitted in the literature, have to be explicitly noted in the sequence. To support the user in finding the correct name of the sugar building-block, a list of all implemented templates can be activated. In this way the complete saccharide sequence information can be easily created by users who are familiar with the carbohydrate nomenclature. This sequence is performed by SWEET as it has been outlined in the above section. No user interaction during the process of optimization is currently implemented.

Output

The current implementation of W3-SWEET produces only one of many possible conformations based on the energy surface of the van der Waals interactions for each disaccharide subunits. The result output consists from the following elements:

• 3D coordinates of the resulting pre-optimized carbohydrate structure in PDB format.

• simple representations of the underlying Φ, Ψ conformational maps to analyse in more detail why a certain conformation has been selected by the outlined procedure.

• ASCII-file containing a protocol of the SWEET procedure. Errors and failures are also reported here.

• direct visualisation of the generated oligosaccharide using a molecular display program like RASMOL [11]. (http://www.umass.edu/mirobio/rasmol) as an external helper application.

• a file containing the information as required for the Virtual Reality Modeling Language (VRML 1.0) (http://vag.vrml.org).

Figure 7 represents a typical view of the screen during a SWEET session.

Results and discussion

The main purpose of W3-SWEET is to offer an easy access to 3D-structures of carbohydrates using Internet tools. It provides the rapid conversion of the generally used sequence information of carbohydrates into a preliminary but reliable 3D model. Interactivity is an absolute prerequisite for each WWW application to be a useful tool in this environment.

Table 1 *Comparison of the Φ, Ψ torsion angles assigned by SWEET with values taken from the literature applying more comprehensive approaches. Some biologically interesting glycosidic linkages have been selected*

Linkage	Ref.	Φ, Ψ Ref.	Φ, Ψ SWEET	Remark
Glcα(1-4)Glcβ	26	40/15 -60/-40 -5/-40	-22/-24	CHARMM, highest population
Manα(1-3)Manβ	28	-45/-5	-49/-9	Results from distance mapping
Xylβ(1-2)Manβ	28	25/30	63/-33	Results from distance mapping
Manβ(1-4)Glcβ	28	55/0 10/-55	60/0	Results from distance mapping
Galβ(1-4)Glcβ	29	54/2 36/180 180/-18	50/5	MM3+ highest population 99% adiabatic map
Neu5Acα(2-3)Galβ	30	-161/-25 84,34 -78/19	175/-11	GM3, distance mapping, MM2,CVFF
Galβ(1-2)Galβ	31	40/20 -78/19 40/-40 180/0	- 50/10	RAMM-MM2[87], CVFF
Galβ(1-3)Galβ	32	40/-60 60/-30 40/30	60/-15	RAMM-MM2[87], CVFF
Fucβ(1-2)Galα	33	40/15	40/15	Φ: 30-50 Ψ: 10-40 CICADA7/MM3
Galβ(1-3)GalαNAc	33	50/-10	50/0	Φ: 60-40 Ψ: 0- (-20) CICADA7/MM3
Galβ(1-3)GalβNAc	33	50/-10	55/0	Φ: 60-40 Ψ: 50- (-60) CICADA7/MM3
Galβ(1-4)GlcβNAc	33	45/5	50/5	Φ: 40-50 Ψ: 5- 20 CICADA7/MM3
Fucα(1-3)GlcβNAc	33	40/30	50/15	Φ: 35-45Ψ: 25-35 CICADA7/MM3

The perception of carbohydrate sequence information as well as loading and joining of the 3D templates are very fast procedures. The calculation of the non-bonded interaction is by far the routine which demands the majority of the needed computational power. A regular grid analysis involving 360° rotation in D increments about N different rotable bonds in oligosaccharides requires a calculation of (360/D) N conformations. When advancing from a monosaccharide (N=6) to a disaccharide (N=10) to a pentasaccharide (N=22), the number of conformational microstates which need to be calculated increases dramatically. Thus, a regular grid search considering all conformational degrees of freedom for oligosaccharides places extraordinary demands on computer time.

These considerations clearly demonstrate that rather restrictive assumptions (rigid rotation approach) had to be made in order to fulfil the requirement of an interactive program. It has been found that treatment of pyranose rings of carbohydrates as rigid is often a useful simplification to scan quickly the general topology of the potential surface of a glycosidic linkage. However, the constraints of a rigid geometry reduces considerably the accessible conformational space. The conformational flexibility of the pyranose rings and the exocyclic

groups play an important role for a number of carbohydrate physical behaviour, especially in lowering the barriers between two conformations [29].

Thus, the user of W3-SWEET should be aware of the fact that there is absolutely no guarantee that the generated structures exhibit the most favourable conformation. The only guarantee which can be given is that strongly unfavourable conformations will not be produced by the applied procedure.

The needed computational time to pre-optimize oligosaccharides using the W3-SWEET approach increases directly with the number of glycosidic linkages in a linear chain. Using increments of 20°, the energy values of 18×18= 324 grid points have to be calculated for the normal glycosidic linkages. This number increases to 18×18×18=5832 for a 1-6 linkage since three degrees of freedom have to be optimized simultaneously. Consequently the optimization of a 1-6 linkage will take approximately 18 times longer than a normal glycosidic linkage. To optimize branched oligosaccharides, all adjacent residues next to a branching point are included in the calculation, since the time required to calculate the van der Waals interactions increases roughly with the square of the number of atoms to evaluate. It may also be prohibitive to generate highly branched structures using W3-SWEET. For these CPU-time demanding cases we plan to install a batch mode. The user can generate the sequence information using the standard interface and the results will be sent back later via electronic mail.

The current version of SWEET is implemented on a 486 PC (33 MHz) using Linux as operating system. The required computational power is directly proportional to the number of glycosidic linkages to be rotated. The complexity of this problem is n^2 if bonds to new substituents have to be derived and 1 if the bond is stored in the library. The amount of bytes to be transferred via the net depends on the size of the generated molecule and the selected visualisation option. It ranges in the order of a few kBytes. Thus we think that modeling of oligosaccharides up to the complexity of a hexasaccharide is a reasonable size which is still acceptable for WWW applications. Up to this structure size, computing time plus transferring time do not exceed a few seconds. An analysis of SugaBase showed that 65.5 % of the 1300 entries consist of di- to hexasaccharides. Another 3.5% are hepta- to decasaccharides. 55% of the structures consist of linear chains, 45% are branched structures and 10% have a 1-6 linkage. These numbers indicate that, in spite of the inherent limitation of the interactive version W3-SWEET, approximately half of the entries collected in SugaBase are in principle accessible with this tool.

Probably one of the most interesting questions for glycoscientists is to know how 'realistic' the structures generated with SWEET are. Table 1 lists the Φ, Ψ values generated with SWEET for some glycosidic linkages of biological interest and compares them with those derived from more comprehensive methods to explore the conformational space of oligosaccharides (relaxed and adiabatic maps, CICADA [30], and RAMM [24, 25] approach). As it has already been emphasised, the current version of W3-SWEET generates only one conformation out of a manifold. However, in most of the selected examples the Φ, Ψ values of the minimum found by the SWEET procedure are quite similar to values as found with the more comprehensive methods. For two reasons, an exact correspondence cannot be expected: Firstly, the simplifying assumptions made in SWEET are drastic and reduce the accessible conformational space considerably. Secondly, each Φ, Ψ grid point in a two-dimensional conformational map represents an entire family of conformations with about 10°, 10° orientations of the exocyclic groups. Thus, a difference in Φ, Ψ of about 10°, 10° can be regarded as the 'intrinsic noise' of the method.

An alternative way which could reduce considerably the needed computational time has been described recently [10]. The authors have stored adiabatic glycosidic linkage potential energy surfaces calculated on disaccharides for glycosidic linkages in a data base. For linkages which are present in the data base only the corresponding torsion angles have to be looked up and applied to the structure. If a linkage is missing in the data collection, the values for the characteristic torsion angles have to be added by hand. Our idea is to create a similar database for the most frequently occurring glycosidic linkages and perform a calculation of the nonbonded interactions as outlined above only for those linkages where no entry can be found in the data base. The generated conformational map can be used as the basis of a new entry to the data base. The conformational map has to be analysed automatically, the characteristics of that specific linkage have to be extracted and converted to the format as needed to add a new entry to the database.

Conclusion

The program SWEET [20, 21] has been designed to assist all glycoscientists dealing with structural and conformational aspects of oligo-and polysaccharides. The WWW interface of SWEET offers access to its main purpose: the rapid conversion of the generally used sequence information of complex carbohydrates into a preliminary but reliable 3D model. The advantages of W3-SWEET for potential users are manifold: the program can be accessed worldwide by a standard interface using many different hardware platforms. No additional work to implement and to update the program is necessary. To guide the user, a beginners' version is offered that explains the novices how to find their way. The pre-optimised structures can directly be downloaded in PDB format for biological macromolecules. Thus the structures can be visualised, analysed and changed by all standard molecular modeling programs and submitted to other more comprehensive computational methods.

Despite of the applied simplification and time restrictions described above, for a great variety of glycosidic linkages W3-SWEET is able to produce realistic 3D-models of complex oligosaccharides. The procedure to explore the conformational space for each linkage selects only one conformation out of a manifold, although it is well known that oligosaccharides normally exhibit several conformations in so-

lution. Since this is a severe limitation for a detailed conformational analysis, which may even prevent potential users from applying this tool, we will probably add this possibility to select specific conformations for a detailed evaluation of the energy hypersurface to the next version of W3-SWEET.

W3-SWEET supports working in small local groups and, nevertheless, sharing common knowledge and material. Thus W3-SWEET can provide a link and communication base in the multiple-step process of glycoconjugate modeling.

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