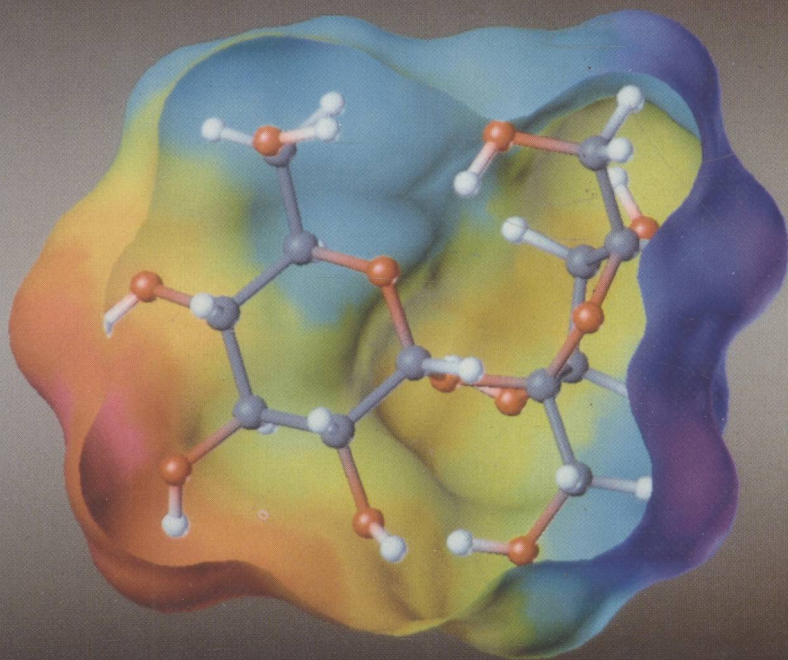


Carbohydrates as Organic Raw Materials

Edited by
Frieder W. Lichtenthaler



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Developed from a Workshop Sponsored
by Südzucker AG, Mannheim/Ochsenfurt
at the Technische Hochschule Darmstadt,
April 11-12, 1990



E200000308

Weinheim · New York · Basel · Cambridge



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The *cover illustration* shows the hydrophobicity potential profile of sucrose projected onto its contact surface in an sixteen color code ranging from violet (most hydrophobic) to red (most hydrophilic region). For generation of the solid state molecular geometry of sucrose the neutron diffraction data of G. M. Brown and H. A. Levy, *Acta Crystallogr., Sect. B* **29** (1973) 790–797 were used. The picture was generated on a Silicon Graphics workstation using the molecular modelling program MOLCAD, developed by Prof. J. Brickmann, of the Technische Hochschule Darmstadt. For further comments see p. 14 ff. of this monograph.

Published jointly by
VCH Verlagsgesellschaft, Weinheim (Federal Republic of Germany)
VCH Publishers, New York, NY (USA)

Editorial Director: Dr. Hans-Joachim Kraus
Production Manager: Max Denk

Library of Congress Card No. applied for.

British Library Cataloguing-In-Publication Data
Conference on Progress and Prospects in the Use of Carbohydrates as Organic Raw Materials (1990 Darmstadt, Germany)
Carbohydrates as organic raw materials.
I. Lichtenthaler, Dr. Frieder W.
547.1

ISBN 3-527-28280-7

CIP-Titelaufnahme der Deutschen Bibliothek

Carbohydrates as organic raw materials: developed from a workshop at the Technische Hochschule Darmstadt, April 11 – 12, 1990 / sponsored by Südzucker AG, Mannheim/Ochsenfurt.

Ed. by Frieder M. Lichtenthaler. – Weinheim; New York; Basel; Cambridge: VCH, 1991

ISBN 3-527-28280-7 (Weinheim ...)

ISBN 1-56081-131-5 (New York)

NE: Lichtenthaler, Frieder W. [Hrsg.]; Technische Hochschule <Darmstadt>

© VCH Verlagsgesellschaft mbH, D-6940 Weinheim (Federal Republic of Germany), 1991

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Composition and printing: Colordruck, Kurt Weber GmbH, D-6906 Leimen.
Bookbinding: J. Schäffer GmbH & Co. KG, D-6718 Grünstadt
Printed in the Federal Republic of Germany

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© VCH Verlagsgesellschaft mbH, D-6940 Weinheim (Federal Republic of Germany), 1991

Distribution:

VCH, P.O. Box 10 11 61, D-6940 Weinheim (Federal Republic of Germany)

Switzerland: VCH, P.O. Box, CH-4020 Basel (Switzerland)

United Kingdom and Ireland: VCH (UK) Ltd., 8 Wellington Court, Cambridge CB 1 1HZ (England)

USA and Canada: VCH, Suite 909, 220 East 23rd Street, New York, NY 10010-4606 (USA)

ISBN 3-527-28280-7

ISBN 1-56081-131-5

Foreword

The workshop conference "Progress and Prospects in the Use of Carbohydrates as Organic Raw Materials" was held on April 11–12, 1990 at Darmstadt jointly by the Technische Hochschule Darmstadt and the scientific committee of CITS (Commission International Technique de Sucrerie). The organizers of this event were Prof. Frieder W. Lichtenthaler of the TH Darmstadt and Dr. Huber Schiweck, head of our central laboratories at Obrigheim/Pfalz. The present book aims at making the lectures held at this conference available to a broader audience.

Considering the fact that there is no lack of conferences on "Carbohydrate Chemistry" and "Renewable Resources", and that the last-mentioned topic is finding ample room in press, what were the reasons that prompted Südzucker to sponsor this conference? We believe that most of the scientific congresses have too broad and too academic a base as to attract a larger audience from industry. This causes these meetings to miss one of their aims, i. e., to bring about an intensive exchange of ideas between representatives from academia, chemical industry, and producers of renewable commodities such as plant fibres, vegetable oils, starch, and sugar.

On the other hand, what we need are new ideas, an intensive research and development phase, and close cooperation between the three aforementioned groups to achieve our long-term goal of making renewable resources an integral component in the production of chemicals. That would not only alleviate the pressure on fossil raw materials, it would also be an appropriate contribution towards the utilization of the agricultural surplus production.

Currently, in Germany, the utilization of renewable resources is characterized by the fact that they comprise only about 10 % of the raw materials used by chemical industry and that only a fraction of this figure stems from German agriculture. This fraction corresponds to an agricultural area of about 34,000 hectares for rapeseed oil, 140,000 hectares for starch containing products (potatoes, cereals), and 5,000 hectares for sugar beet. With such figures the problem of agricultural surplus production cannot be solved.

The broad interest this workshop has found equally by scientists and in the industry justifies the hope that similar conferences may help us achieve the aim outlined here.

October 1990
Mannheim/Ochsenfurt

Dr. Klaus Korn
Member of the Board
SÜDZUCKER AG

Preface

Upon being approached to host and organize a meeting on Carbohydrates as Organic Raw Materials, the reflex response was positive despite of discouraging thoughts on the organizing efforts required. Such a meeting, I felt, was an important forum for transmitting the newest thoughts in an area to which chemical industry has still a rather cautious, stand-by type relationship with little indication for a rapid change. There are plausible reasons for this, of course, the major ones being that comparatively few basic organic chemicals are derivable from our regrowing resources on an economic, industrial scale, and that more elaborate, high value-added products – as of now – cannot be generated on a competitive economic basis. The challenge emerging therefrom is obvious, and has led to multifold efforts towards broad-scale, practicality-oriented basic research at academic institutions, mainly making it increasingly difficult for the industrial chemist in particular, to keep abreast of the new developments in the field.

To steer against this situation the attempt was made to cover the various endeavours towards industrial utilization of carbohydrates in a 2-day workshop by presentations of leading authorities in the field whereby emphasis was placed on the chemistry of low-molecular-weight carbohydrates, i.e. the large-scale accessible mono- and disaccharides. Despite of thus inevitably excluding starch and cellulose chemistry, the resonance to the workshop was exceedingly positive: with a turnout of 200, half of them from European countries other than Germany, and about two third from industrial institutions, the participation surpassed the expectations.

The workshop eventually resulted in the production of this monograph, containing all of the lectures presented, save one. The scope of this monograph, however, goes far beyond the material covered in the oral presentations, since all of the authors have substantially extended their written accounts to include new results as well as novel lines of research. In addition, one topic not presented at the workshop has been included because it was considered relevant to the focus of the book: the computer modeling of sucrose and related substances and their structural representation of various properties on their surfaces, which – in my evaluation – adds a new dimension in the visual perception of sugars and in understanding their chemistry and biology.

The workshop – and hopefully this monograph also – was the first of what promises to be a continuing series, the second one being held at the University of Lyon in July 1992 with G. Descotes as the chairman. I am pleased to have been able to foster the incipency of an “industrial information turntable” which was made a success by the combined efforts of Südzucker AG, most notably Dr. H. Schiweck of their central laboratories, and of myself with participation of essentially all of my research group, where Mrs. Gerda Schwinn and Dipl.-Ing. Uwe Kreis bore the major organizational burden. For their diligent and resourceful assistance with the many tasks that had to be done for the workshop and for this monograph, I would like to express my sincere appreciation.

VIII *Preface*

It is hoped that this monograph will foster, unify, and consolidate the research and developments in this new and challenging area of utilization of "Carbohydrates as Organic Raw Materials". Where will it lead? One thinks of the next decade with optimism. A careful read through this book should give at least a glimpse of what to expect.

October 1990
Darmstadt

F. W. Lichtenthaler

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Old Roots – New Branches : Evolution of the Structural Representation of Sucrose

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Institut für Organische Chemie, Technische Hochschule Darmstadt
D-6100 Darmstadt, Germany

*A picture may instantly present what a book
could set forth only in a hundred pages.*

Ivan Sergeyevich Turgenev

Summary. Following a historical account on the establishment of the constitutional formula of sucrose and of its conformational features, the present possibilities for interactive graphics display of its molecular geometry, based on X-ray structural data, are given. In addition, the MOLCAD program-computed contact surface is presented as well as the electrostatic potential and, most relevant for structure-sweetness relationship considerations, its hydrophobicity potential profile on the contact surface. Finally, an attempt is made towards a preliminary assessment of the computer-generated distribution of hydrophilic and hydrophobic regions over the surface of the sucrose molecule (cf. cover photo) in terms of the "sweetness triangle" AH-B-X concept.

1. Introduction

Knowledge of the structure of a molecule is of fundamental importance, inasmuch as its *composition* (molecular or sum formula), *constitution* (type of bonding between elements), *conformation* (three dimensional arrangement of elements) and its *dynamic stereochemistry* (time and solvent dependent aspects of conformation) not only determine the physical, chemical, and biological properties, but – ultimately – the industrial applications as well. This most pertinently applies to the fairly complex molecule of sucrose, which with an annual production of over a 100 million tons is certainly the most readily available, lowest cost, crystalline organic compound.

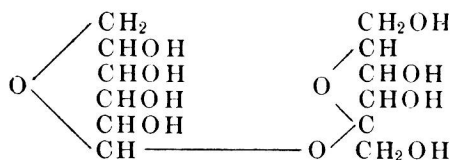
Sucrose being a leading world commodity for centuries, it is not surprising that the roots of its "structural tree" – to adopt the metaphoric picture used in the title – reach back to the very beginnings of organic chemistry as it gradually unfolded with the advent of reasonably exact elemental analyses. The first, albeit not very accurate combustion analyses by Prout in 1827¹ and their interpretations by Liebig,² Peligot,³ Berzelius,⁴ and Dubrunfaut⁵ eventually led to the correct molecular formula $C_{12}H_{22}O_{11}$. Its expansion into a satisfactory constitutional formula mystified a number of great organic chemists and proceeded in a number of distinct phases, each reflecting the progress in experimental methodology: methylation and periodation studies leading to the correct ring structures,⁶ investigations on the chemical and enzymatic hydrolysis of sucrose establishing the anomeric configurations about the intersaccharidic junction,⁶ X-ray- and neutron diffraction-based structural data unravelling ring conformations and non-bonded interactions between the saccharide portions⁷ and NMR studies providing first insights into the dynamic stereochemistry of sucrose in solution.⁷ The newest phase of structural visualization of the sucrose molecule appears to have been launched by the availability of reasonably advanced computer-based graphic and computational tools that allow molecular modeling with the potential of eventually understanding structure-activity (sweetness) relationships.

In the sequel, an account is given on the gradual evolvement of the structure of sucrose from its molecular formula $C_{12}H_{22}O_{11}$ to the color-coded visualization of its hydrophobicity potential profile (cf. cover) with particular emphasis to the current possibilities in computer-aided molecular modeling.

2. The Constitutional Formula of Sucrose

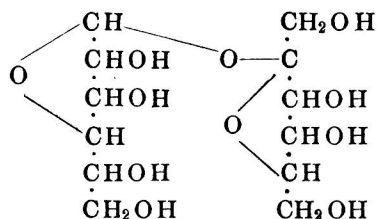
As early as 1883, Tollens⁸ advanced the glucoseptanosyl fructofuranoside formula **1** for sucrose, followed, 10 years later, by Emil Fischer's proposition⁹ that sucrose rather is a glucofuranosyl fructofuranoside (**2**).

Neither formulation contained configurational implications, nor were their ring structures adequately supported by experimental evidence of which Fischer was well aware: "Ich halte die schon von Tollens vor längerer Zeit aufgestellte, allerdings nur ungenügend begründete Structurformel mit einer kleinen von mir vorgenommenen Änderung im Wesentlichen für richtig."⁹



1

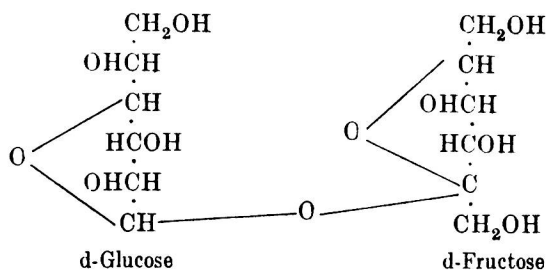
B. Tollens, 1883



2

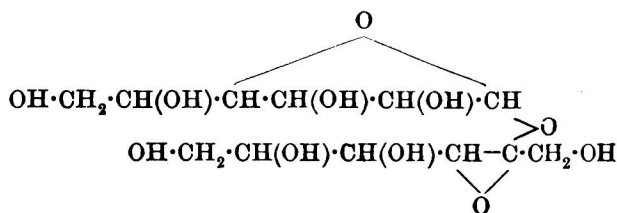
E. Fischer, 1893

Around 1915 structural representations of the type 3,¹⁰ 4,¹¹ and 5¹² appeared to be the state of the art. Thereby it is worthy to note that the Tollens formulation 3 contains the configurational features for the glucose and fructose portions as established by E. Fischer in 1891,¹³ whereas Haworth¹¹ and Hudson,¹² obviously, were not prepared yet to accept Fischer's projection formulae representation advanced 25 years earlier.



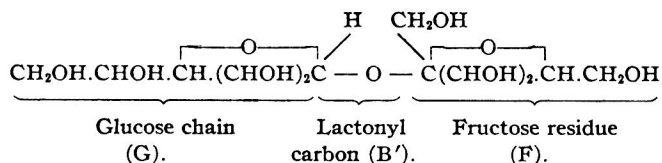
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B. Tollens, 1914



4

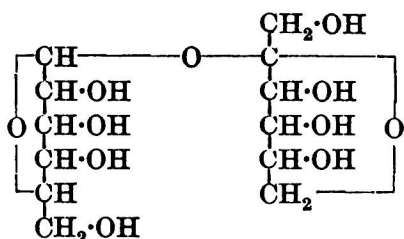
W. N. Haworth, 1916



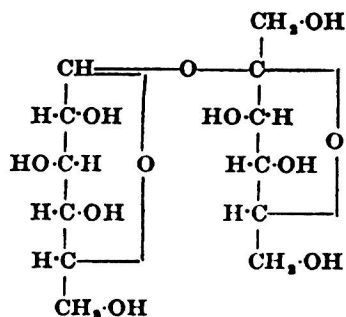
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C. S. Hudson, 1916

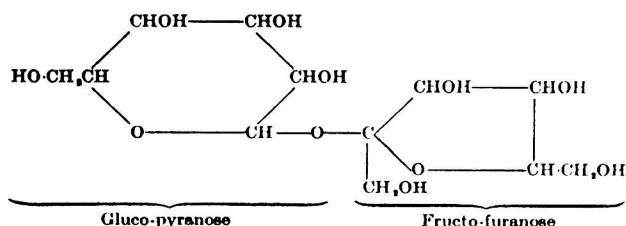
It was not until 1926 – a hundred years after Prouts combustion analyses¹ – that Haworth and his coworkers,¹⁴ on the basis of their classical methylation studies, deduced the correct ring structures for sucrose as depicted in the representations **6**¹⁴ (without configurational assignments), **7**¹⁵ (implementing configurational relationships), and **8**.¹⁵ The latter, in fact, appears to be a first, cautious formulation of what was to become the "Haworth perspective formula", that in the ensuing years found general acceptance in the form propagated by Pigman,¹⁶ Purves,¹⁷ and others. The particularly lucid, didactically auspicious formulation **10** used by Morrison and Boyd¹⁸ in the first edition of their textbook on Organic Chemistry (1959) appears to be the first instance where conformational concepts were incorporated.

**6**

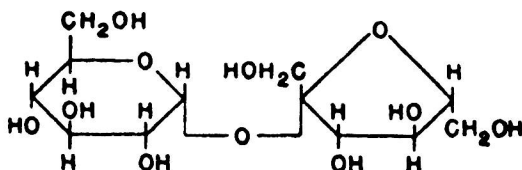
W. N. Haworth, 1926

**7**

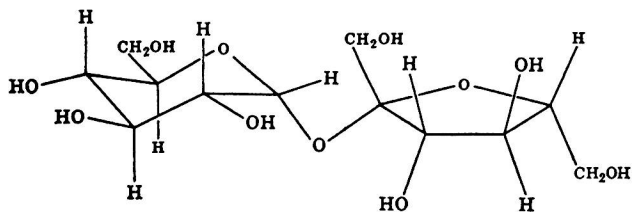
W. N. Haworth, 1929

**8**

W. N. Haworth, 1929

**9**

W. W. Pigman, 1948



(+) - Sucrose

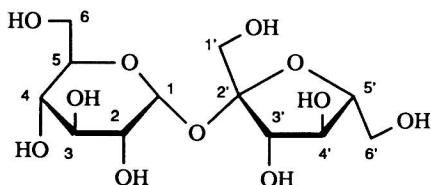
 α -D-Glucopyranosyl β -D-fructofuranoside β -D-Fructofuranosyl α -D-glucopyranoside(no anomers; *non-mutarotating*)

10

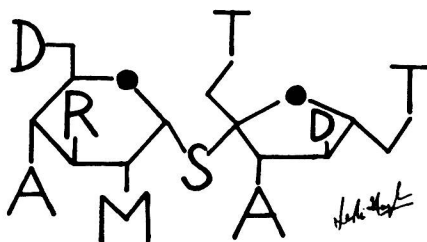
R. T. Morrison,

R. N. Boyd, 1959

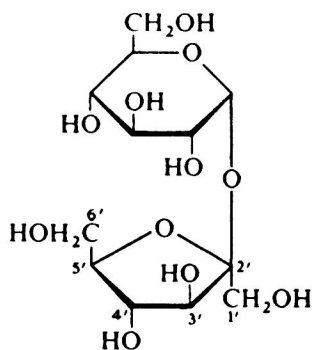
Except for writing the respective C-hydrogens, these formula representations are still used today, as, for example, the formulation 11 favoured by Hough,⁷ which is sufficiently clear and simple to straightforwardly develop the chemistry of sucrose (see this monograph, pp. 33 ff.) and which, as evidenced by 12,¹⁹ may even be subjected to unusual substitution to account for carbohydrate symposium meeting places.



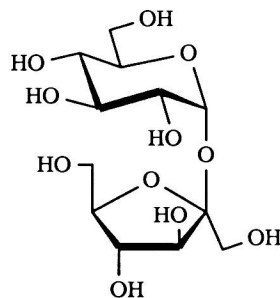
11



12



13



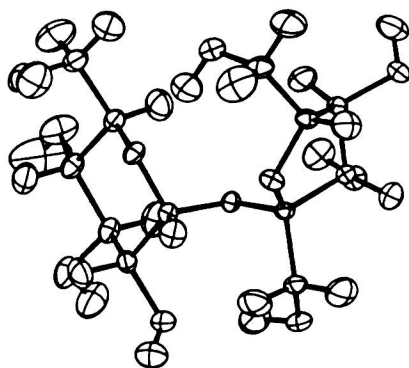
14

Another representation that is reasonably clear and economical in space are formulae 13²⁰ and the ChemText²¹ graphics program-generated 14. Both do not

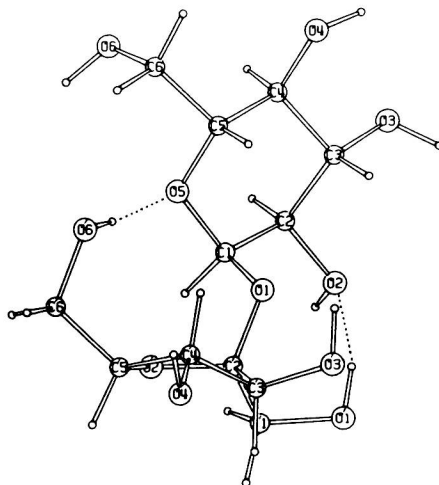
give, of course, the correct disposition of the glucose and fructose portions in the solid state or in solution, but have the didactic advantage that the configurational relationships of the two monosaccharide units, i.e. identical arrangements at C-3 to C-5 of pyranose and furanose rings, become particularly obvious.

3. The Conformation of Sucrose

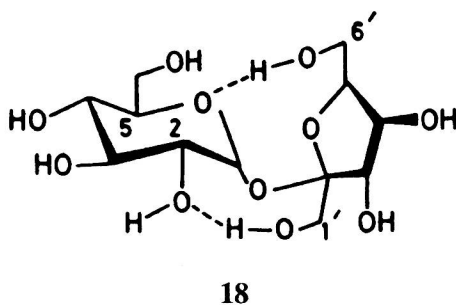
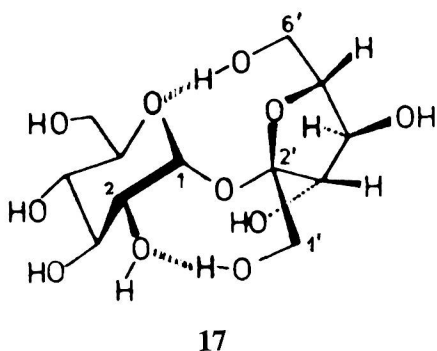
A new possibility to further probe into the structural subtleties of sucrose opened up by crystal structure determinations. The first measurements accurate enough to locate the positions of the hydrogen atoms, were based on neutron diffraction data by Brown and Levy in 1963,²² which upon later refinement^{23,24} resulted in structure 15: the glucose portion adopts a 4C_1 conformation whereas that of the fructofuranose residue is a 4T_3 twist. The two rings are approximately at right angles, yet the overall structure, most notably, is determined by two strong intramolecular hydrogen bonds: one between the terminal 6'-OH of fructose to the pyranoid ring oxygen of 1.89 Å length, the other, even shorter, reaching from the primary 1'-OH of fructose to O-2 of glucose (1.85 Å), as depicted in formulae 16²³, 17²⁵, and 18²⁶. These hydrogen bonds serve to fix the molecule in a well-ordered, rigid conformation.



15



16



As inter- and intramolecular hydrogen bonding in the solid state is influenced by packing effects, it cannot be expected that the fixed overall shape as illustrated by formulations **15** - **18** is retained in solution, since the hydroxyl groups could satisfy their hydrogen bonding requirements by bonding with the solvent. Accordingly, it is surprising that through probing with several NMR criteria in conjunction with hard sphere *exo*-anomeric (HSEA) calculations, Bock and Lemieux²⁷ provided strong evidence that the overall conformation of sucrose is approximately the same in dimethyl sulfoxide and water solutions, and that this conformation is similar to that observed in the solid state. Only the longer, and, hence, weaker 5-O^g \cdots HO-1^f hydrogen-bond is disintegrated by solvation.²⁷ These conclusions are supported by detailed analysis of ¹³C-NMR spin-lattice relaxation experiments of aqueous sucrose solutions, showing its conformation to be independent of temperature and concentration in the 0.1-1 molar range,^{28,29} and by recent SIMPLE ¹H-NMR isotope-shift measurements.^{30,31} The latter revealed the presence of two intramolecular hydrogen-bonded conformations **19** and **20** for DMSO as well as for aqueous solutions of sucrose, in which the 2-oxygen of the glucose portion (i.e. O-2^g) acts as the acceptor for either the 1'-OH or 3'-OH of the fructose moiety:

