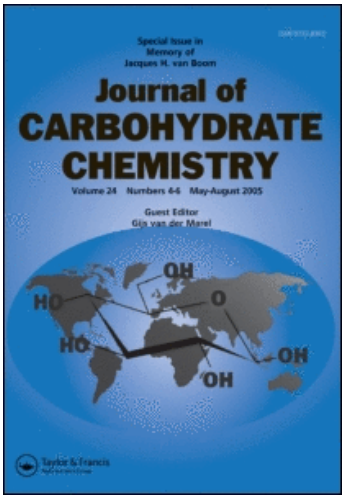

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Stéphan Houdier[a]; Serge Pérez[b]
[a] DRFMC/SESAM/Laboratoire des Macromolécules Végétales, Grenoble Cédex, France [b] Ingéniérie Moléculaire, INRA, Nantes Cédex, France

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ASSESSING SUCROSE HYDROXYL ACIDITIES THROUGH SEMIEMPIRICAL CALCULATIONS

Stéphan Houdier[a] and Serge Pérez[b]

[a]DRFMC/SESAM/Laboratoire des Macromolécules Végétales, CEA/CENG, BP 85X, 38041 Grenoble Cédex (France)

[b]Ingéniérie Moléculaire, INRA, BP 527, 44026 Nantes Cédex 03 (France)

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ABSTRACT

Modeling the relative reactivity of the hydroxy functions of carbohydrates may be of interest to understand and predict selective synthesis. In the present work, the chemical reactivity of sucrose has been evaluated using semiempirical molecular orbital (AM1 and PM3) frameworks. A simple conformational equilibrium of sucrose consistent with NMR experiments was taken into account. The Potential Electrostatic Surface computed from partial atomic charges failed to provide useful information, in part because of the multiconformational problem. Semiempirical calculations of deprotonation enthalpies (DPEs) could provide a comparative scale for acidity of the various hydroxyl groups. DPE averaging showed that the O-2g hydroxy function is by far the most acidic position of the molecule. These results, which are in good agreement with experimental chemical observations, indicate that intramolecular hydrogen bonds also play a key role on the acidity of the sucrose hydroxyls. The order of acidity of the various hydroxyl groups is O-2g_H-2g>>O-3g_H-3g>O-3f_H-3f>O-1f_H-1f=O-4g_H-4g>O-4f_H-4f>>O-6g_H-6g>>O-6f_H-6f. Despite these encouraging results it should be stressed that the application of such modeling techniques is not yet straightforward, and that the enhanced conformational flexibility of sucrose, including the secondary hydroxyl groups orientation, is still a limiting factor in a complete unravelling of the chemical reactivity of this carbohydrate molecule.

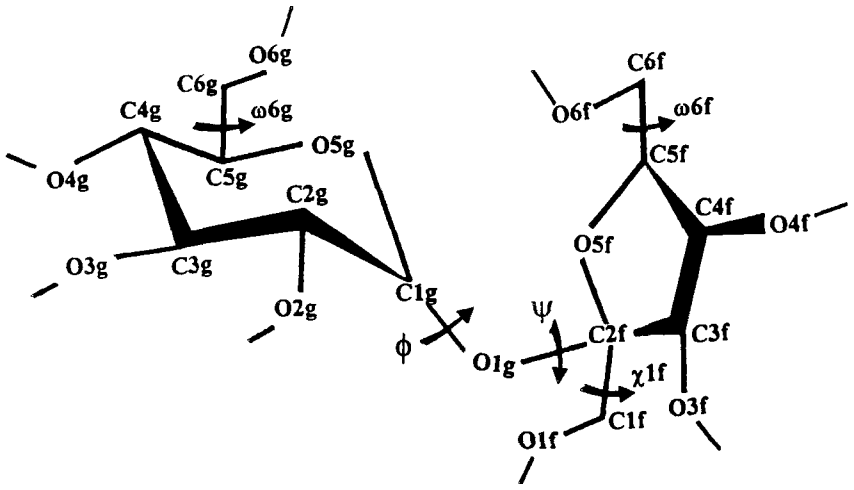


Figure 1. Schematic representation of sucrose, along with labelling of the atoms and structural descriptors of interest (Φ = Θ(O-5g—C-1g—O-1g—C-2f), Ψ = Θ(C-1g—O-1g—C-2f—O-5f), τ = Θ(C-1g—O-1g—C-2f), ωg = Θ(O-5g—C-5g—C-6g—O-6g), ωf = Θ(O-5f—C-5f—C-6f—O-6f), χf = Θ(O-5f—C-2f—C-1f—O-1f)). Hydrogen atoms bonded to carbon atoms are not shown.

INTRODUCTION

Understanding of the chemistry[1-4] of sucrose (Figure 1) is important because of the large availability and the low cost of this sugar. Partially substitued sucrose derivatives are important as products of commercial significance or as synthons in more general sugar chemistry.[5,6] For instance, chlorinated sucrose derivatives are commercially available as high intensity sweeteners.[3,7,8] One example is the 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose, i.e, sucralose, which is directly synthetised by chlorination of 6-*O*-esterified sucrose.[9] Also, fatty acid esters of sucrose are currently used as emulsifying agents in foods, cosmetics or pharmaceuticals.[5,10,11]

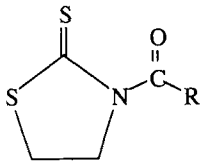
Because of similar relative reactivities of the alcohol groups, selective monosubstitution of the sucrose molecule remains almost impossible and mixtures of polymodified derivatives are generally obtained.[12]

The most selective reactions of sucrose generally involve the least hindered primary hydroxyl groups[12-17] with [O-6g ≥ O-6f > O-1f > secondary-OH] as the observed reactivity order.[12,15,16]

Unfortunately, steric hindrance considerations are not able to determine *a priori* differences in the reaction rates for the three primary and five secondary hydroxyl groups

Table 1. Product distribution and experimental conditions for etherification or esterification of sucrose as reported in the literature.[18,11]

				product distribution (in %) at positions				
Alkyl or Acylating reagent	Base	Solvent	total yield %	C-2g	C-3g	C-1f	C-3f	ref
$PhCH_2Br$	e-	DMF	48	48		39	13	18
CH_3I	e-	DMF	63	54		27	19	18
$CH_2=CH-CH_2Br$	e-	DMF	28	39		61		18
i	NaH	pyridine	72	97	3			11
ii	NaH	pyridine	68	95	5			11
ii	Et_3N	DMF	54	85	15			11
$CH_3(CH_2)_6NCO$	Et_3N	DMF	50	100				11



i $R=(CH_2)_{10}-CH_3$
ii $R=(CH_2)_{16}-CH_3$

of sucrose, and as with many other carbohydrate molecules, the reactivity of all the hydroxyl groups depends upon reagents and experimental conditions.

Recently Hamann et al.,[18] using electrochemical synthesis and Chauvin et al.,[11] with classical chemical synthesis, showed that selective alkylation or acylation could be completed. An initial deprotonation step was performed in aprotic media, such as DMF or pyridine, transforming hydroxyl groups into oxyanions. The reactions of these alcoholate ions induced electrochemically or by base catalysis with suitable alkylating or acylating reagents gave the corresponding ethers or esters of sucrose. In both cases, a good to high selectivity for reaction at the O-2g position of the glucose residue was observed (Table 1).

On the basis of molecular mechanics and molecular electrostatic potential calculations Lichtenthaler et al.,[19] proposed that such experimental results could be explained by considering four equilibrated oxyanions derived from structures A-D (Figure 2) generated from two stable conformations A and B. These two conformations,

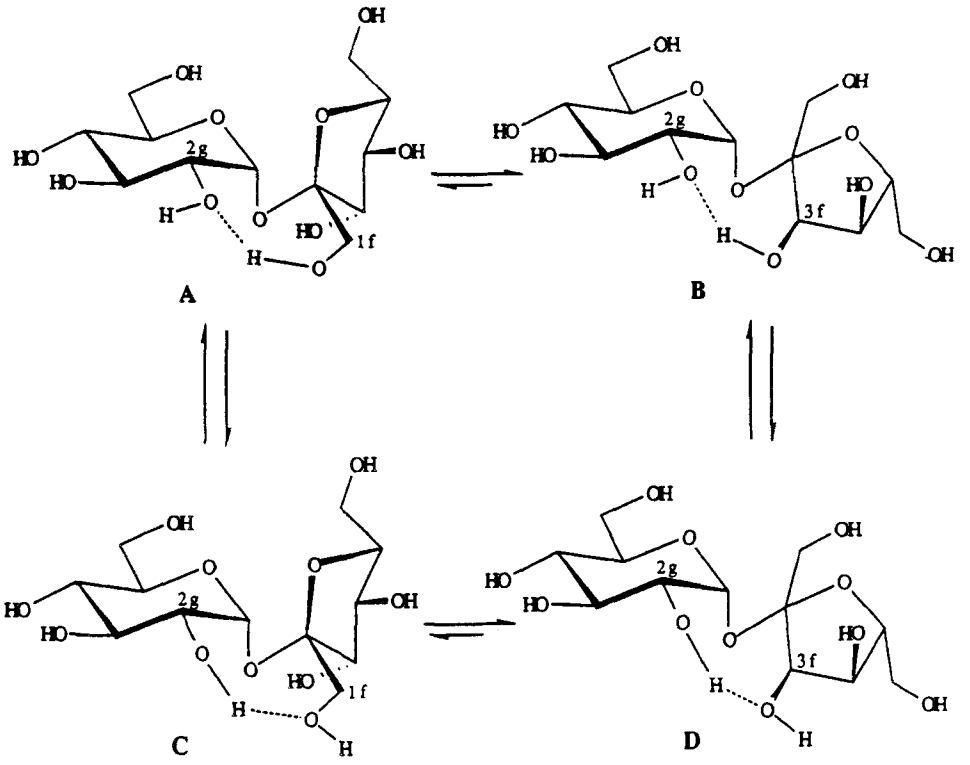


Figure 2. Conformation A-D of sucrose considered for semiempirical calculations.

defined by two different sets of Φ, Ψ glycosidic torsional angles, have been previously observed in a 2 : 1 equilibrium from NMR experiments in DMSO-d6.[20,21] Conformation A exhibits a O-2g ... H-1f—O-1f hydrogen bond whereas conformation B exhibits a O-2g ... H-3f—O-3f one. Hydrogen bonding in A and B suggests that molecules are easily ionized at the O-2g position giving A and B anions which can also rapidly be transformed by donor-acceptor inversion into C and D anions. Assuming the same reactivity for each species, electrophilic reagent approach should yield a 3 : 2 : 1 distribution of O-2g : O-1f : O-3f substitued products as observed by Hamann et al..[18] However, such a distribution was not found by Plusquellec et al.,[11] who observed a better selectivity at the O-2g position.

One way to estimate the relative acidities of polyalcohols such as sugars is to calculate the DeProtonation Enthalpies (DPEs)[22] of each hydroxyl group found in the molecule. Such a descriptor is obtained through the following equation :

$$DPE\ (R\text{-}OH) = \Delta H_f\ (H^+) + \Delta H_f\ (R\text{-}O^-)\ .\ \Delta H_f\ (R\text{-}OH)$$

where ΔH_f is the heat of formation at standard states for the proton (H^+), the ionized sugar ($R\text{-}O^-$) and the nonionized sugar (R-OH). When DPEs for each hydroxyl of the same molecule are compared, a scale for reactivity of these groups toward nucleophilic reagents can be proposed. Such calculations with carbohydrates such as glucose and maltose have been already reported by Brewster et al. using semiempirical methods.[23]

It is the aim of the present work to investigate how electrostatic potential and DPEs can be used to estimate the relative acidities of the eight hydroxyl groups of the sucrose molecule. Also, the role of intraresidue hydrogen bonding on the acidies by consideration of the various orientations of the secondary hydroxyl groups is estimated. Ultimately, the results of the computations are examined in view of those of experimental evidences.

RESULTS AND DISCUSSION

The Starting Conformers. Molecular Mechanics was used to determine the four initial structures A, B, C, and D. A relaxed residue potential energy surface (Figure 3a) of sucrose with starting structures (different combinations of side group orientations) has been calculated using the MM3(92)[24] program following a procedure described previously.[25] The starting atomic coordinates were taken from the neutron-diffraction crystal structure.[26] On such a map, several regions of low energy conformations can be clearly identified. The main ones are respectively centered around $\Phi = 80°$, $\Psi = -50°$ (type A), $\Phi = 90°$, $\Psi = -160°$ (type B), and $\Phi = 90°$, $\Psi = 40°$. As it has already been shown by high resolution NMR spectroscopy,[20,21] in aprotic solvents, only representatives of the first two types need to be considered. To assess the best combination to be given to the exo-cyclic rotatable bonds, maps were calculated for all combinations of primary alcohol group orientations. The individual maps are identified by their primary alcohol orientations in the order O-6g, O-6f, and O-1f. The O-2g...O-1f and O-2g...O-3f interoxygen iso-distances were also reported on each map to locate energy minima corresponding to the occurrence of O-2g—H-2g...O-1f and O-2g—H-2g...O-3f hydrogen bonds as observed in conformations A and B.

For all the maps the global minimum for the former hydrogen bond was located on the gt/gg/tg map with $\Phi = 120°$ and $\Psi = -50°$ whereas the minimum for the latter was located on gt/gg/gg map with $\Phi = 90°$ and $\Psi = -160°$. These two conformations were then submitted to a further optimization with MM3(92) yielding the A and B conformers. Orientation of the O-2g—H-2g and O-1f—H-1f bonds for the A structure were then performed to allow the formation of the the O-1f...H-2g—O-2g hydrogen bond. Further

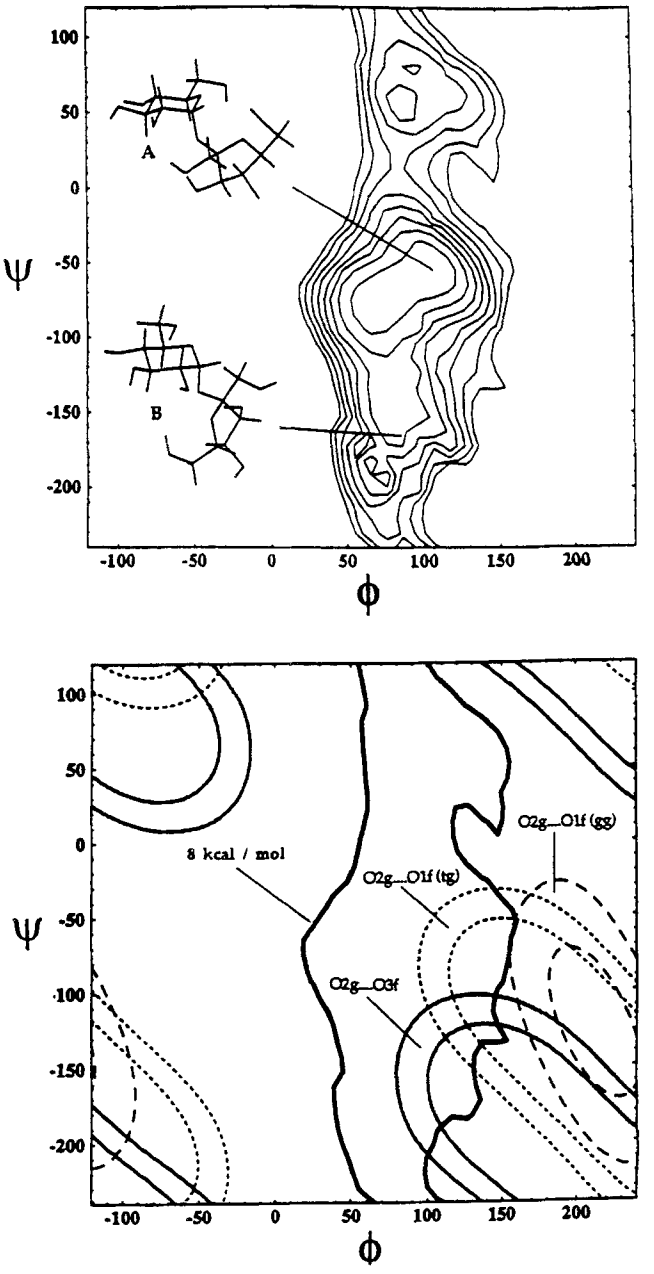
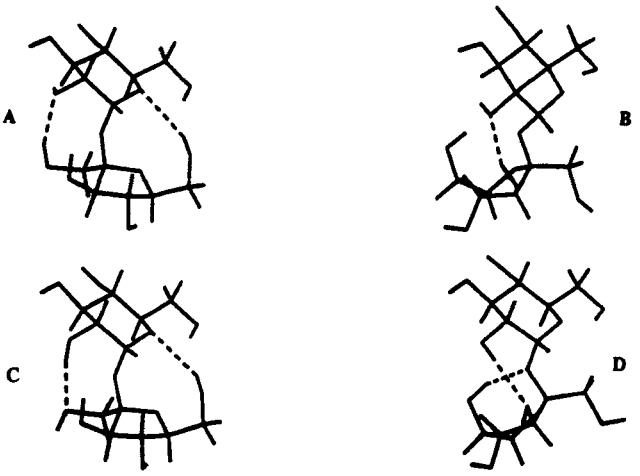


Figure 3. a) MM3 relaxed map of sucrose as a function of Φ and Ψ torsion angles. Contours are drawn at increments of 1 kcal/mol with respect to the absolute minimum. b) Iso-distance contours superimposed on the external contours of the iso-energy map of Figure 3a for the variations of the following respectives distances O-2g...O-1f (χf = gg), O-2g...O-1f (χf = tg) and O-2g...O-3f as a function of the variations of Φ and Ψ torsional angles. The iso-distance contours have been drawn for distances ranging from 2.55 to 3.10 Å.



Conformers	E (kcal/mol)	τ	Φ	Ψ	ω6g	ω1f	ω6f
A	33.4	117.2	114.6	-59.4	66.1	-67.0	-177.6
B	33.8	117.4	113.5	-59.0	66.3	-67.4	178.1
C	36.9	117.6	91.8	-157.4	66.8	-61.5	-62.8
D	34.2	117.6	89.3	-159.5	68.4	-63.0	-63.7

Torsional angles (°) for $H(C_i)$-C_i-O_i-H_i

Conformers	2g	3g	4g	6g	1f	3f	4f	6f
A	-18.3	53.6	-57.2	71.7	-66.7	154.2	8.9	68.6
B	-162.1	62.7	-57.1	72.7	74.5	160.2	5.3	69.7
C	44.1	28.3	-55.1	70.8	-116.2	-173.0	5.2	59.3
D	-66.4	57.5	-58.9	72.7	176.4	-46.4	-14.2	56.2

Scheme 1. Structural and energetic characteristics for structures A-D.

optimization with MM3(92) gave the C conformer. The same procedure was followed to obtain the D structure by proper optimization of the orientations of the O-2g—H-2g et O-3f—H-3f. The significant stereochemical features and energetics corresponding to the conformers A-D along with molecular drawings are given in Scheme 1.

Electrostatic Potential. The first level of investigation used the electrostatic potential as a descriptor. The starting conformer, A, was used in the calculation of the electrostatic potential from the MNDO atomic charges. Actually the higher electropositive

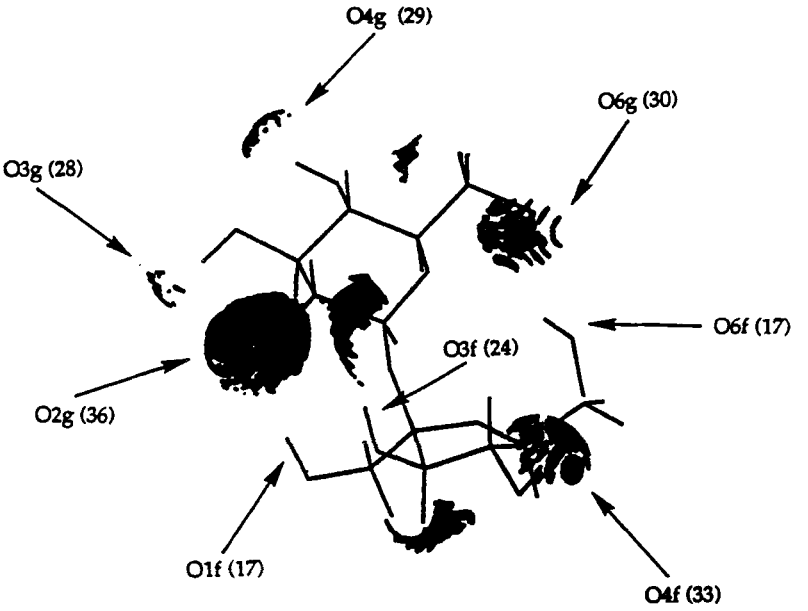


Figure 4. Representation of the electrostatic potential for a cut-off value of +26 kcal/mol calculated for the A conformer of sucrose. Only the areas shaded with a magnitude higher than the cut-off are represented. Value of the local electrostatic potential in the vicinity of each of the eight hydroxyl groups is given in parenthesis.

potential values on each hydroxyl hydrogens of the molecule were calculated. Deprotonation will be favoured for the positions that have the highest positive potential values. Figure 4 shows the areas where the electrostatic potential is greater than +26 kcal/mol.

The highest potential region is observed for the hydrogen bond acceptor O-2g. The existence of an electropositive area between H-1 and H-2 bound to C-2g in the vicinity of O-2g—H-2g extends the size of this region and increases subsequently the electrophilic character of O-2g—H-2g. This result agrees with the experimental observations. Similarly, H-1f and H-6f which act as donors in hydrogen bonds have the lowest electropositive potential. This explains well the low acidity observed for them. However, such similar agreement is not observed with the high potential at H-4f and to a lesser extent at H-6g. For this structure we proposed the following order of acidity : O-2g—H-2g > O-4f—H-4f > O-6g—H-6g > O-4g—H-4g > O-3g—H-3g > O-3f—H-3f > O-1f—H-1f > O-6f—H-6f. The electrostatic potential seems to be convenient to assess the influence of hydrogen bonding and thereby to determine the most and the least acidic

positions of the molecule. However, inability to provide, for a set of conformations "averaged" nucleophile or electrophile features is also a strong limitation of this approach.

Using the Deprotonation Enthalpy (DPE). In a second step, the deprotonation enthalpy was calculated. Results for enthalpies of formation and the deprotonation enthalpies of the hydroxyl groups given in Table 2 relate to structures A, B, C, and D. AM1 always yielded values of ΔH_f lower than those given by the PM3 method. The highest magnitudes for the heats of formation were observed with the MNDO method. As for the DPEs the MNDO give the highest values followed by AM1 and PM3. There are differences between the magnitudes of ΔH_f provided by AM1 and PM3. Nethertheless, both methods provide the same hierarchy of acidity for each hydroxyl group and for each of the starting structures. Quite different classifications are found when the MNDO method is used. To our knowledge no comparisons between experimental and AM1, PM3 or MNDO calculated heats of formation (consequently DPEs) for carbohydrates has been reported. For many organic or inorganic compounds, it has been previously observed that PM3 is generally more accurate in predicting ΔH_f than either AM1 or MNDO. Overall errors for PM3 are reduced by about 40% relative to AM1 and the same difference in accuracy is observed between AM1 and the previous release of MNDO.[27,28] We considered that due to the similarity between the results for DPEs, PM3 and AM1 instead of MNDO were adequate to describe acidity of sugar hydroxyls.

An important feature is the influence of hydrogen bonding on DPE values. On both conformers A and B, O-2g accepts a hydrogen bond. As were shown above this position is more acidic than any other in the glucose or fructofuranose moieties. Similarly, conformers C and D, because O-1f and O-3f oxygen atoms are hydrogen bond acceptors, have respectively more acidic alcohol groups in the 1 and 3 positions of the fructofuranose residue. DPE values for these positions are lower by 3.1 (C structure) to 13.5 kcal/mol (A structure) than those calculated for the second most acidic positions. It is also noteworthy that hydrogen bonding effects seems to be propagated beyond the acceptor hydroxyl group. The secondary hydroxyl group that accepts the hydrogen bond is generally more acidic than the donor. As observed by Brewster et al.[23] for glucose and maltose primary hydroxyl groups, sucrose O-6g—H-6g and O-6f—H-6f hydroxyls have by far the highest deprotonation enthalpies.

DPE values were then averaged over the four conformations using a Boltzmann distribution at 25 °C. Potential energies obtained from the MM3(92) previous minimization procedure were considered. This should yield a straightforward comparison with experimental observations providing that conformers A, B, C, and D

Table 2. Result of semiempirical calculations for sucrose structures A to D.

ionized structure	ΔHf (AM1)	ΔHf (PM3)	ΔHf (MNDO)	ΔPE (AM1)	ΔPE (PM3)	ΔPE (MNDO)
uncharged	-514.1	-456.1	-426.3			
A-O-2g	-522.0	-470.7	-429.8	359.3	352.6	363.7
A-O-3g	-508.9	-457.2	-417.8	372.4	366.1	375.6
A-O-4g	-505.2	-452.2	-414.1	376.0	371.2	
A-O-6g	-494.9	-443.2	-403.3	386.4	380.1	390.2
A-O-1f	-496.5	-444.7	-415.0	384.7	378.6	378.5
A-O-3f	-499.6	-446.8	-415.2	381.7	376.5	378.2
A-O-4f	-502.1	-447.5	-408.4	379.2	375.8	385.0
A-O-6f	-487.8	-437.6	-403.9	393.4	385.7	389.6
uncharged	-517.0	-458.0	-423.6			
B-O-2g	-504.9	-452.8	-420.4		372.3	370.3
B-O-3g	-504.4	-451.3	-408.6	379.8	373.8	382.2
B-O-4g	-504.5	-450.6	-408.1	379.8	374.6	382.6
B-O-6g	-497.3	-444.7	-400.3	386.9	380.4	390.5
B-O-1f	-515.3	-463.4	-419.9	369.0	361.8	370.9
B-O-3f	-512.1	-459.2	-422.0	372.1	365.9	368.8
B-O-4f	-510.5	-455.2	-411.2	373.7	370.0	379.6
B-O-6f	-492.8	-441.5	-403.1	391.4	383.7	387.7
uncharged	-510.4	-454.7	-431.2			
C-O-2g	-512.4	-463.0	-429.2	365.2	358.9	369.2
C-O--3g	-508.5	-459.0	-425.0	369.0	362.9	373.4
C-O-4g	-501.2	-450.3	-418.9	376.4	371.6	379.5
C-O-6g	-491.7	-440.4	-407.1	385.8	381.5	391.4
C-O-1f	-496.6	-445.3	-412.1	380.9	376.6	386.3
C-O-3f	-496.7	-447.7	-425.8	380.9	374.2	372.6
C-O-4f	-499.2	-447.2	-414.3	378.4	374.7	384.1
C-O-6f	-487.5	-438.8	-408.3	390.1	383.1	390.1
uncharged	-510.7	-455.4	-437.2			
D-O-2g	-501.3	-451.6	-425.7	376.6	370.9	378.7
D-O-3g	-496.5	-446.8	-419.2	381.4	375.8	385.2
D-O-4g	-496.3	-445.3	-419.3	381.6	377.3	385.1
D-O-6g	-491.8	-441.0	-412.9	386.1	381.6	391.6
D-O-1f	-499.4	-448.6	-419.4	378.5	374.0	385.1
D-O-3f	-510.7	-460.4	-433.1	367.2	362.2	371.3
D-O-4f	-504.0	-453.1	-425.1	373.9	369.5	379.3
D-O-6f	-485.3	-436.8	-413.3	392.6	385.7	391.2

ΔHf and DPE are in kcal/mol.

Table 3. Averaged DPE (in kcal/mol) values at each hydroxy function of sucrose.

	Hydroxy function							
Method	O-2g	O-3g		O-6g	O-1f	O-3f	O-4f	O-6f
PM3	360.9	369.7	377.9	386.5	373.1	371.4	373.2	385.1
AM1	367.6	375.8		380.4	379.3	376.8	376.8	392.7
MNDO	367.8	378.9	381.2	390.5	377.3	374.5	382.6	389.3

were the only reactive conformations in solution. Averaged DPE values are listed in Table 3. The order of acidity of the various hydroxyl groups is O-2g—H-2g >> O-3g—H-3g > O-3f—H-3f > O-1f—H-1f = O-4g—H-4g > O-4f—H-4f >> O-6g—H-6g >> O-6f—H-6f with the PM3 method. Inversion between O-4g—H-4g and O-4f—H-4f is found when the AM1 calculation is used. These observations establish clearly that the O-2g is the most acidic position of the sucrose molecule; this is in accordance with the experimental findings reported in Table 1. Average DPE values for O-2g are 8.8, 8.2, and 6.7 kcal/mol lower than for the second most acidic positions (i.e., O-3g for PM3 and AM1 or O-3f for MNDO). Such differences indicate a very preferential deprotonation at the O-2g center in such a way that subsequent trapping of the alkoxide by a suitable reagent would yield preferentially 2-O acylated or alkylated sucrose derivatives. Contrary to MNDO, PM3 and AM1 computations also show that O-3g is more acidic than the O-3f and O-1f.

Hence, our results agree with the observations reported by Chauvin et al.,[11] who obtained only minute amounts of O-3g acylated compounds. On the other hand, Hamann et al.,[18] observed a significant substitution in the O-1f and O-3f positions. Possibly, concentration effects and the nature of reagents but more likely adsorption phenomena of sucrose at the electrode surface in electrochemical experiments could be responsible for such discrepencies. As observed for the isolated A, B, C, D structures O-6g—H-6g and O-6f—H-6f were found to be the least reactive positions.

Our calculations provide the same enhanced acidity for the O-2g—H-2g function for conformers A and B which both have O-2g as hydrogen bond acceptor. Actually, our results suggest that the reaction of sucrose in aprotic solvents like DMF or pyridine might be based on a small number of conformations that allow suitable hydrogen bonds. However, these conclusions are not consistent with those obtained when 48 structures each corresponding to one of the three local minima observed on 16 MM3(92) relaxed maps of sucrose, were considered as the starting conformations for MOPAC ΔH_f

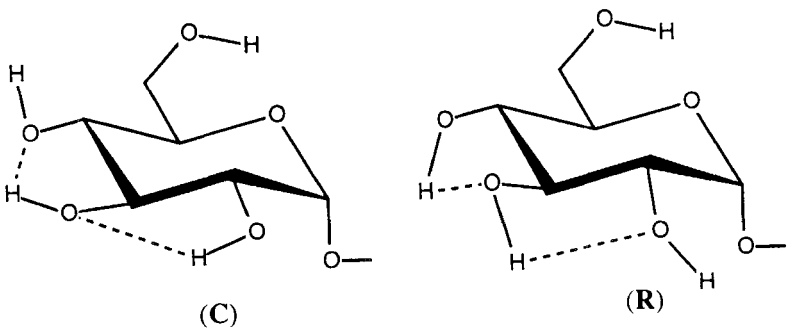


Figure 5. Clockwise (C) and Reverse Clockwise (R) orientations for secondary hydroxyl groups of the glucose residue.

computations. In this study each map was refered to a preferred orientation of the primary hydroxyl groups (see before) and to a clockwise or anti-clockwise orientation of the glucose secondary hydroxyl's network. Boltzmann averaged values for DPE indicated an acidity order of O-1f >> O-2g > O-4g > O-3g > O-3f > O-4f > O-6g > O-6f with the PM3 method and O-1f >> O-4g > O-2g > O-3g > O-4f > O-3f > O-6g > O-6f with the AM1 method supposing favorable alkyl or acyl substitution at the O-1f position. No agreement with experimental observations could be reached in this case in contrast to the agreement which was found when a subset of four conformations (A-D) was considered.

Influence of Secondary Hydroxyl Groups Orientations. As we saw before intramolecular interresidue hydrogen bonding seems to have a major influence on the acidity of the donor or acceptor hydroxy functions of the sucrose molecule. As primary hydroxyl groups of pyranoses usually exist in staggered positions, secondary hydroxyl groups occurred with similar relative orientations allowing formation of cooperative rings of intramolecular hydrogen bonds. These orientations are generally described as clockwise (C) or counter-clockwise (R).[20,29] With (C) orientation, the cooperative ring of the glucose moiety is such that the O-4g oxygen is the final acceptor whereas it is the O-2g oxygen with (R) orientation (Figure 5). Thus (C) or (R) orientations should, respectively, enhance acidity of O-4g—H-4g or O-2g—H-2g.

In order to estimate the influence of the hydrogen bonding cooperativity on hydroxyl acidities we investigated the calculation of DPE at the O-2g position for various orientations of the O-3g—H-3g hydroxyl group. Other geometric parameters were not modified and no further energy minimization was done. Conformation A involving

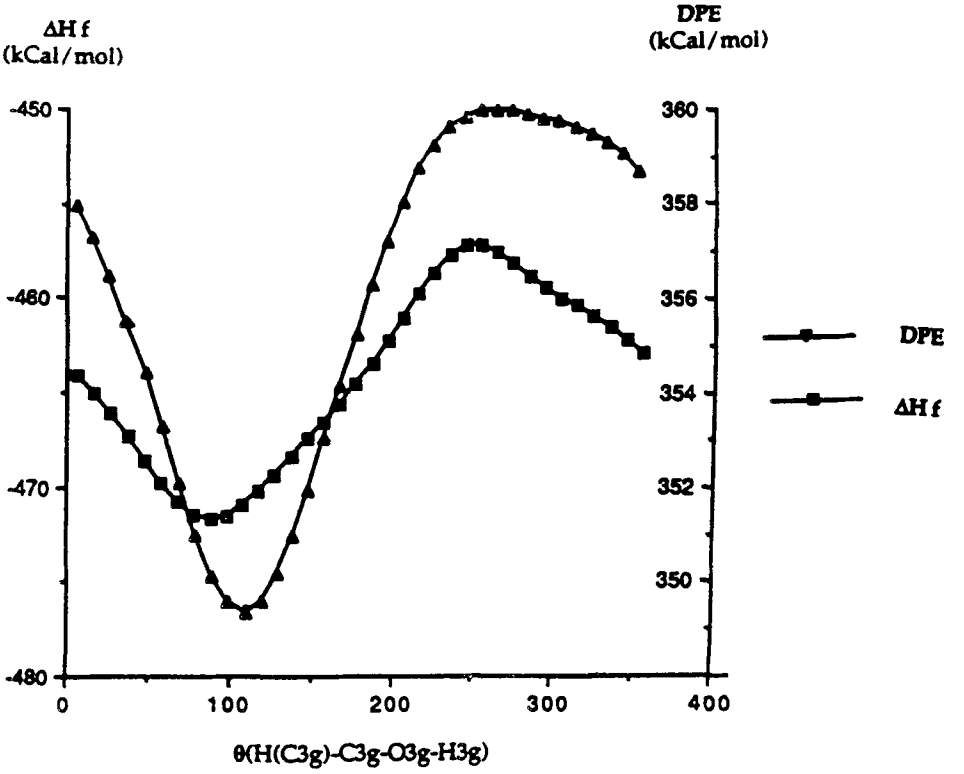


Figure 6. Variations of ΔHf and DPE for a O-2g ionized structure, as a function of the diheral angle Θ(HC-3g—C-3g—O-3g—H-3g).

interresidual hydrogen bonding between O-1f—H-1f (donor) and O-2g (acceptor) was chosen for this computation. DPE and ΔHf for O-2g ionized structures are plotted on Figure 6 for each dihedral angle value. As can be seen, DPE values for O-2g are very sensitive to neighboring hydroxyl group orientation. The minimum value is obtained for an angle of 100° corresponding to the minimum distance between O-2g and H-3f (i.e., 2.40 Å). This position corresponds also nearly to the best orientation for hydrogen bonding between O-4g—H-4g (donor) and O-3g (acceptor) thereby increasing the strengh of the donor character at the ring ended O-2g acceptor atom.

As a result of this study it appears that the various possible orientations of the secondary hydroxy functions must also be considered when calculating physical parameters, like deprotonation enthalpy, influenced by hydrogen bond considerations. This should be done for both the glucose and fructofuranose residues.

CONCLUSION AND PERSPECTIVES

Semiempirical calculations of deprotonation enthalpies (DPEs) investigated herein can provide a comparative scale for acidity of the various hydroxy groups of the sucrose molecule. DPE values have been calculated, for each group, on four starting conformations as previously observed by NMR experiments. DPE averaging shows that the O-2g hydroxy function is by far the most acidic position of the molecule. This result is in good agreement with experimental chemical observations. It also shows that the reaction of sucrose in aprotic solvents might be based on a small number of conformations. Interresidual hydrogen bonds are also confirmed to play a significant role on the acidity behaviour of the sucrose hydroxyls. These conclusions are by no mean contradictory to those proposed for the conformational behaviour of sucrose[30] and chlorinated derivatives[31] in aqueous solution.

Nevertheless, some limitations of this approach have to be stressed. It has been shown that DPE values are very sensitive to orientation of secondary hydroxyl groups. As a result, several possible orientations of these groups on both the glucose and fructofuranose residues must be considered. In the case of sucrose this would have increased considerably the complexity of the study and the CPU time as well. Understanding of the influence of secondary alcohol groups orientations on the DPE values is under investigation with monosaccharides as more simple models. As we observed, the DPE calculation approach does not provide an order of acidity for the various hydroxyl groups similar to the order observed when calculating electrostatic potential from partial atomic charges.

METHODS OF CALCULATIONS

Nomenclature. The torsion angles which describe the conformations about the glycosidic linkage are Φ and Ψ, whereas those describing the orientation of the primary hydroxyl groups are ωg, ωf, and χf. The orientations of the O-6g, O-6f, and O-1f primary hydroxyl groups are also refered to as either *gauche-gauche* (*gg*), *gauche-trans* (*gt*), and *trans-gauche* (*tg*). In this terminology the terms trans or gauche characterize the torsion angles O-5—C-5—C-6—O-6 first and C-4—C-5—C-6—O-6 second.[32]

Molecular Mechanics Calculations. The conformational work was performed with molecular mechanics MM3(92)[24] program obtain from Technical Utilization Corporation, Inc., Powell, Ohio, USA. MM3(92) force field takes into

account the stretching, bending, stretch-bending, torsional, dipolar contributions and Van der Waals interactions. Partial atomic charges were not used since MM3 calculate dipole-dipole interaction energy from stored bond moments. The block-diagonal minimization method, with a default convergence criterium of 3.6 cal/mol, was used. A dielectric constant ε of 4.0 was used.

Electrostatic Potential Calculations. Electrostatic potential[33] was calculated from partial atomic charges obtained by MNDO semiempirical calculations. Whereas PM3 and AM1 have been shown to be mediocre methods for providing atomic charges,[34] MNDO is well recognised to give electrostatic potentials similar to those obtained with *ab initio* methods.[35-37]

DPE Calculations. Computations were performed with the MOPAC 5.0 program[27] available on the Sybyl 6.02 molecular modeling package.[38] The deprotonation enthalpy was calculated for each primary and secondary hydroxyl groups of the four starting conformers using the three semiempirical PM3,[39] AM1[40] and MNDO[41] Hamiltonians. Oxyanions were obtained by deleting the chosen hydrogen atom and by assigning a -1 charge to the molecule. The molecules were assumed to be ground-state singlets. The MOPAC program was used and no further geometry optimization was done. The experimental value of 367.2 kcal/mol was taken for ΔH_f (H^+).[22]

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