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# Acoustical Spectroscopy of Carbohydrate Aqueous Solutions: Saccharides; Alkyl Glycosides; Cyclodextrins. Part I. Conformer Variations

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Acoustical attenuation spectra in the frequency range 12 kHz – 2 GHz and non-equilibrium time domain measurements are briefly reviewed for aqueous solutions of various mono- and disaccharides as well as alkyl glycosides. Several relaxation regimes emerge with relaxation times between $10^{-11}$ s and $10^{3}$ s. In this paper relaxation terms reflecting conformational changes are discussed, particularly mutarotation ($10^{3}$ s), chair-chair ring inversion (1 μs), two modes of pseudorotation (100 ns, 10 ns), disaccharide ring isomerisation (10 ns), and exocyclic side group rotation (1 ns).

**Keywords:** acoustical spectroscopy, non-equilibrium spectroscopy, carbohydrate solutions.

## 1. Introduction

Carbohydrates constitute the most abundant class of material in the biosphere where they hold a key position in the maintenance and function of life. Beyond their roles as prime polymeric contributors to the structure of the extra-cellular matrix and as the main resource of energy of cells they are major elements in the molecular logic of life (Ernst *et al.*, 2000; Lindhorst, 2000; Hurtley *et al.*, 2001; Sears, Wong, 2001; Bertozzi, Kiessling, 2001; Dove, 2001; Maeder, 2002; Kogelberg *et al.*, 2003; Gabius *et al.*, 2004). Linked to proteins and lipids, carbohydrates act as biological code in cellular recognition and signalling processes and thus contribute to the functioning of the immune system (Sears, Wong, 1999; Gabius, 2000).

Carbohydrate-mediated recognition is provided by the rich stereochemical variety and conformational flexibility of mono-, di- and oligosaccharides (Sears,

Wong, 1999; Gabius, 2000). Acoustical spectroscopy which, via changes in the molecular volume, couples to saccharide conformer variations is thus an adequate method to investigate the kinetics of these elementary processes. In principle, acoustical spectroscopy is available in a range from audio (10 kHz) to hypersonic (10 GHz) frequencies, enabling the study of molecular processes with relaxation times between about 20 μs and 20 ps (Akashi *et al.*, 2000; Stenger *et al.*, 2000; Polacek *et al.*, 2002; Hagen, Kaatze, 2004; Haller, Kaatze, 2008a). In addition to conventional frequency domain spectroscopy in this wide band, non-equilibrium time-resolved measurements of saccharide solutions have extended the available range of investigations into saccharide conformational variations to relaxation times of the order of hours (Polacek *et al.*, 2001; Behrends, Kaatze, 2004).

Acoustical spectroscopy is indeed a rather sensitive and almost universally applicable method that favourably probes the native system under consideration. It lacks, however, specificity. For this reason, external parameters, such as concentration, temperature, solvent composition, or solute properties are often varied in order to reach a clear assignment of relaxation terms in the acoustical spectra to molecular processes. Saccharides offer most favourable conditions for the assignment of relaxations because of the diversity of available stereoisomers. The structure of a few monosacharides is shown in Fig. 1 to illustrate the modest stereochemical modifications which can be utilized in measurements of this group of carbohydrates.

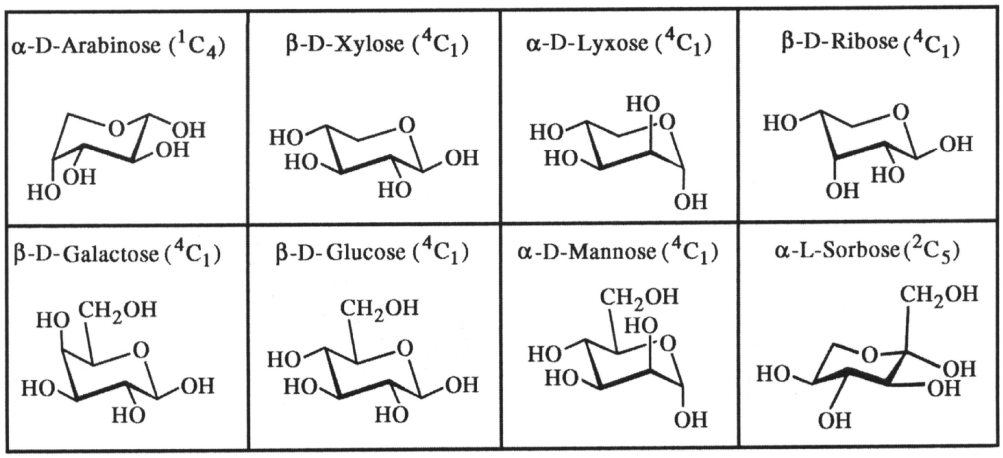


Fig. 1. Structure of some monosaccharides. Upper line: pentoses $(CH_2O)_5$; lower line: hexoses $(CH_2O)_6$. The most frequent conformation of each molecule is depicted.

Saccharides form also the hydrophilic head group of alkyl glycosides, a category of nonionic surfactants which receives increasing interest after technical processes for the grand scale industrial production have been developed

(Hill *et al.*, 1997). Alkyl glycosides can be produced from renewable resources. They are readily biodegradable and do not appreciably irritate skin. Due to these beneficial features wide spread applications of such surfactants are to be found in medicine, in biochemical, pharmaceutical and cosmetic formulations, as well as in large-scale cleaning, wetting and separation processes (von Rybinski, Hill, 1998; Fukada *et al.*, 2000; Shirota *et al.*, 2001; López *et al.*, 2001; Pillion *et al.*, 2002). In water, alkyl glycosides form various complexes, often spherical or cylindrical micelles (Aoudia, Zana, 1998). Whereas phase diagrams of alkyl glycoside/water systems have been determined and the structures of different phases have been investigated by several experimental techniques, less attention has been directed toward the molecular dynamics of the solutions. Again acoustical spectrometry is a favourable method for the study of alkyl glycosides in water. On the one hand, it is capable to monitor the conformational variations of the saccharide head groups on the surface of micellar aggregates and to thus reveal differences with respect to non-associated molecules. On the other hand, it provides the opportunity to study the monomer exchange kinetics with a view to a comparison to other nonionic micelle solutions (Haller, Kaatze, 2009a; 2009b).

Another class of carbohydrate-related molecules that attracts much attention currently is cyclodextrins. Cyclodextrins are naturally available cyclic oligosaccharides accessible from degradation of starch. Common cyclodextrins are comprised of six, seven, or eight glucose residues, forming a shallow truncated cone. The centre cavity is to a greater extent hydrophobic whereas the outer surface is rather hydrophilic. The exohydrophilic character provides a reasonable solubility of the cyclic oligomers in water and the more hydrophobic cavity enables the molecules to form inclusion complexes with guests (Balcerzak *et al.*, 2002), preferably with lipophilic molecules or organic ions (Fukahori *et al.*, 2004a). Encapsulating the guests cyclodextrins do not only serve as carriers by increasing the solubility of complexed molecules in aqueous environment. They also serve as protectants, preventing the guests from degradation by oxidation, hydrolysis or light, and they provide a controlled delivery of substances, such as drugs. Broad and diverse application is to be found in pharmaceutics, diagnostics, and biotechnology. Because of the wide fields of applications considerable efforts have been undertaken to elucidate the properties of cyclodextrins, in particular of their complex formation with different molecules and ions (Fukahori *et al.*, 2004b; Reinborough, Stephenson, 2004; Yamaguchi *et al.*, 2005; Valente *et al.*, 2005; Jutunen *et al.*, 2005; Hazekamp, Verpoorte, 2006; Fukahori *et al.*, 2006; Nishikawa, Kondo, 2006; Haller *et al.*, 2006; Panneer Selvam, Geetha, 2008; Balcerzak, 2008; Haller, Kaatze, 2008b; Bae, Lee, 2009; Haller, Kaatze, 2009c). Here the focus will be the interplay of complex formation and self-aggregation in solutions containing both, cyclodextrin and surfactant (Haller, Kaatze, 2008b; 2009c).

This review presents results for aqueous solutions of mono- and disaccharides, as well as of alkyl glycosides and cyclodextrin in order to demonstrate the poten-

tial of broadband ultrasonic spectroscopy to investigate conformational variations and, in the second part of the paper, association and complex formation of solutes.

## 2. Experimental evidence

### *2.1. Broadband attenuation spectra*

In Fig. 2 the acoustical attenuation spectrum of an aqueous solution of D-fructose is displayed in both common formats. The frequency normalized representation, in which the attenuation coefficient per squared frequency, $\alpha/\nu^2$, is plotted *versus* frequency, $\nu$, strongly accentuates the low-frequency part of the spectrum. Towards high frequencies the data asymptotically approach a frequency-independent value $B' = Bc_s$, shown by the dashed line. Here $c_s$ denote the sound velocity of the solution. $B$ (like $B'$) is due to viscous and thermal con-

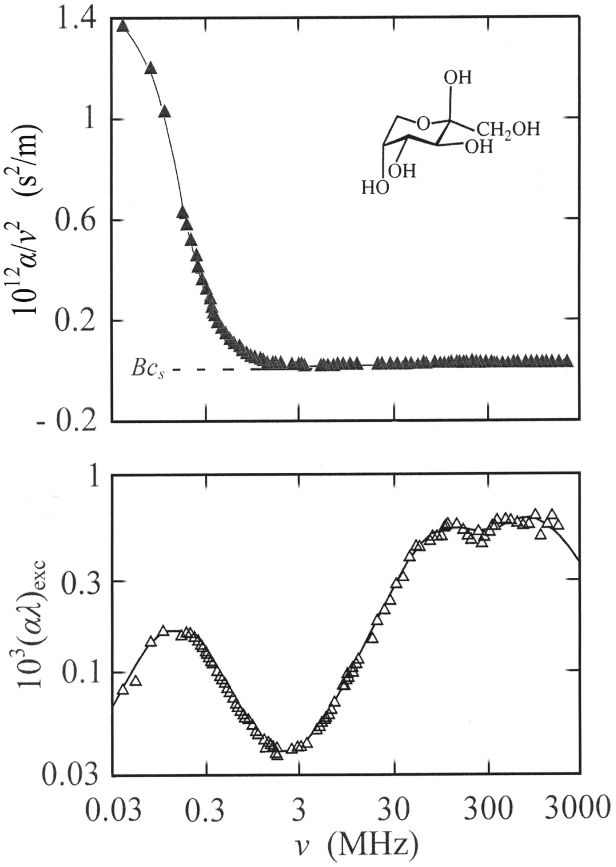


Fig. 2. Ultrasonic attenuation spectrum for a solution of D-fructose (0.5 mol/l) in water at 25°C: frequency normalized attenuation coefficient (top) and excess attenuation per wavelength (bottom) *versus* frequency (Polacek *et al.*, 2002; Behrends, Kaatze, 2004).

ductivity losses as well as relaxation processes with relaxation frequencies well above the frequency range of measurement (BHATTIA, 1967). Since we are not interested in the high-frequency contribution the spectra will be mostly displayed as excess attenuation per unit wavelength

$$(\alpha\lambda)_{\text{exc}} = \alpha\lambda - B\nu, \tag{1}$$

where $\lambda = c_s/\nu$. Accentuating the high-frequency part of the spectrum the $(\alpha\lambda)_{\text{exc}}$ – *versus* – $\nu$ plot in Fig. 2 reveals three relaxations. It will be shown below that, within the frequency range under consideration, altogether five relaxation regions exist in the acoustical spectra of monosaccharide aqueous solutions.

Because of the quadratic frequency dependence of the asymptotic high-frequency term, the sonic attenuation coefficient of liquids varies enormously within the measurement frequency range. In order to reach maximum sensitivity, two different methods and a variety of different sample cells have been used in $\alpha$ measurement. At low frequencies ($\nu \leq 20$ MHz), where normally $\alpha$ is small, the resonator principle was appropriate. It is based on the idea to increase the effective path length of interaction of the sonic field with the sample by convoluting the acoustical path via multiple reflections (EGGERS, KAATZE, 1996). Calibration measurements with carefully adjusted sound velocity and, as far as possible, density have been performed in order to correct measured data for intrinsic cell losses. A spherical cell ($12.5 \leq \nu \leq 150$ kHz; POLACEK, KAATZE, 2001a) and several cylindrically shaped cavities for quasi-one-dimensional wave propagation (80 kHz $\leq \nu \leq$ 20 MHz) have been employed. The cells mainly differed from one another by their dimensions and by the shape of their reflectors. Biplanar (EGGERS, KAATZE, 1996), plano-concave (EGGERS *et al.*, 1994), and biconcave (POLACEK, KAATZE, 2003) resonators were used. In the upper frequency range ($\nu \geq 10$ MHz), absolute $\alpha$ measurements have been performed by transmitting pulse-modulated sonic waves through a cell of variable sample length (EGGERS, KAATZE, 1996; KAATZE *et al.*, 1988; 1993; 1996). Modern electronics enable sophisticated measuring routines, e.g. scanning the complete transfer function of resonators to properly consider the effects from higher order modes in the principal resonance peaks and running regularly calibration routines in the variable-path-length method. Electronics also facilitate the reduction of statistical errors by easily allowing for multiple measurements and averaging. The uncertainty $\Delta\alpha$ in the attenuation coefficient depends on several parameters. Normally relative uncertainties $\Delta\alpha/\alpha$ are between 0.005 and 0.05, depending on frequency.

### *2.2. Non-equilibrium time-domain data*

As already briefly mentioned before, carbohydrate molecules may form a multitude of isomers. As an example Fig. 3 shows the tautomer equilibrium scheme of D-fructose in water (FLOOD *et al.*, 1996). The monosaccharide is available in four ring conformations, two pyranose (six membered rings) and two fura-

nose forms (five-membered rings). Each tautomer can reform to another one only via the open linear configuration. Hence conversion of a cyclic tautomer to another one involves breakage and reformation of a chemical bond. At room temperature the characteristic time constant for such conversion, called mutarotation, is on the order of hours and thus not accessible to acoustical frequency domain spectroscopy. In order to investigate mutarotation, it is, however, possible to utilize the effect that carbohydrates crystallize from different solvents with different equilibrium concentrations of tautomers. D-fructose is available in crystalline form as $\beta$-anomer. Establishment of the equilibrium distribution of tautomers, when $\beta$-D-fructopyranose is dissolved in water, may be followed by acoustic measurements that couple to the chair-chair ($^2C_5 \leftrightarrow {}^5C_2$) equilibrium of the $\alpha$-D-fructopyranose anomer (Fig. 3).

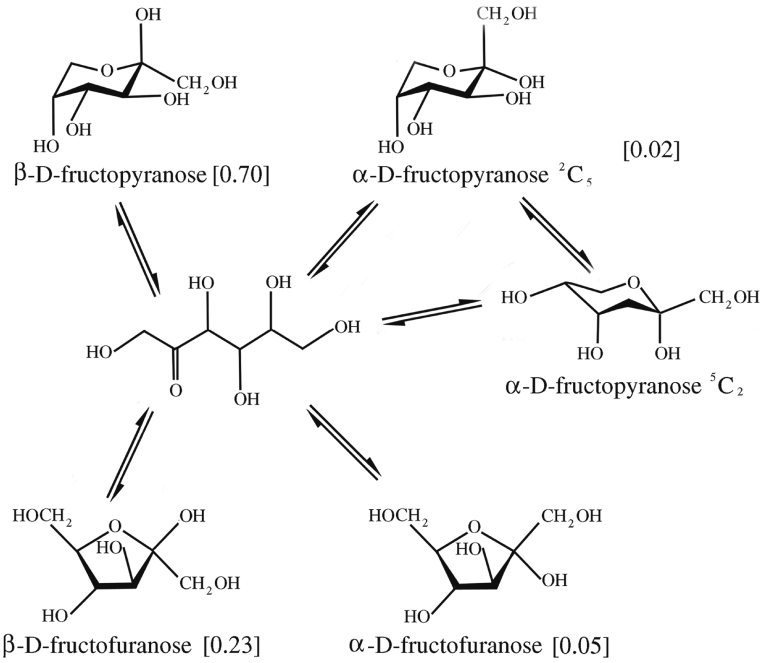


Fig. 3. Mutarotation scheme of D-fructose in water (Flood *et al.*, 1996). Figures in brackets show the equilibrium mole fraction of tautomers at room temperature.

As will be discussed with details below (Subsec. 3.1) this equilibrium between both chair conformations is reflected by the low frequency relaxation, with relaxation frequency $\nu_\alpha$ around 100 kHz in the attenuation spectra (Fig. 2). According to our expectations, the relaxation frequency $\nu_\alpha$ corresponding with the chair – chair conformational equilibrium, essentially a zero-order reaction, is independent of concentration (Fig. 4) and the relaxation amplitude is proportional to $\alpha$-D-fructopyranose concentration. Hence $(\alpha\lambda)_{\rm exc}$ ($\approx \alpha\lambda$, $B \approx 0$) at any frequency within the range of the low-frequency relaxation, preferably at $\nu_\alpha$,

measures the concentration of the $\alpha$-furanose, capable of the chair – chair conformational change. For a D-fructose solution at room temperature, Fig. 5 shows the relative increase

$$F(t) = \frac{\alpha(t) - \alpha(\infty)}{\Delta}, \qquad \Delta = |\alpha(t_0) - \alpha(\infty)| \tag{2}$$

in $\alpha$ and thus in the $\alpha$-D-fructopyranose concentration with time (Polacek *et al.*, 2001).

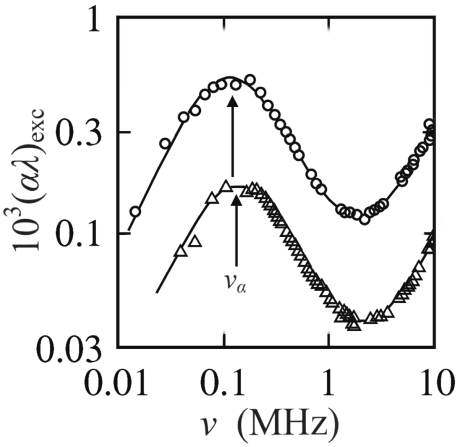


Fig. 4. Low-frequency part of the excess-attenuation spectra for solutions of D-fructose (Δ, 0.5 mol/l; ∘, 1.5 mol/l; Polacek *et al.*, 2002) in water at 25°C. Arrows mark the relaxation frequency $\nu_\alpha$.

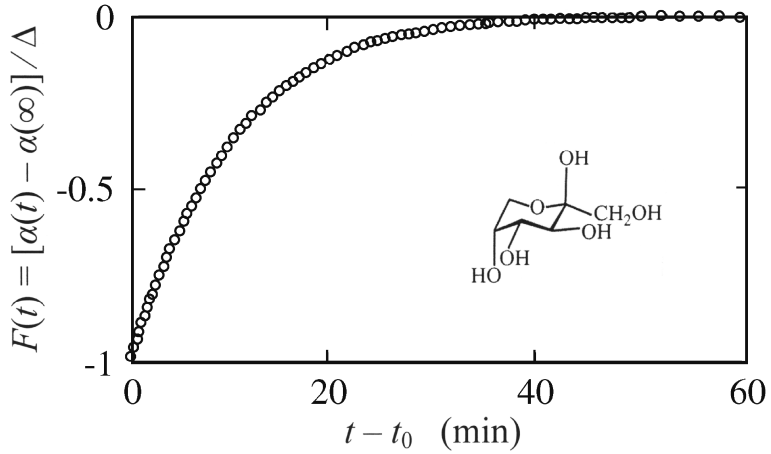


Fig. 5. Time dependence in the sonic attenuation coefficient at 380 kHz of a freshly prepared solution of D-fructose (1 mol/l) in water at 20°C. Measurement of $\alpha$ started $t_0 = 3$ min after preparation of the sample (Polacek *et al.*, 2001; Behrends, Kaatze, 2004). See Eq. (2) for Δ.

### *2.3. High resolution sound velocity traces*

Present-days sound velocimeters can reach a resolution as high as $\Delta c_s/c_s \approx 10^{-7}$ (Kaatze *et al.*, 2008) but still cover a limited frequency band only. Sound velocity data which, with inferior resolution, have been also obtained as a byproduct from attenuation coefficient measurements, are thus used to monitor phase transitions of samples only. An example, exposing the shift in the critical micelle concentration cmc on addition of complexing cyclodextrin to a surfactant solution, is presented in Fig. 6. The $c_s$ data have been recorded at around 5 MHz using a specially designed fixed path cavity resonator cell. Twin cells with one cavity filled with a suitable reference (Kaatze *et al.*, 2008) allow for reduced effects from temperature fluctuations.

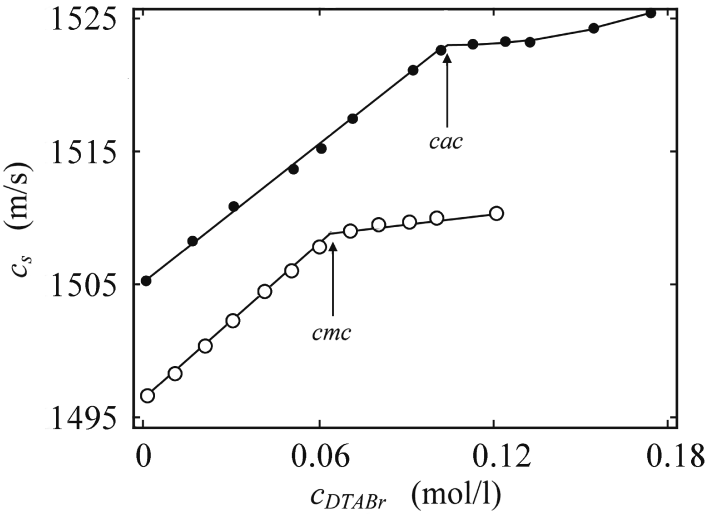


Fig. 6. Sound velocity $c_s$ at 25°C *versus* total surfactant concentration $c_{CTABr}$ for aqueous solutions of *n*-decyltrimethylammonium bromide without (○) and with (●) α-cyclodextrin (0.05 mol/l) added (Haller, Kaatze, 2008b). The critical aggregate concentration *cac* of the latter exceeds the critical micelle concentration *cmc* of the surfactant solution by 0.04 mol/l.

## 3. Results and discussion

### *3.1. Monosaccharide attenuation spectra*

In order to demonstrate the relaxation regions a selection of excess-attenuation-per-wavelength spectra for solutions of monosaccharide in water is presented in Fig. 7. Altogether five relaxation regimes are to be distinguished which are labelled by Greek letters in the diagram. Careful analysis of the experimental spectra shows that all contributions from relaxation processes can be well rep-

resented by a relaxation term with discrete relaxation time $\tau(= [2\pi\cdot$ relaxation frequency$]^{-1})$. Hence relaxation terms

$$\frac{A2\pi\nu\tau}{1+(2\pi\nu\tau)^2}, \tag{3}$$

with amplitude $A$ have been used in the regression analysis of the experimental data. The five relaxation times relevant to the monosaccharide aqueous solutions are of the order of 1 μs ($\tau_\alpha$), 100 ns ($\tau_\beta$), 10 ns ($\tau_\gamma$), 1 ns ($\tau_\delta$), and 100 ps ($\tau_\varepsilon$), respectively (Polacek *et al.*, 2002). The latter relaxation term has been tentatively discussed in terms of association (Stenger *et al.*, 2000; Polacek *et al.*, 2002). Terms "$\alpha$" to "$\delta$" are being assigned to conformational variations as will be briefly set below.

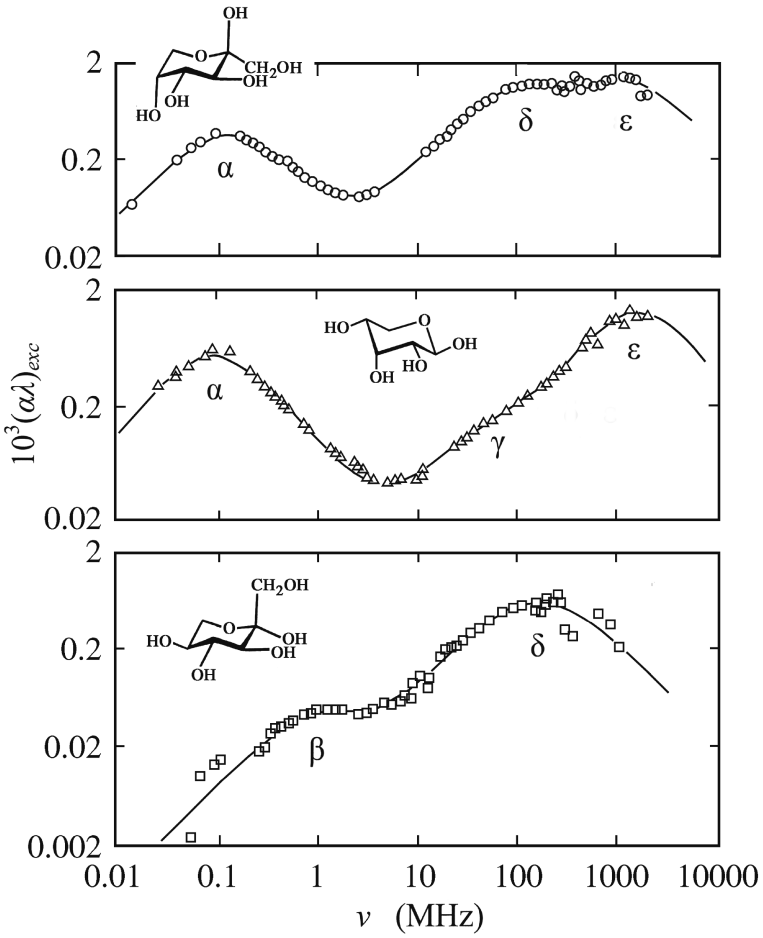


Fig. 7. Ultrasonic excess attenuation spectra at 25°C for 1 molar aqueous solutions of D-fructose (○; top), D-arabinose (Δ; middle), and L-sorbose; (□; bottom). Greek letters mark relaxation regimes (Polacek *et al.*, 2002).

### *3.2. Chair – chair ring inversion*

Independence of the relaxation time $\tau_\alpha$ of D-fructose solutions from solute concentration $c$ and the linear increase of $A_\alpha$ with $c$ (Fig. 8) point at an underlying unimolecular (zero-order) reaction, such as a transition between conformers S and S$^*$ of a saccharide. For unimolecular reactions the relaxation rate

$$\tau_\alpha^{-1} = k_f^\alpha + k_b^\alpha \tag{4}$$

is given by the forward ($k_f^\alpha$) and backward ($k_b^\alpha$) rate constants and the amplitude

$$A_\alpha = \frac{\pi}{\kappa_S RT} \Gamma \Delta V_S^2 \tag{5}$$

is controlled by the isentropic volume change

$$\Delta V_S = \Delta V - \frac{\alpha_p}{\rho C_p} \Delta H_0 \tag{6}$$

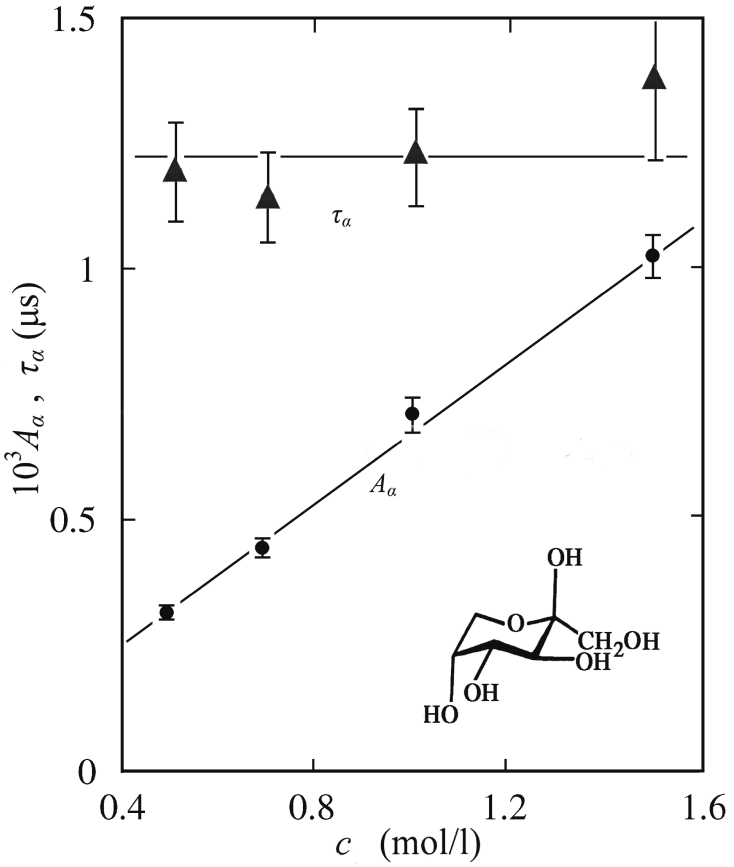


Fig. 8. Relaxation amplitudes $A_\alpha$ (▲) and relaxation times $\tau_\alpha$ (●) of the low-frequency term in the acoustical spectra of solutions of D-fructose in water at 25°C and at different saccharide concentrations $c$ (Polacek *et al.*, 2002).

and a stoichiometric factor

$$\Gamma = [\mathrm{S}][\mathrm{S}^*]/([\mathrm{S}] + [\mathrm{S}^*]) = ([\mathrm{S}] + [\mathrm{S}^*])K_\alpha/(1 + K_\alpha), \tag{7}$$

which is proportional to the concentration $[\mathrm{S}] + [\mathrm{S}^*]$ of the saccharide tautomer. In the above relations $\kappa_S = \rho^{-1}c_s^{-2}$ is the adiabatic compressibility, $R$ is the universal gas constant, $\alpha_p$ and $C_p$ are the thermal expansion coefficient and specific heat, respectively, at constant pressure, $\Delta V$ denotes the isothermal reaction volume and $\Delta H_0$ the interaction enthalpy difference. $K_\alpha = k_f^\alpha/k_b^\alpha$ is the equilibrium constant.

The behaviour of the relaxation times and amplitudes at varying monosaccharide concentration is indeed compatible with a chair – chair conformational equilibrium ${}^i\mathrm{C}_j \leftrightarrow {}^j\mathrm{C}_i$. More specific information for the attribution of the low-frequency ($\alpha$) relaxation to this equilibrium comes from the synopsis of findings for a variety of saccharides. Only for the four monosaccharides listed in Table 1 an $\alpha$-relaxation term has been found, in conformity with predictions from the literature. Evidently, a ${}^i\mathrm{C}_j \leftrightarrow {}^j\mathrm{C}_i$ ring inversion is only possible when the corresponding interaction energy change $\Delta U$ is on the order of thermal energy (= 2.5 kJ/mol at room temperature). Such small interaction energies are typically correlated with a balanced number of axial ($N_a$) and equatorial ($N_e$) exocyclic hydroxy and hydroxy methyl groups of the monosaccharide. A ${}^i\mathrm{C}_j \leftrightarrow {}^j\mathrm{C}_i$ ring inversion converts an axial group into an equatorial and *vice versa*. Hence saccharides with $N_a/N_e = 1$ are in favour because the ring conformational variation does not alter the number of relevant axial and equatorial groups. An exception with unbalanced number is $\beta$-D-ribose ($N_a/N_e$ = 3:1). It may be taken to indicate that other factors, such as the overall arrangement of groups with respect to the water structure, are also influencing the $\Delta U$ values.

**Table 1**. Mole fraction $X$ of anomers (Angyal, 1984; Lehmann, 1996; Galema, 1992), interaction energy difference $\Delta U$ (Lehmann, 1996; Galema, 1992) as well as reaction volume $\Delta V$ (Polacek *et al.*, 2002) of chair – chair ring inversion for monosaccharides displaying an $\alpha$-relaxation term in the acoustical spectra of their aqueous solutions.

| Carbohydrate | $X$ | | $\Delta U$ [kJ/mol] | | $\Delta V$ [cm$^3$/mol] |
|---|---|---|---|---|---|
| | $\alpha$ | $\beta$ | $\alpha$ | $\beta$ | |
| D-arabinose | 0.60 | 0.355 | 4.8 | 2.1 | 0.9 |
| D-lyxose | 0.70 | 0.28 | 2.3 | 4.4 | 1.4 |
| D-ribose | 0.315 | 0.585 | 0.4 | 2.5 | 1.4 |
| D-fructose | 0.02 | 0.70 | 2.7 | 11.5 | 7.5 |

Another indication for the assignment of the $\alpha$-relaxation term to the chair – chair ring inversion is the fact that aqueous solutions of D(+)-saccharose do not display a low-frequency ultrasonic relaxation (Fig. 9). D(+)-saccharose is composed of a glucopyranose and a fructofuranose ring. The latter (five-membered

ring) anomer of fructose (Fig. 3) is unable to undergo the ring inversion. Further evidence has been obtained from solutions of D-fructose in mixtures of water with ethanol (Polacek, Kaatze, 2001b). The small content of the $\alpha$-D-fructopyranose anomer, which is capable of the chair-chair inversion in water (Fig. 3), even decreases when ethanol is added. Correspondingly, the amplitude of the low-frequency relaxation term in the acoustical spectra decreases to become zero at sufficiently high ethanol concentration. Also non-equilibrium time-domain measurements support the assignment of the $\alpha$-relaxation term to the chair-chair conformational equilibrium. D-arabinose, for example, can be crystallized as $\beta$-anomer, the one that is capable of the ring inversion. When dissolved in water, this monosacharide, in correspondence with D-fructose, establishes its equilibrium via mutarotation (Subsec. 3.5). However, whereas with D-fructose the content of the relevant anomer (and thus the amplitude of the $\alpha$-relaxation term) increases, the relaxation amplitude decreases with D-arabinose solutions. This decrease, consistent with the drop in the $\beta$-anomer concentration when equilibrium is established, is a further confirmation of the correlation of the low-frequency relaxation with the chair – chair ring inversion.

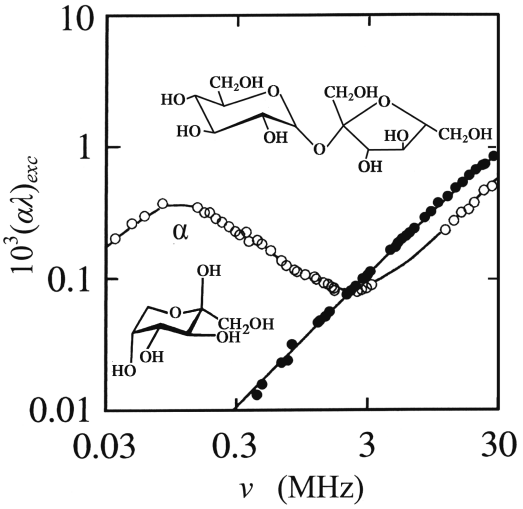


Fig. 9. Low-frequency parts of the acoustical excess attenuation spectra of aqueous solutions of D(+)-saccharose (•, 1 mol/l) and D-fructose (◦, 1 mol/l) at 25°C (Hagen, Kaatze, 2004).

Assuming the change $\Delta G_0$ of free energy associated with the unimolecular chair – chair inversion to be given by the interaction energy difference $\Delta U(\approx \Delta H_0 \approx \Delta G_0)$, van't Hoff equation may be simply used in the form

$$K_\alpha = \exp(-\Delta U/RT) \tag{8}$$

to obtain the equilibrium constant. This form allows us to use $\Delta U$ data from Table 1. It also implies $\Delta H_0 \approx 0$, so that $\Delta V \approx \Delta V_S$. On these assumptions $\Delta V$ values between 0.9 and 1.4 $\mathrm{cm}^3$/mol result for the aldopentoses D-arabinose,

D-lyxose, and D-ribose, whereas significantly larger $\Delta V = 7.1$ cm$^3$/mol follows for the ketohexose $\alpha$-D-fructopyranoside (Table 1). The distinctly larger volume change of the ketohexose has been considered to reflect participation of the exocyclic hydroxy methyl group in the ring inversion. Such group, which is missing with the aldopentoses, may require a significantly more pronounced rearrangement of the hydration shell when the monosaccharide changes its ring conformation.

Using Eyring theory (Glasstone *et al.*, 1941)

$$\tau_\alpha^{-1} = \frac{k_B T}{h}(1 + K_\alpha) \exp\left(\frac{\Delta S_b^\#}{R}\right) \exp\left(\frac{-\Delta H_b^\#}{RT}\right) \tag{9}$$

relaxation rate $\tau_\alpha^{-1}$ can be related to the entropy $\Delta S_b^\#$ and enthalpy $\Delta H_b^\#$ of activation of the backward process. In Eq. (9) $k_B$ and $h$ are Boltzmann's and Planck's constants, respectively. Evaluation of temperature dependent relaxation rates of D-fructose solutions reveals $\Delta H_0 \ll \Delta H_b^\#$, thus $\Delta H_b^\# \approx \Delta H_f^\#$. Assuming $K_\alpha$, $\Delta S_b^\#$, and $\Delta H_b^\#$ to only weakly depend upon $T$,

$$\frac{d \ln(h\tau_\alpha^{-1}/k_B T)}{dT^{-1}} = -\frac{\Delta H_b^\#}{R} - \frac{K_\alpha}{1 - K_\alpha}\frac{\Delta H_0}{R} \tag{10}$$

results from Eq. (9). With $\Delta H_0 = \Delta U = 2.7$ kJ/mol (Table 1) $\Delta H_b^\# = (42 \pm 4)$ kJ/mol follows from acoustical spectroscopy of D-fructose solutions at temperatures between 15 and 35°C (Polacek *et al.*, 2002). This value is in nice agreement with text books on carbohydrates (Lehmann, 1996).

### *3.3. Exocyclic hydroxy methyl group isomerisation*

The parameters of relaxation term $\delta$ in the acoustic spectra of carbohydrate aqueous solutions indicate also an underlying unimolecular reaction. Figure 10 illustrates fair constancy of the relaxation rates $\tau_\delta^{-1}$ for solutions of two monosaccharides and a disaccharide. Following a suggestion by Tvaroska and Bleha (1989), the $\delta$-term has been assigned to the rotation of the exocyclic hydroxymethyl ($-CH_2OH$) group. Frequently this rotation, basically a gauche-trans isomerisation, is named $\omega$-rotation. The above assignment is effectively supported by the acoustical relaxation spectra of carbohydrate aqueous solutions which, with two exceptions to be discussed below, reveal a $\delta$-term if the carbohydrate possesses an exocyclic hydroxymethyl group but do not show a $\delta$-term if such group is missing. A prominent example is shown in Fig. 11 where frequency-normalized spectra for solutions of D-glucose and of 1,6-anhydro-glucopyranoside are presented. With the latter bicyclic saccharide the exocyclic $-CH_2OH$ group is fixed by a chemical bond. Consequently, in the frequency range under consideration, the acoustical spectrum of the 1,6-anhydro-glucopyranoside solution does not display relaxation characteristics. Also NMR measurements (Hajduk *et al.*,

1993) and molecular dynamics simulations, combined with quantum mechanics and molecular mechanics calculations (Kirschner, Woods, 2001), support the correlation of the $\delta$-relaxation term with the exocyclic hydroxymethyl group rotational isomerization.

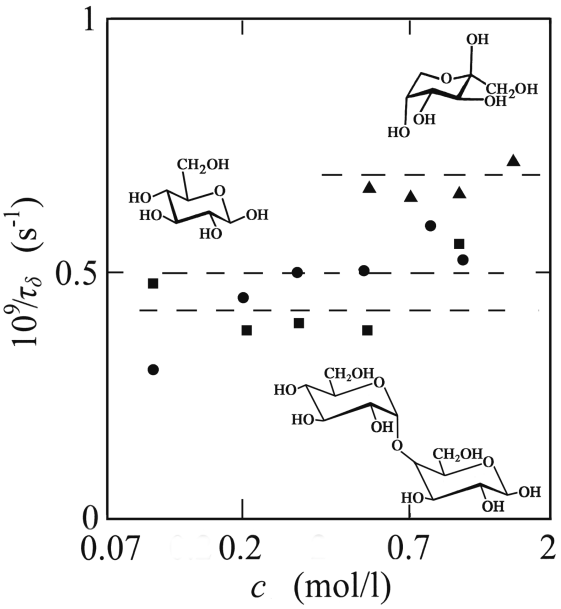


Fig. 10. Relaxation rates $1/\tau_\delta$ *versus* saccharide concentration for aqueous solutions of D-glucose (•; Polacek *et al.*, 2002; Haller, Kaatze, 2008a), D-fructose (▲; Polacek *et al.*, 2002), and D-maltose (■; Hagen, Kaatze, 2004; Haller Kaatze, 2008a) at 25°C.

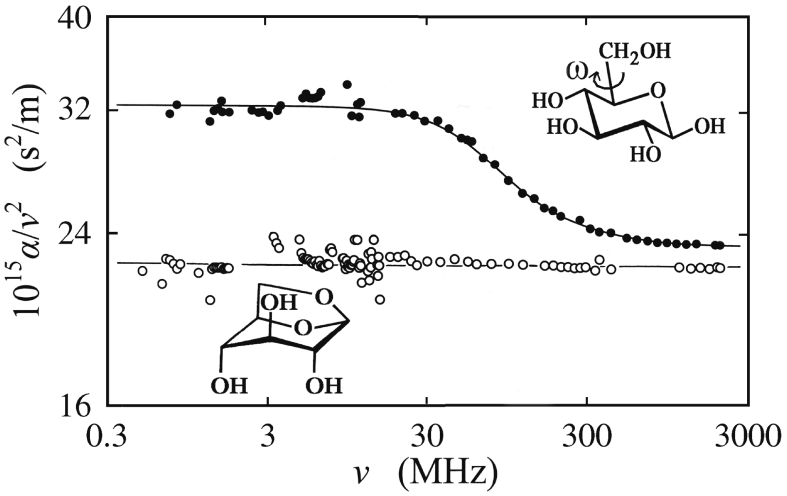


Fig. 11. Acoustical attenuation spectra in the frequency normalized format for 0.5 mol/l solutions of glucose (•) and 1,6-anhydro-$\beta$-D-glucopyranoside in water at 25°C (Polacek *et al.*, 2002).

Applying Eq. (5) analogously allows for an evaluation of relaxation amplitudes $A_\delta$ in terms of the isentropic reaction volume $\Delta V_s$ ($\approx \Delta V$) if the rotamer distribution of the exocyclic $-CH_2OH$ group is taken from NMR data (NISHIDA *et al.*, 1984) or molecular dynamics simulations (OTT, MEYER, 1996). The following reasonable values result for aqueous solutions at room temperature: $\Delta V_s = 1.7$ cm$^3$/mol, D-glucose (HALLER, KAATZE, 2008a); $\Delta V_s = 2.4$ cm$^3$/mol, methyl-$\beta$-D-glucopyranoside (STENGER *et al.*, 2000); $\Delta V_s = 1.5$ cm$^3$/mol, D-maltose (HALLER, KAATZE, 2008a); $\Delta V_s = 1.3$ cm$^3$/mol, D-trehalose (HAGEN, KAATZE, 2004); $\Delta V_s = 1.1$ cm$^3$/mol, D-lactose (HAGEN, KAATZE, 2004). In deriving these data identical reaction volumes have been assumed for the exocyclic hydroxymethyl groups of both rings of disaccharides. Furthermore, $\Delta V_s = 1.9$ cm$^3$/mol, *n*-hexyl-$\beta$-D-glucopyranoside monomers (HALLER, KAATZE, 2009a); $\Delta V_s = 1.3$ cm$^3$/mol, *n*-hexyl-$\beta$-D-maltopyranoside monomers (HALLER, KAATZE, 2009b. For alkyl glucopyranoside and alkyl maltosides forming micelles, enhanced reaction volumes are found, e.g. $\Delta V_s = 2.5$ cm$^3$/mol for *n*-alkyl-$\beta$-D-monoglucopyranosides (HALLER, KAATZE, 2009a) and even larger values for the inner ring of the maltoside head group (HALLER, KAATZE, 2009b). The larger $\Delta V_s$ values for aggregated molecules are taken to reflect the need of free volume for $-CH_2OH$ group isomerisation at the micellar surface. When the monomers are embedded in micelles this volume has to be made available by neighbouring surfactant molecules. For completeness it is mentioned that for the alkyl glycosides the above reaction volumes are minimum values, calculated on the assumption of the maximum stoichiometric factor $\Gamma$ ($= 0.25c$). Since the distribution of conformers in D-glucose aqueous solutions yields $\Gamma = 0.25c$ the minimum values likely agree fairly with the true volume changes.

The relaxation rates $\tau_\delta^{-1}$ for solutions of alkyl maltosides ($\tau_\delta^{-1} = 8 \cdot 10^8$ s$^{-1}$; HALLER, KAATZE, 2009b) almost agree with those for alkyl glycosides ($\tau_\delta^{-1} = 7.6 \cdot 10^8$ s$^{-1}$; HALLER, KAATZE, 2009a). The values for both surfactant systems, however, are larger than those for glucose ($\tau_\delta^{-1} = 5.2 \cdot 10^8$ s$^{-1}$) and maltose ($\tau_\delta^{-1} = 4.3 \cdot 10^8$ s$^{-1}$) aqueous solutions (HALLER, KAATZE, 2008a). Obviously, rotation of the exocyclic hydroxymethyl group is faster on the surface of a micelle than in the fully hydrated state of a monomer.

Surprisingly, a $\delta$-relaxation term is missing in the spectra of D-galactose, though NMR measurements have revealed different exocyclic hydroxymethyl group isomers for this monosaccharide. The only interpretation of this finding seems an extremely small reaction volume associated with the isomerisation of D-galactose, leading to an unverifiable relaxation amplitude $A_\delta$. The other exception in the correlation between the existence of a $\delta$-relaxation term and the availability of an exocyclic hydroxymethyl group is a $\delta$-relaxation term in the acoustic spectra for aqueous solutions of methyl-$\beta$-D-xylopyranoside (STENGER *et al.*, 2000). This monosaccharide does not possess an exocyclic $-CH_2OH$ group. It is tentatively assumed that the $-OCH_3$ group at the anomeric center of the molecule causes a rotation with relaxation time on the order of $\tau_\delta$.

### *3.4. Pseudorotation*

Relaxation terms $\beta$ and $\gamma$ in the acoustic spectra are still incompletely understood. For methyl-$\beta$-D-xylopyranoside solutions $\tau_\beta$ is almost independent of saccharide concentration, thus again pointing at a unimolecular reaction (Stenger *et al.*, 2000). However, no such data have so far emerged for the $\gamma$-relaxation term. An interesting aspect is the fact that no saccharide displaying $\alpha$-, $\beta$- and $\gamma$-terms simultaneously has been found. Only combinations of $\alpha$- and $\gamma$-terms or of $\beta$- and $\gamma$-terms exist in the acoustical spectra.

In addition to the chair – chair ring inversion, cyclic molecules may pass through other conformational changes. Acoustical spectra for solutions of methyl cyclohexane in xylene have been discussed assuming a boat configuration as intermediate state between the chair isomers (Piercy, 1961). NMR studies of D-idose solutions in water suggested skew forms of $\alpha$-D-idopyranose (Snyder, Serianni, 1986). It is, therefore, an obvious attempt to relate the $\beta$- and $\gamma$-terms to tran-

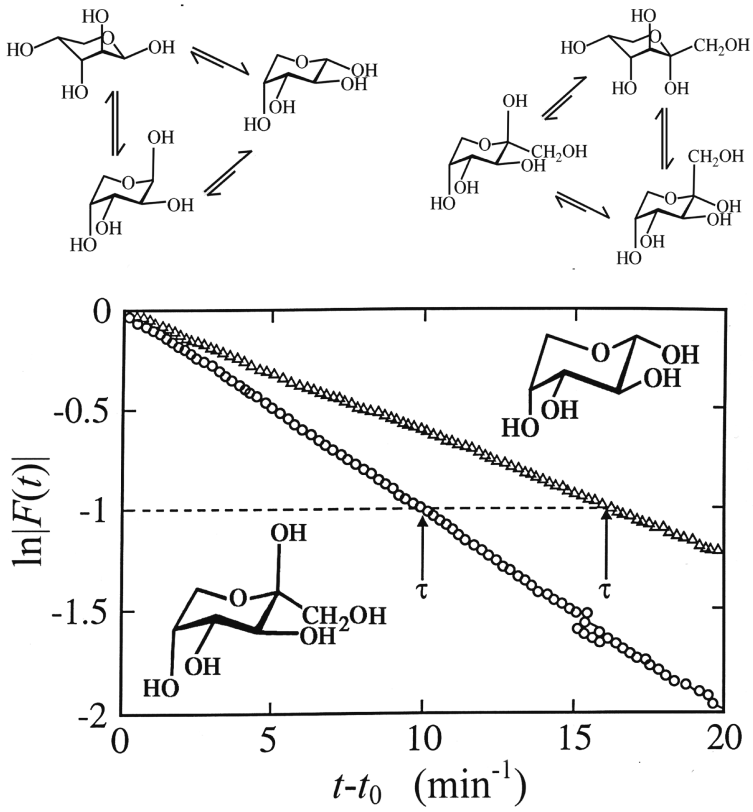


Fig. 12. Natural logarithm of function $F$ (Eq. 2) for aqueous solutions of D-arabinose ($\Delta$, 1.5 mol/) and D-fructose ($\circ$, 1 mol/l) at 20°C displayed as a function of time $t - t_0$ after preparation of the samples (Polacek *et al.*, 2001; Behrends, Kaatze, 2004). Above the diagram essential parts of the mutarotation schemes for arabinose (left hand side) and fructose (right hand side) are shown.

sition between such more labile forms and/or to transitions between such form and a chair configuration. Presently, however, evidence from acoustic relaxation spectra is insufficient for clear-cut conclusions on such processes.

### *3.5. Mutarotation*

Results of time-resolved non-equilibrium measurements (Subsec. 2.2) of two monosaccharide solutions are shown in a log-lin plot in Fig. 12. The acoustical attenuation coefficient of both solutions exhibits an exponential variation with time. The relaxation times are 980 s (D-arabinose) and 600 s (D-fructose) at 20°C. Mutarotation is normally observed by optical activity measurements and the time dependence in the tautomer kinetics is expressed as

$$F(t) = 10^{-mt}. \tag{11}$$

In terms of this function, $m = 0.027$ min$^{-1}$ (D-arabinose) and $m = 0.043$ min$^{-1}$ (D-fructose) followed from the non-equilibrium acoustical measurements, whereas optical activity observations yielded $m = 0.030$ min$^{-1}$ for the former and $m = 0.054$ min$^{-1}$ for the latter monosaccharide (20°C; Behrends, Kaatze, 2004). For fructose solutions the larger $m$ from optical measurements is in agreement with a likewise faster variation of the static (electric) permittivity. It simply reflects the fact that variations of the optical as well as dielectric properties include different pathways in the mutarotation scheme of fructose (Fig. 3). In contrast, variations of the acoustical attenuation refer solely to the conversion of $\beta$-pyranose to $\alpha$-pyranose.

### *3.6. Disaccharide ($\Phi$, $\Psi$)-rotation*

Disaccharide solutions feature an acoustical relaxation term which does not exist with the relevant monosaccharides. Figure 13 illustrates this aspect by comparing the excess attenuation spectrum for a 0.1 mol/l solution of D-maltose to that of 0.2 mol/l solution of glucose. Both spectra display the $\delta$-relaxation term due to the isomerisation of exocyclic hydroxymethyl groups. The spectrum of the maltose solution exhibits an additional relaxation term with relaxation frequency at around 10 MHz. Such relaxation term, with relaxation times between 3.6 and 19 ns, has been also found in spectra of D-trehalose, D-saccharose, and D-lactose solutions (Hagen, Kaatze, 2004) and also of solutions of alkyl maltosides (Haller, Kaatze, 2009b). For maltose solutions of moderate concentrations ($c \leq 1$ mol/l) the relaxation time of the term is independent of $c$ (Haller, Kaatze, 2008a), thus indicating again an underlying unimolecular reaction. This relaxation characteristic of disaccharides has been assigned to the rotation of a ring moiety around the glycosidic bond angles ($\Phi$, $\Psi$). Several local minima exist in the $\Phi$, $\Psi$-potential-energy surface (Ott, Meyer, 1996; Best *et al.*, 2001; Kuttel, Naidoo, 2005; Schnupf *et al.*, 2007). Hence the disac-

charide $\Phi$, $\Psi$-relaxation is assumed to reflect changes of the molecules from one such minimum to another one.

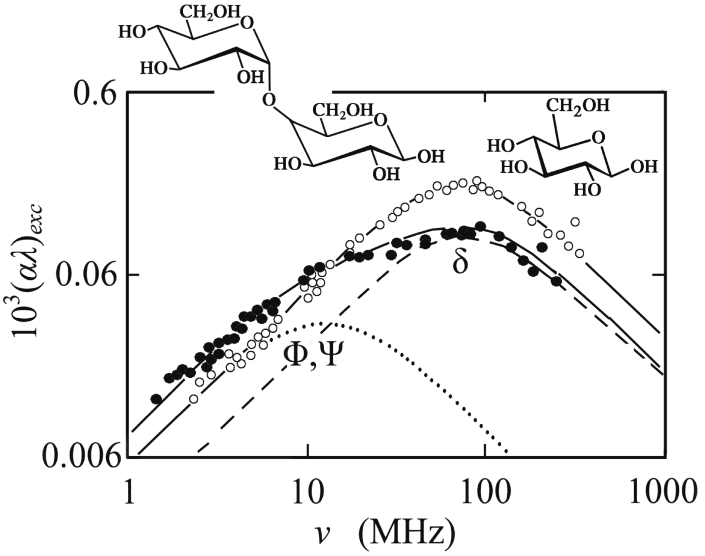


Fig. 13. Ultrasonic excess attenuation spectra for aqueous solutions of D-glucose (○, 0.2 mol/l) and D-maltose (●, 0.1 mol/l) at 25°C (Haller, Kaatze, 2008a). For the latter spectrum dashed and dotted lines indicate the subdivision into two relaxation terms, designated "$\delta$" and "$\Phi$, $\Psi$", respectively.

The idea of a $\Phi$, $\Psi$-relaxation is in conformity with an increase of the relaxation time $\tau_{\Phi,\Psi}$ of maltose solutions at high solute concentrations (Hagen, Kaatze, 2004), because the rotation of a ring moiety will be controlled by the viscosity of the solution. Viscosity increases significantly with $c$ (e.g. $\eta_s = 1.69 \cdot 10^{-3}$ Pa·s, $c = 0.5$ mol/l; $\eta_s = 13.77 \cdot 10^{-3}$ Pa·s, $c = 1.8$ mol/l; 25°C; Hagen, Kaatze, 2004). Assuming equipartition of disaccharide rotamers ($\Delta H_0 = 0$), activation enthalpies $\Delta H^{\#}_{\Phi,\Psi} = 24$ kJ/mol and $\Delta H^{\#}_{\Phi,\Psi} = 17$ kJ/mol have been derived from temperature dependent relaxation time data for D-maltose and D-trehalose solutions, respectively, using Eq. (10) analogously. The former value corresponds with the activation enthalpy of the hydrogen network fluctuations in water (Hasted, 1973). The $\Phi$, $\Psi$-relaxation term in the spectra for alkyl glycoside solutions features more complex behaviour. Figure 14, for example, reveals relaxation times $\tau_{\Phi,\Psi}$ for maltosides which increase with surfactant concentration. However, the relaxation times of these systems represent a combination of various head group rotational isomerisation. They include rotations of the outer glucose ring around the bond to the inner glucose moiety (glucose-glucose isomerisation) and of the inner moiety around the bond to the alkyl chain of the surfactant (glucose-alkyl isomerisation). In addition to the fact that the relative impact of these rotations in the $\tau_{\Phi,\Psi}$ data may change with $c$, the contribution from alkyl glyco-

side monomers relative to molecules in micelles changes, too. Furthermore, at increasing surfactant concentration alkyl glycoside micelles tend to form non-globular micelles with closer packing of molecules (Haller, Kaatze, 2009a). Variation of the packing will also exercise an effect on the head group isomerisation.

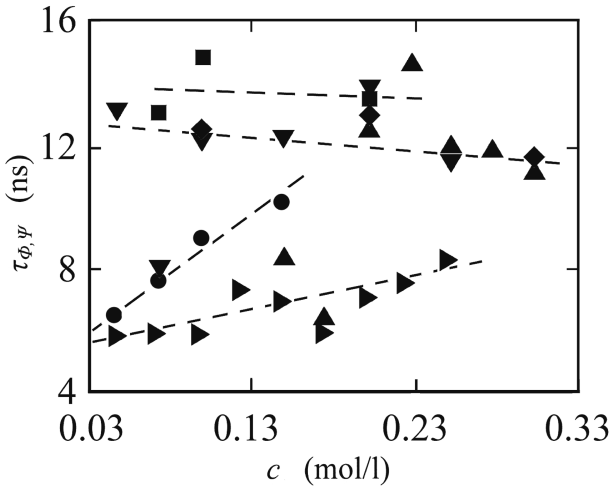


Fig. 14. Relaxation times $\tau_{\Phi,\Psi}$ for aqueous solutions of alkyl maltosides at 25°C shown as a function of solute concentration $c$: ▲, $n$-hexyl-$\beta$-D-; ●, $n$-octyl-$\beta$-D-; ■, $n$-nonyl-$\beta$-D-; ▼, $n$-decyl-$\beta$-D-; ►, $n$-decyl-$\alpha$-D-maltopyranoside (Haller, Kaatze, 2009b). Also shown are $\tau_{\Phi,\Psi}$ data for D-maltose solutions at the same temperature (♦; Haller, Kaatze, 2008a).

## 4. Conclusions

Broadband acoustical spectrometry can provide monitoring of fast conformational variations of carbohydrates in solutions which are difficult to access otherwise. In combination with a non-equilibrium time-domain technique, mutarotation, chair - chair ring inversion, pseudorotation and exocyclic hydroxymethyl group rotation can be detected by acoustical measurements. The parameters of the relaxation terms associated with these elementary reactions can be discussed to yield thermodynamic as well as kinetic parameters, such as the reaction volume and enthalpy, the activation enthalpy, as well as rate and equilibrium constants. Solutions of disaccharides reveal, in addition, a relaxation process due to the rotation of a monosaccharide moiety around the glycosidic bond angles, virtually a rotation of one ring relative to the other one. This isomerisation, including rotation of a ring around the saccharide-alkyl chain bond angle, appears also by a relaxation term in spectra of alkyl glycoside surfactant solutions, allowing thus to study the effect of head group packing in micelles. Correspondingly,

the exocyclic hydroxymethyl group isomerisation contributes also a relaxation term to the spectra of cyclodextrin solutions. This term may be used to monitor structural changes of this interesting class of molecules.

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