Substitution of acyclic sugar acetals. Perchloric acid catalyzed acetolysis of poly-*O*-acetyl acyclic oxygen and sulfur acetals and epimerization of monothioacetals

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The rate constants are reported for the substitution of acyclic sugar poly-*O*-acetyl diethyl dithioacetals, poly-*O*-acetyl diethyl acetals, and poly-*O*-acetyl dimethyl acetals and for the epimerization of poly-*O*-acetyl *S*-ethyl monothioacetals when catalyzed by perchloric acid in acetic acid. All the reactions are pseudo first order. Monothioacetals substitute faster than oxygen acetals, and oxygen acetals substitute faster than sulfur acetals. A group bonded to C_1 of these acyclic sugar derivatives is substituted faster than when the group is bonded to C_1 of poly-*O*-acetyl pyranose derivatives.

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Poly-*O*-acetyl diethyl dithioacetals (I) of common monosaccharides, when dissolved in acetic acid and acetic anhydride containing either mercuric acetate (1) or perchloric acid (2), give products which have an acetoxy group substituted for one ethylthio group. The products of this substitution, diastereomeric poly-*O*-acetyl *S*-ethyl monothioacetals (II), epimerize in acetic acid solutions (2) containing a strong acid. We have proposed the steps shown in Scheme 1 to describe the perchloric acid catalyzed substitution of dithioacetals and the epimerization of the monothioacetals (2). These steps are an extension of the mechanism of acetal hydrolysis first proposed by O'Gorman and Lucas (3) and our proposal for the mechanism of anomerization of glucose pentaacetate in solutions of acetic acid (4).

We should, provided our interpretation of the reactions is correct, observe the same kinetic behavior for the reactions just described as is observed when acetylated pyranosyl derivatives are substituted. Measurements of the substitution rates of 2,3,4,5,6-penta-*O*-acetyl-D-glucose diethyl dithioacetal (I*a*) when catalyzed by perchloric acid in solutions of acetic acid, or in mixtures of acetic acid plus acetic anhydride or methylene dichloride, were interpreted on the basis that the rate-determining step is a first-order dissociation of the substrate conjugate acid (5). The rate constants were first order in perchloric acid, and increased when part of the acetic acid solvent was replaced by acetic anhydride or methylene dichloride, as had been found when the rate constant for the inversion of glucose pentaacetate was measured under the same experimental conditions (6). Substitution of the acyclic monothioacetal, 1,2,3,4,5,6-hexa-*O*-acetyl-D-glucose 1-^{14}C-acetoxy-*S*-ethyl monothioacetal (α-II*a*), is specific for C_1-acetoxy. The acid-catalyzed acetoxy exchange of α-II*a* was measured (5) in the same way as the C_1-acetoxy exchange of pyranose pentaacetates (7–9).

One C_1-alkoxy group of acyclic poly-*O*-acetyl acetals of monosaccharides is substituted by an acetoxy group to give monoacetals (10) by the action of a strong acid in acetic acid. The acid-catalyzed rotation changes of these acetals give plots of log $(a_t - a_\infty)$ versus time which indicate that the reaction is first order in acid. The reaction products (diastereomeric monoacetals) epimerize when dissolved in acetic acid containing perchloric acid.

The reaction described by the examples cited is substitution of an acetoxy group for a group bonded to C_1 of an acyclic sugar derivative. The rotation differences between the product and substrate are large enough in most cases so that rate constants can be calculated from the rotation measurements. We can thus measure the substitu-

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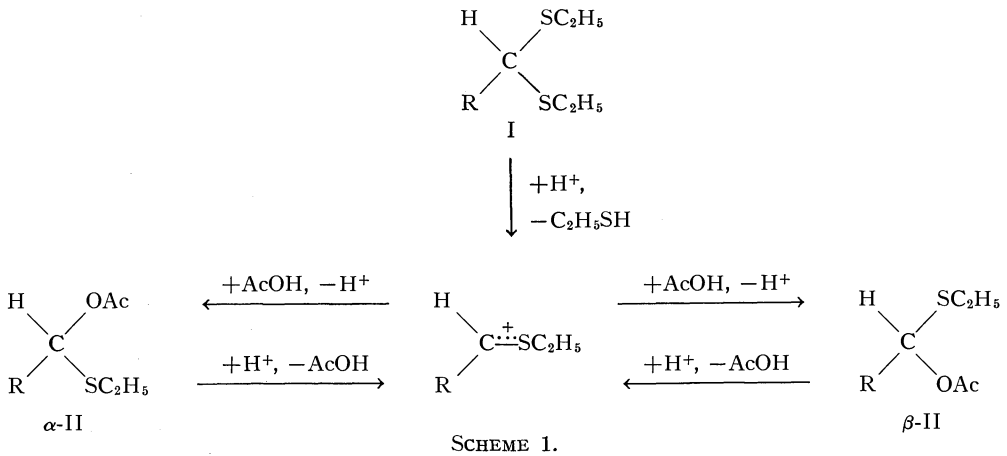


SCHEME 1.

tion rates of poly-*O*-acetyl sugar acetals and the epimerization rates of the mono-acetals in nonaqueous solvents. The rate constants for the substitution of two acyclic substrates (I*a* and α-II*a*) (5) indicate that acyclic substrates substitute faster than pyranose substrates.

RESULTS

The rate constants have been calculated from measurements of the rotation changes which occur when a strong acid is added to a solution of a poly-*O*-acetyl acyclic sugar substrate (I–IV) dissolved in acetic acid. The substrate groups and products of the substitutions are illustrated in eqs. [1]–[4].

The individual rate constants calculated from the rotation changes during runs measuring the substitution rate of two different substrates and the inversion rate of one substrate are shown in Table I. The rate of each of the four reactions was followed at two or more perchloric acid concentrations, and the rate constant was first order in perchloric acid for each substrate tested. This observation permits the rate constants to be calculated as recorded ($k_{obs}/[HClO_4]$) in the tables for M $HClO_4$, so that the rate constants are readily comparable.

Rate constants taken from the literature are compared with ours. The activation energies (E_a) calculated for the perchloric acid catalyzed substitutions of acyclic substrates in acetic acid are smaller than those Chu (11) reports for pyranose pentaacetates. The changes in the relative rate constants over the temperature range we can measure substitution rates are minor compared with the differences in the magnitude of the rate constants for different substrate groups. Chu (11) found that within the same substrate group (the pentaacetates of the common sugars) the range of E_a was small.

The rate constants for the substitution

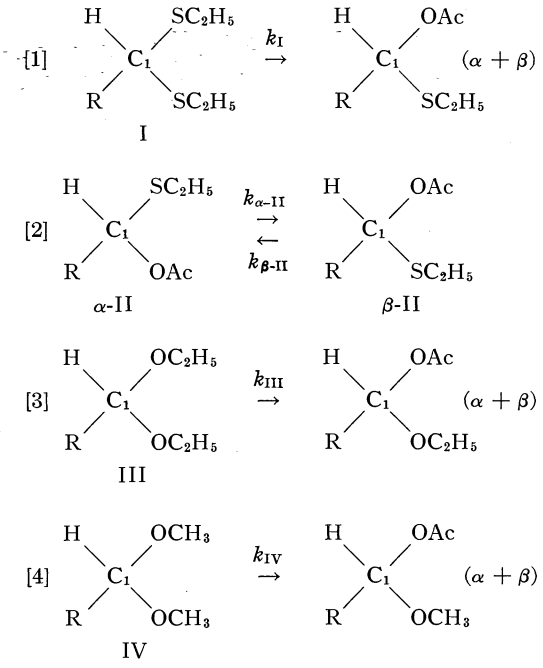


TABLE I

The individual rate constants during runs at 25° in acetic acid containing 4% acetic anhydride

2,3,4,5,6-Penta-*O*-acetyl-D-glucose dimethyl acetal (0.092 *M*) with 1.25×10^{-3} *M* $HClO_4$			2,3,4,5,6-Penta-*O*-acetyl-D-glucose diethyl dithioacetal (0.0800 *M*) with 8.3×10^{-3} *M* $HClO_4$			β-1,2,3,4,5-Penta-*O*-acetyl-L-arabinose *S*-ethyl monothioacetal (0.0477 *M*) with 2.58×10^{-4} *M* $HClO_4$		
Time (min)	$\alpha_t - \alpha_\infty$	$10^2 k_{obs}$ (min^{-1})	Time (min)	$\alpha_t - \alpha_\infty$	$10^2 k_{obs}$ (min^{-1})	Time (min)	$\alpha_t - \alpha_\infty$	$10^2 k_{obs}$ (min^{-1})
0	0.865		0	0.48		0	0.290	
6	0.650	4.74	20	0.36	1.43	4	0.240	4.77
8	0.595	4.63	30	0.31	1.44	6	0.215	5.00
14	0.450	4.65	50	0.22	1.56	10	0.180	4.76
18	0.375	4.63	60	0.19	1.49	12	0.160	4.94
22	0.312	4.59	70	0.17	1.49	18	0.120	4.91
26	0.260	4.63	120	0.08	1.50	22	0.100	4.84
35	0.170	4.65	140	0.06	1.49	26	0.080	4.96
45	0.110	4.58						
Average		4.64			1.49			4.88

TABLE II

The rate constants for the acid-catalyzed acetolysis of acyclic sugar poly-*O*-acetyl diethyl dithioacetals in acetic acid at 25°

Substrate	$10^3[HClO_4]$ (*M*)	$10^2 k_{obs}$ (min^{-1})	$k_{obs}/[HClO_4]$	$k_{relative}$
2,3,4,5,6-Penta-*O*-acetyl-D-glucose diethyl dithioacetal (I*a*)	8.3	1.50	1.83	1
2,3,4,5,6-Penta-*O*-acetyl-D-galactose diethyl dithioacetal (I*b*)	8.3	5.48	6.60	3.61
2,3,4,5,6-Penta-*O*-acetyl-D-mannose diethyl dithioacetal (I*c*)	8.3	4.00	4.83	2.46
2,3,4,5-Tetra-*O*-acetyl-L-arabinose diethyl dithioacetal (I*d*)	8.3	3.91	4.71	2.57
3,4,5,6-Tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexose diethyl dithioacetal (I*e*)	0.0206	11.8	5.7×10^3	3.1×10^3

of five dithioacetals are given in Table II. Except for the 2-deoxy substrate I*e*, a special case which will be considered later, the rate differences are much smaller than those found when the reaction was acetoxy exchange (8, 9) of the corresponding pyranose acetates.

The rate constants for the inversion of three monothioacetals (Table III) differ much less than the rate constants for the inversion of the pyranose pentaacetates (also monoacetals) of the same sugars. Chu (11) and Bonner (12) found that the rate of anomerization of arabinose pentaacetate was about 20 times faster than the rate of anomerization of glucose pentaacetate when the reaction was measured in 1:1 acetic acid – acetic anhydride catalyzed by perchloric acid and by sulfuric acid. Steric factors would be expected to influence the reaction rates of relatively rigid pyranose rings far more than those of relatively flexible chains of acyclic sugars.

The rate constants for the substitution of the dimethyl and diethyl acyclic sugar acetals which carry an acetoxy group at C_2 show less variation between the methyl and ethyl sugar acetals than the factor 8.5 (ethyl is the faster) that Skrabal and Eger (13) report for the hydrolysis of dimethyl and diethyl acetals. The differences are, however, larger than those Timell (14) reports

TABLE III

The rate constants for the acid-catalyzed epimerization of cyclic poly-*O*-acetyl sugar *S*-ethyl monothioacetals in acetic acid at 25°

Substrate	$10^4[HClO_4]$ (M)	$10^2(k_\alpha + k_\beta)_{obs}$ (min^{-1})	$k_{obs}/[HClO_4]$
α-1,2,3,4,5,6-Hexa-*O*-acetyl-D-galactose *S*-ethyl monothioacetal (II*b*)	2.05	2.74	134
α-1,2,3,4,5,6-Hexa-*O*-acetyl-D-mannose *S*-ethyl monothioacetal (II*c*)	2.05	5.80	283
β-1,2,3,4,5-Penta-*O*-acetyl-L-arabinose *S*-ethyl monothioacetal (II*d*)	2.58	4.91	190

TABLE IV

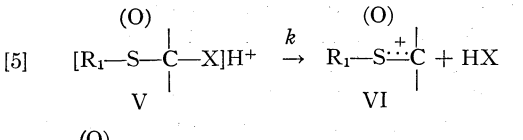
The rate constants for the acid-catalyzed acetolysis of acyclic poly-*O*-acetyl sugar diethyl and dimethyl acetals in acetic acid at 25°

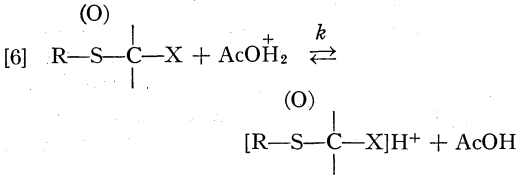
Substrate	$10^4[HClO_4]$ (M)	10^2k_{obs} (min^{-1})	$k_{obs}/[HClO_4]$
2,3,4,5,6-Penta-*O*-acetyl-D-galactose diethyl acetal (III*b*)	8.3	74.0	169
2,3,4,5-Tetra-*O*-acetyl-L-arabinose diethyl acetal (III*d*)	12.5	25.0	200
3,4,5,6-Tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexose diethyl acetal (III*e*)	0.206	>100	$>5\times10^4$
2,3,4,5,6-Penta-*O*-acetyl-D-glucose dimethyl acetal (IV*a*)	12.5	4.6	37
2,3,4,5,6-Penta-*O*-acetal-D-galactose dimethyl acetal (IV*b*)	8.3	4.4	53
2,3,4,5-Tetra-*O*-acetyl-L-arabinose dimethyl acetal (IV*d*)	12.5	7.4	59

for the rate constants for the hydrolysis of methyl and ethyl β-glucosides.

DISCUSSION

We believe that the rate-determining step for all of the substitutions we describe (eqs. [1]–[4]) is the dissociation of substrate conjugate acid (V), where X = C_2H_5S, CH_3O, C_2H_5O, or CH_3CO_2 (eq. [5]). The concentration of V is dependent upon the acid–base equilibrium (eq. [6]) when acetic acid is the solvent. The rate then is dependent upon cleavage of a C—X bond of a substrate (V), with a concentration dependence upon the basicity of X. The relative ability of S and O to stabilize the onium ion VI will influence the rate of cleavage of the C—X bond.





We have no measure of the base strength of the acetoxy group. Based on the ease of hydrolysis of esters in acid solutions, the acetoxy group may be the most basic of the groups listed. The inversion rate constants ($k_{\alpha\text{-II}} + k_{\beta\text{-II}}$) for the monothioacetals (Table III) are indeed larger than the substitution rate constants for the dithioacetals (Table II). Monothioacetals (II*b*–II*d*) substitute at a rate as large as, or larger than, their rate of inversion (reaction [2]).

Anomeric pentaacetates (which are monoacetals) give ratios of substitution rate constant to inversion rate constant which range from 1 to 14.6 (9). We have measured the ^{14}C-acetoxy exchange rate of II*b* (15), and found it to be 19 times the inversion rate ($k_{\alpha\text{-II}}$). This means that the main reaction is α-II*b* $\rightarrow$ α-II*b*. We are confident that, for substrates from the same sugar, the rate constants for the substitution of acyclic monothioacetals are larger than those for the substitution of acyclic acetals (Tables II and IV).

Arnett (16) has tabulated data which permit a comparison of the relative basic strength of weak bases. No measurements of the basicities of acetals are given, but the relative basic strength of oxygen and sulfur acetals should parallel the basic strength of the ethers. Dimethyl ether is a stronger base than dimethyl sulfide; the pK_a values in aqueous sulfuric acid are -3.84 and -4.25, respectively. Diethyl ether gave a pK_a of -4.1 in acetic acid containing perchloric acid. The data suggest that the concentration of substrate conjugate acid (V) is larger when the substrates are oxygen acetals than when they are sulfur acetals. The pK_a measured in acetic acid also suggests that the value of K (eq. [6]) is small, as our kinetic results require.

The ability of sulfur and oxygen to act as electron donors and contributors to the formation of VI can be ascertained by comparing the relative solvolysis rates of α-chloromethyl ethers. The oxygen ether solvolyzed some 10^4 times faster than the sulfur ether. This result and estimates of the basicities of divalent sulfur and oxygen both indicate that the oxygen acetal should substitute much faster. For the acetals of the same sugars, the oxygen acetals substituted faster by factors of only 47 and 89.

The rate constants for the substitution of an acetoxy or methoxy group are much larger for acyclic sugar substrates than for pyranose substrates. Table III records additional data showing that the inversion rate of the poly-*O*-acetyl monothioacetals is much faster than that of pyranose acetates (11). To obtain a more useful comparison of the acyclic and pyranose inversion rates, the inversion rates of the poly-*O*-acetyl monoacetals are needed. These acetals are the products given by substitutions [3] and [4]. Although we have isolated some of these products, the differences between the specific rotations of α- and β-diastereomeric pairs (17) are so small that large amounts of the diastereomers are needed to measure the difference between the rotation of the α or β isomer and that of the equilibrium mixtures.

When the group substituted was methoxyl and the electron donor was oxygen, the rate constants for the substitution of acyclic acetals (Table IV) were much larger than those for the substitution of the α- and β-pyranose acetals (7). The rate constants are not strictly comparable, because different catalysts (sulfuric and perchloric acids) were used and the reactions were carried out in different acetic acid – acetic anhydride mixtures. However, the difference between the rate constants (2,3,4,5,6-penta-*O*-acetyl-D-glucose dimethyl acetal substituted more than 10^3 times faster than methyl-2,3,4,6-tetra-*O*-acetyl β-glucopyranoside) is much too large to be attributed to experimental conditions.

The data in Fig. 1 show that the rate constant for the inversion of an acyclic monoacetal (α-II*b* $\rightleftarrows$ β-II*b*) in mixtures of acetic acid and acetic anhydride increases as the solvent fraction of acetic anhydride becomes larger. The influence of the solvent composition on the rate of inversion of the acyclic substrate is almost identical with the influence of the solvent composition on the rate of inversion of glucopyranose pentaacetate (4). We have found that an acetoxy group from the solvent exchanges with the C_1-acetoxy group when acyclic substrates are inverted. Exchange occurs when pentaacetates are inverted (8).

The rate constants for the substitution of the deoxy acyclic substrates (II*e* and III*e*) are much larger than those for other substrates. The larger rate constants are due to the influence (largely inductive) of the C_2-hydrogen in place of the C_2-acetoxy group. The influence of substituents at C_2 on the rate constants for the substitution of

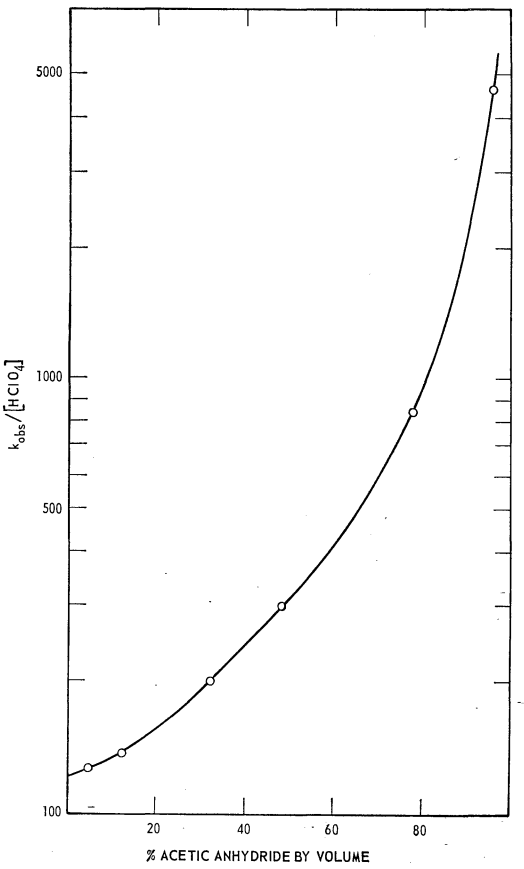


FIG. 1. The effect of solvent composition on the inversion rate of α-1,2,3,4,5,6-hexa-*O*-acetyl-D-galactose *S*-ethyl monothioacetal.

acetals is considered in the accompanying paper (15).

EXPERIMENTAL

The poly-*O*-acetyl diethyl dithioacetals (I*a*–I*d*) and the poly-*O*-acetyl *S*-ethyl monothioacetals (II*b*–II*d*) were prepared by methods previously described (1, 2). The deoxy dithioacetal, 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexose diethyl dithioacetal (I*e*), was prepared from 2-deoxy-D-*arabino*-hexose diethyl dithioacetal (18) by esterification with acetic anhydride saturated with sodium acetate (1).

The *O*-acetyl diethyl acetals (III*b* and III*d*) and dimethyl acetals (IV*a*, IV*b*, and IV*d*) were prepared by substitution of both ethylthio groups of the dithioacetals by the action of mercuric chloride in absolute ethanol or methanol (19, 20) in the presence of an alkaline earth carbonate. Excess mercuric chloride was removed by reduction of Hg^{2+} to Hg^{+} with Hg^{0}. These techniques have enabled us to synthesize 3,4,5,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexose diethyl acetal (III*e*). The crude product was recrystallized from ether until the melting point (52–53°) was constant, $[\alpha]_D^{25}$ 34.1° (*c*, 4 in AcOH).

Anal. Calcd. for $C_{18}H_{30}O_{10}$: C, 53.19; H, 7.44; acetoxy, 4 equivalents/406 g. Found: C, 53.3; H, 7.29; acetoxy, 4.09 equivalents.

We have not explored the usefulness of the acid-catalyzed substitution of a single alkoxyl group as a method of preparing monoacetals as extensively as its use as a method of preparing monothioacetals. However, we have isolated products which assure us that we are measuring the rates of substitutions [2] and [3]. The procedure for the isolation of poly-*O*-acetyl methyl (or ethyl) monoacetals was as follows. The poly-*O*-acetal was dissolved in a 1:1 mixture of acetic acid and acetic anhydride, a catalytic amount of perchloric acid added, and the rotation followed until it was constant. The reaction was then quenched by the addition of anhydrous sodium acetate, and the solvent was removed *in vacuo*. The organic product was dissolved in warm methylene dichloride, and the salt residue was separated by filtration. Removal of the solvent at a reduced pressure yielded a crystalline mass or a syrup, depending upon the substrate.

Both α- and β-1,2,3,4,5-penta-*O*-acetyl-D-arabinose methyl monoacetal (17, 21) have been isolated from the products of IV*d*. The product of the substitution of IV*d* was dissolved in ethyl ether, petroleum ether was added, two distinct crystalline forms (needles and flat plates) were separated mechanically, and each was recrystallized to give the α form, m.p. 67°, $[\alpha]_D^{25}$ −34.5° (*c*, 2.1 in $CHCl_3$), and the β form, m.p. 74°, $[\alpha]_D^{25}$ −26.4° (*c*, 2.2 in $CHCl_3$). Samples of the isomers and substrate dissolved in acetic acid gave the following data before and after a drop of perchloric acid was added.

	Specific rotation	
Substrate	Initial	At acid-catalyzed equilibrium
α form	−26.9°	−23.6°
β form	−17.5°	−24.2°
IV*d*	−16.8°	−23.2°

*1,2,3,4,5-Penta-O-acetyl-*L*-arabinose Ethyl Monoacetal*

The product of the substitution of III*d* was recrystallized from ethyl ether – petroleum ether several times to give one isomer, m.p. 117–118°, $[\alpha]_D^{22}$ −27.7° (*c*, 2.5 in CH_3COOH).

Anal. Calcd. for $C_{17}H_{26}O_{11}$: C, 50.36; H, 6.43; acetoxy, 5 equivalents/406 g. Found: C, 50.34; H, 6.60; acetoxy, 4.96 equivalents.

One drop of sulfuric acid changed the specific rotation to −23.7°. The rotation obtained from one of our kinetic runs on the acetal (III*d*) was −22.5°; presumably, the diastereomer isolated is formed by a highly stereoselective reaction.

At least one of the crystalline diastereomers has been isolated from the product given by five of the substrates in Table IV. We have not succeeded in isolating a crystalline poly-*O*-acetyl monoacetal from the substitution products of the deoxy derivative III*e*.

The rate constants were calculated from the polarimetric measurements as described previously (5).

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