The Silicate-Mediated Formose Reaction: Bottom-Up Synthesis of Sugar Silicates

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Science **327**, 984 (2010);
DOI: 10.1126/science.1182669

The Silicate-Mediated Formose Reaction: Bottom-Up Synthesis of Sugar Silicates

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Understanding the mechanism of sugar formation and stabilization is important for constraining theories on the abiotic origin of complex biomolecules. Although previous studies have produced sugars from small molecules through the formose and related reactions, the product mixtures are complex and unstable. We have demonstrated that simple two- and three-carbon molecules (glycolaldehyde and glyceraldehyde), in the presence of aqueous sodium silicate, spontaneously form silicate complexes of four- and six-carbon sugars, respectively. Silicate selects for sugars with a specific stereochemistry and sequesters them from rapid decomposition. Given the abundance of silicate minerals, these observations suggest that formose-like reactions may provide a feasible pathway for the abiotic formation of biologically important sugars, such as ribose.

Sugars are essential elements of biochemistry, including energy processing (e.g., glycogen and starch), structure (e.g., cellulose and cell walls), and genetics (e.g., DNA and RNA). The synthesis of sugars in a prebiotic world therefore plays a key role in any theory of the origin of life. The formose reaction (*1*, *2*) is a possible process whereby sugars form abiotically (*3*, *4*). This reaction converts formaldehyde (HCHO; C1) to a variety of sugars, in the presence of strong bases (*5*), organic bases (*6*), or minerals (*7*–*11*). The generally accepted mechanism (fig. S1) (*12*) involves conversion of formaldehyde to higher sugars, with autocatalysis by glycolaldehyde [$(CHO)CH_2OH$; C2] (*13*, *14*). Aldol reactions then sequentially produce glyceraldehyde [$(CHO)CH(OH)CH_2OH$; C3] and higher sugars.

Despite the effectiveness of an autocatalytic reaction, the current prebiotic formose model has limitations (*7*, *15*, *16*). Most notably, the reaction generates a plethora of unstable sugars, of which the key sugar, ribose, is present in a very small proportion (*17*–*19*). Although the problem of sugar instability is unresolved, some molecules, such as borates, phosphates, and cyanamide, select for the synthesis of certain sugars (*20*–*24*). All these reactions require alkaline conditions such as those found naturally in hydrothermal vents, in some lakes, and at the surfaces of aluminosilicate minerals (*25*–*27*). An additional drawback is that the products from the formose mechanism (*13*) are racemic, whereas sugars under terrestrial biological conditions are homochiral. Recent results suggest that the aluminosilicate environment of certain clays (*28*, *29*) may provide this chirality.

C5 and C6 sugars react with aqueous sodium silicate to form stable complexes (*30*–*32*). Silicate minerals constitute the major component of Earth's crust and mantle, as well as those of the moon, asteroids, and other rocky planets. Amorphous silica is readily soluble in aqueous solution at pH 9, and its solubility rises appreciably at higher alkalinity (*33*). Here, we report simple reactions under these same conditions at room temperature with only C1, C2, or C3 as the reactants (*12*). Formaldehyde by itself does not oligomerize readily when placed in sodium silicate solution, as it does not possess an alpha hydrogen required to initiate the base-catalyzed reaction (*4*, *13*, *14*). Glycolaldehyde at room temperature is in equilibrium with its hydrate [$HOCH_2CH(OH)_2$] and several dioxane dimers (*34*). Within 20 min after exposure to aqueous sodium silicate, new peaks in the ^{13}C nuclear magnetic resonance (NMR) spectrum replaced all former peaks except those from the hydrate (fig. S2). The ^{29}Si spectrum recorded after 30 min contained several peaks in the region δ-102 to δ-100, indicative of negatively charged silicon in its pentacoordinated form (fig. S3) (*12*). After conversion of the sugar silicate products of C2 by hydrolysis to the free sugars (no longer complexed with silicate), the ^{13}C spectrum was composed almost entirely of peaks attributable to the C4 sugars erythrose and threose (Fig. 1A), in the approximate ratio of 75/25 (fig. S4). These are the expected products of a simple aldol reaction between two moles of glycolaldehyde (Fig. 1B). The simplicity of the product mixture contrasts with past formose results (*17*–*19*, *35*).

Previous work indicated that sugar silicates, with some exceptions, exist as 2:1 sugar-silicate complexes and can form only when the sugar exists as the furanose (five-membered) form with an unsubstituted anomeric hydroxy group cis to a hydroxy group on the adjacent carbon (*24*, *31*, *32*). The C4 sugars do not have enough carbons to form pyranose (six-membered) rings and are the smallest sugars that can form furanose rings. Thus, C1, C2, and C3 sugars cannot form silicate complexes because four carbons are required to close the ring. As a result, C2 dimerizes to C4, which sodium silicate sequesters as the silicate complex. Three stereoisomers are possible for these 2:1 complexes, in which both sugar rings are syn to the uncomplexed hydroxy group (Fig. 1B), both are anti, or one is syn while the other is anti. Multiple tetrose silicate stereoisomers, plus the possibility of regioisomers and some hexose silicates, supply the observed multiplicity of ^{29}Si resonances (fig. S3).

Electrospray ionization (ESI) mass spectra of the silicate complexes confirmed these results. After 30 min, only 2:1 sugar-silicate complexes were present, primarily C4 with some C6 (Fig. 2A). After 12 hours, C6 complexes were the primary product, with some C4 and C8 (Fig. 2B). Products lacking the ability to form silicate complexes, such as the anomers (C1 stereoisomers) of the structures in Fig. 1A, can isomerize to complex-forming products or can oligomerize further. The reaction also was carried out under the normal formose conditions of

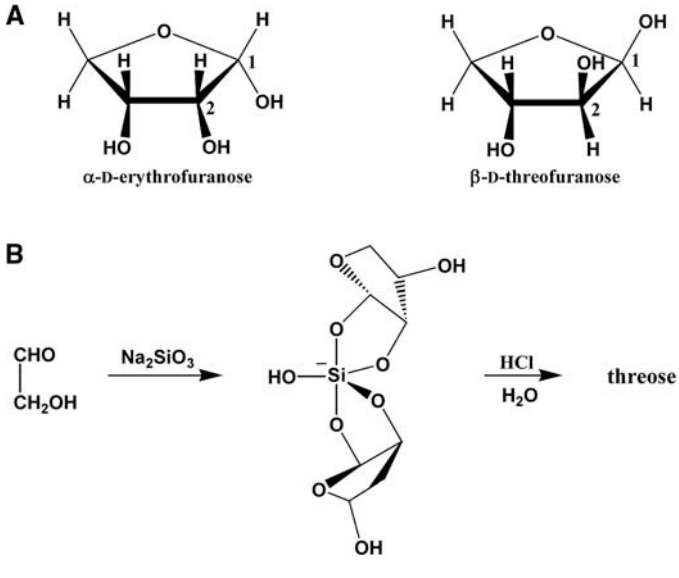

Fig. 1. (**A**) The preferred structures of erythrose and threose for reaction with sodium silicate, in which the 1- and 2-hydroxy groups are cis. (**B**) The bottom-up synthesis of threose from glycolaldehyde. In the presence of sodium silicate, the aldol dimer is sequestered as its 2:1 silicate complex. Hydrolysis liberates the free sugar.

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aqueous NaOH (*3*, *5*), at the same pH but without sodium silicate. Even after 30 min, the C4 products constitute less than half the total (Fig. 2C), and, after 12 hours, a preponderance of higher oligomers and nonsugars indicates an almost fully decomposed product set (Fig. 2D). Thus silicate provides selection and stabilization of the sugars formed, compared with solutions containing only hydroxide as base.

The same experiments with glyceraldehyde (C3) produced even simpler and stabler product mixtures. The NMR spectrum of C3 in neutral water indicates a mixture of its many forms, including the aldehyde, the hydrate, dimer dioxolanes, and dimer dioxanes (*36*). Reaction with sodium silicate at room temperature immediately replaces almost all carbon peaks (fig. S5). The observation of several ^{29}Si peaks in the region δ-102 to δ-100 confirms the pentacoordinated nature of the sugar silicates (fig. S6). The aldol reactions of glyceraldehyde and its keto isomer give branched aldohexoses and straight-chain ketohexoses (fig. S7). The ^{13}C chemical shifts are consistent with ketohexose products such as sorbose and tagatose (*37*), but assignments are not yet certain. The ESI mass spectrum after 12 hours was almost unchanged from that after 30 min (Fig. 3, A and B). In contrast, the ESI mass spectrum of the products of reaction of C3 under classic formose conditions (aqueous sodium hydroxide without silicate) indicates rapid decomposition to nonsugars after 12 hours (Fig. 3, C and D).

We also studied the solutions in which two different, small sugars reacted in basic conditions in the presence of silicate (*12*). Reaction of an equimolar mixture of formaldehyde and glyceraldehyde (C1+C3) in the presence of sodium silicate produced primarily C4 products, resembling those from C2 alone. Not surprisingly on steric grounds, the anion of glyceraldehyde reacts more rapidly with formaldehyde to form C4 products than with another glyceraldehyde molecule to form C6 isomers (fig. S8). Reaction of an equimolar mixture of glycolaldehyde and glyceraldehyde (C2+C3) under the same conditions yielded a complex mixture of sugar silicates containing 30 to 40% pentoses (the single largest component), with smaller amounts of tetroses, hexoses, and higher sugars. The ratios remain nearly constant from 30 min to 12 hours (fig. S9). The reaction mixture decomposes rapidly under classic formose conditions, in the absence of silicate (fig. S10). The aldol reaction of the enolate of glycolaldehyde with glyceraldehyde can give all four of the straight-chain aldopentoses directly (fig. S11). Reaction in the opposite sense gives branched aldopentoses (fig. S12). Isomerization of glyceraldehyde to its ketose isomer (dihydroxyacetone) and reaction with glycolaldehyde can give the straight-chain ketopentoses ribulose and xylulose (fig. S13). Individual hexose structures remain unidentified.

Because formaldehyde, glycolaldehyde, and glyceraldehyde (C1 to C3) have too few carbon atoms to complex with sodium silicate, they oligomerize through base-catalyzed reactions to C4 to C6 sugars, and the first-formed sugar with the appropriate stereochemistry reacts immediately with silicate at room temperature. This bottom-up synthesis of sugar silicates is a plausible prebiotic process. In contrast, C5 and C6 sugars form silicate complexes directly, in a top-down synthesis, and consequently resist base-catalyzed reactions under the same conditions. Furthermore, the C5 and C6 sugar silicates formed in the bottom-up synthesis oligomerize very slowly (Fig. 3, A and B, and fig. S9), the C4 products somewhat faster (Fig. 2, A and B). In the absence of sodium silicate, the uncomplexed higher sugars decompose rapidly under alkaline conditions (Fig. 2, C and D, Fig. 3, C and D, and fig. S10). Only certain structures are selected because of stereo control of silicate formation. Moreover, silicate mediation ameliorates one of the primary impediments to a possible role of the formose reaction in prebiotic sugar synthesis: product instability. The rationale is similar to that proposed for a borate-mediated formose reaction (*23*), with the advantage here of the much wider availability of

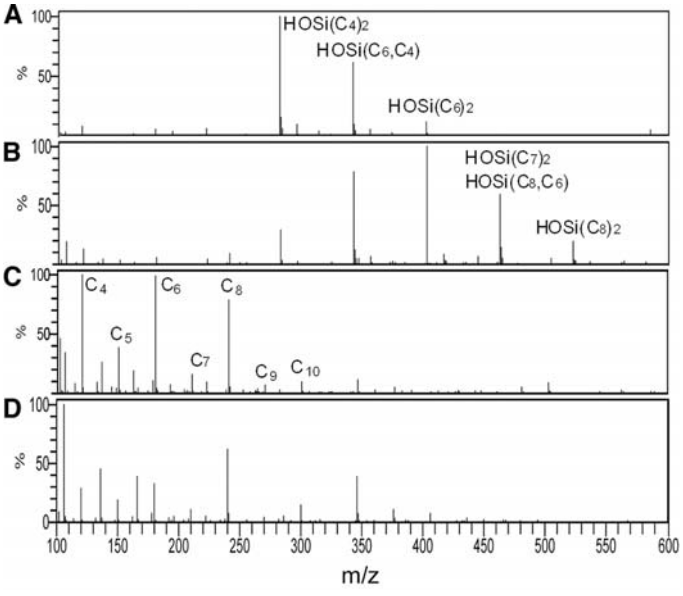

Fig. 2. (**A**) The negative ion ESI mass spectrum of the sugar silicate products of the reaction of glycolaldehyde with aqueous sodium silicate after 30 min at room temperature. The symbol $HOSi(C4)_2$ identifies the mass of any 2:1 sugar-silicate complex containing two C4 sugars. (**B**) The same spectrum after 12 hours. (**C**) ESI mass spectrum of the free sugar products of the reaction of glycolaldehyde with aqueous sodium hydroxide after 30 min at room temperature (classic formose conditions). Carbon numbers (e.g., C4 for all tetroses) identify specific sugar structures. (**D**) The same spectrum after 12 hours.

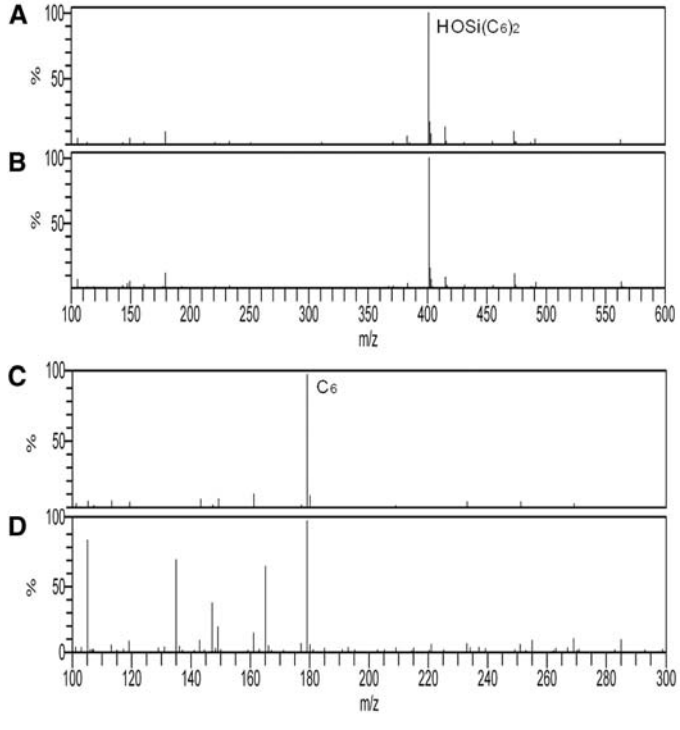

Fig. 3. (**A** and **B**) The negative ion ESI mass spectra of the sugar silicate products of the reaction of glyceraldehyde with aqueous sodium silicate after 30 min and after 12 hours at room temperature. (**C** and **D**) ESI mass spectra of the free sugar products of the reaction of glyceraldehyde with aqueous sodium hydroxide after 30 min and after 12 hours at room temperature.

silicate minerals and hence readily available silicate ions.

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38. This research was supported by the National Science Foundation, Dow Corning Corp., and Schlumberger Ltd.

Supporting Online Material

www.sciencemag.org/cgi/content/full/327/5968/984/DC1
Materials and Methods
Figs. S1 to S13

30 September 2009; accepted 5 January 2010
10.1126/science.1182669

Asymmetric Cooperative Catalysis of Strong Brønsted Acid–Promoted Reactions Using Chiral Ureas

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Cationic organic intermediates participate in a wide variety of useful synthetic transformations, but their high reactivity can render selectivity in competing pathways difficult to control. Here, we describe a strategy for inducing enantioselectivity in reactions of protio-iminium ions, wherein a chiral catalyst interacts with the highly reactive intermediate through a network of noncovalent interactions. This interaction leads to an attenuation of the reactivity of the iminium ion and allows high enantioselectivity in cycloadditions with electron-rich alkenes (the Povarov reaction). A detailed experimental and computational analysis of this catalyst system has revealed the precise nature of the catalyst-substrate interactions and the likely basis for enantioinduction.

The proton (H^+) is the simplest, and arguably the most versatile, catalyst for organic reactions, mediating an extraordinary range of biological and synthetic transformations (*1*). Although a proton cannot be rendered chiral, enantioselective Brønsted acid catalysis is attainable through the influence of the acid's conjugate base and through medium effects. The former strategy, involving the use of chiral acids, has proven particularly useful, as demonstrated in the design and application of chiral phosphoric acids (*2*–*4*), *N*-triflyl phosphoramides (*5*), aryl sulfonic acids (*6*), and Lewis acid– (*7*, *8*) or thiourea-assisted Brønsted acids (*9*, *10*). The use of medium effects has been less straightforward, and chiral solvents have been investigated in asymmetric catalysis with comparatively limited success (*11*). The recent discovery of anion-binding pathways (*12*, *13*) in reactions catalyzed by chiral, small-molecule, H-bond donor catalysts such as urea and thiourea derivatives (*14*) suggests an alternative strategy that combines elements of both approaches. In this scenario, a chiral catalyst might associate with a protonated substrate through the counteranion and induce enantioselectivity in nucleophilic addition reactions to the cationic electrophile through specific secondary interactions with the charged species.

This idea was explored in the context of the formal [4+2] cycloaddition of *N*-aryl imines and electron-rich olefins, also known as the Povarov reaction (*15*). This Brønsted acid–catalyzed reaction affords tetrahydroquinoline derivatives with the concomitant generation of up to three contiguous stereogenic centers, and enantioselective Lewis acid– or phosphoric acid–catalyzed variants have been identified recently (*16*–*18*). The acid-catalyzed Povarov reaction between benzylidene aniline **2a** and 2,3-dihydrofuran **3** was selected as a model reaction (Fig. 1A), and a broad range of chiral urea and thiourea derivatives that were developed and studied previously in our laboratory, as well as several different Brønsted acids, were evaluated as catalysts for this transformation (table S1) (*19*). With this approach, we found that the combination of the bifunctional sulfinamido urea derivative **1a** (*20*) and *ortho*-nitrobenzenesulfonic acid (NBSA) catalyzed the model reaction with high enantioselectivity (Fig. 1, B and C, entry 1). The importance of both the urea and sulfinamide groups in the catalyst became evident in structure-reactivity/enantioselectivity studies. Thiourea derivative **1b** is an efficient catalyst, but it induced lower enantio- and diastereoselectivity (Fig. 1C, entry 2), whereas the diastereoisomeric (*R*,*R*,*S*)-sulfinamido urea **1c** promoted a much slower and poorly selective reaction (Fig. 1C, entry 3). In addition, reactions catalyzed by phosphinic amide urea **1d** displayed a modest selectivity, and pivalamide urea **1e** and amino urea **1f** both induced low reactivity and selectivity (Fig. 1C, entries 4 to 6). These results suggest a cooperative role for the urea and sulfinamide groups of **1a** in the rate- and enantioselectivity-determining steps of the catalytic reaction.

Under optimized conditions, the Povarov reaction that is catalyzed by **1a** was found to be applicable to different nucleophiles and a wide variety of *N*-aryl imines (Fig. 2, A and B). The highest enantioselectivities were observed in reactions that were carried out under cryogenic conditions with a 2:1 ratio of **1a** to NBSA, which was used to ensure complete suppression of the racemic pathway catalyzed by NBSA alone. Lactam-substituted tetrahydroquinoline derivatives $\mathbf{6}_{\mathbf{exo}}$ were obtained in high enantio- and diastereoselectivities by reaction of benzaldimines **2** with vinyllactam **5**. Tricyclic hexahydropyrrolo-[3,2-*c*]quinoline derivatives $\mathbf{8}_{\mathbf{exo}}$ were generated in an analogous manner by the cyclization of *N*-Cbz–protected 2,3-dihydropyrrole **7** with **2**.

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