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Trimerization Products of Trifluoroacetone: Critical Solvent Effect on Position and Kinetics of Anomeric Equilibria

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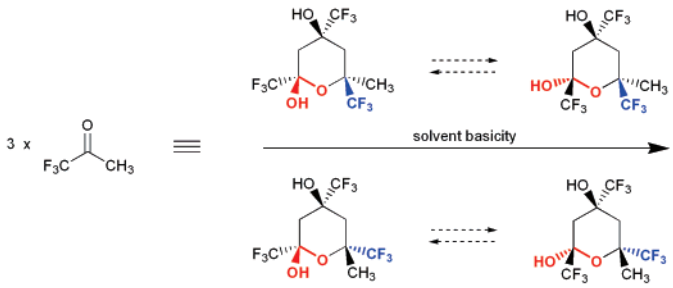

In the presence of bases, trifluoroacetone is known to trimerize leading to configurationally labile 6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-*2H*-pyran-2,4-diols **1a**,**b** and **2a**,**b**, structurally close to fluorinated carbohydrates. We report herein a complete study of their behavior in solution. The remarkable solvent effect on the two equilibria (**1a** ⇔ **1b**; **2a** ⇔ **2b**) was rationalized using solvent basicity measures and polarity scales. Solvents of weak donor number were found to favor the diastereoisomers **1a** and **2a**, which were subsequently isolated. According to their X-ray analyses, they both possess a concave structure with 1,3-cis-diaxial hydroxyl groups. A complementary kinetic study illustrated that acidic conditions can drastically reduce the equilibration rate, allowing the use of a wide range of solvents. Finally, a reexamination of previously published trimerization conditions using sodium or magnesium amalgam revealed that, contrary to the suggestion by two independent reports, 1,3,5-tris(trifluoromethyl)cyclohexane-1,3,5-triol **3**/**4** was neither formed as the principal product in place of **1a**,**b** and **2a**,**b** nor could it be detected as a minor product.

Introduction

Trifluoroacetone shows reactivities that are not habitually observed in common ketones. In addition to its impact on physical properties, the trifluoromethyl group enhances the electrophilicity of the carbonyl center. In aqueous solution, its hydration equilibrium is thus positioned largely on the side of the geminal diol, as is observed for formaldehyde.[1] Trifluoroacetone also shares a certain tendency for trimerization with the latter. In particular, addition of one equivalent of diethylamine to neat trifluoroacetone results in an aldol-type trimerization leading to a mixture of 6-methyl-2,4,6-tris(trifluoromethyl)-tetrahydro-*2H*-pyran-2,4-diols **1a**,**b** and **2a**,**b** (Figure 1).[2] This unusual behavior has been well documented, and a large variety of basic reagents were reported to induce trimerization: diethyl- and dipropylamine,[2] potassium carbonate,[3] barium hydroxide,[4]

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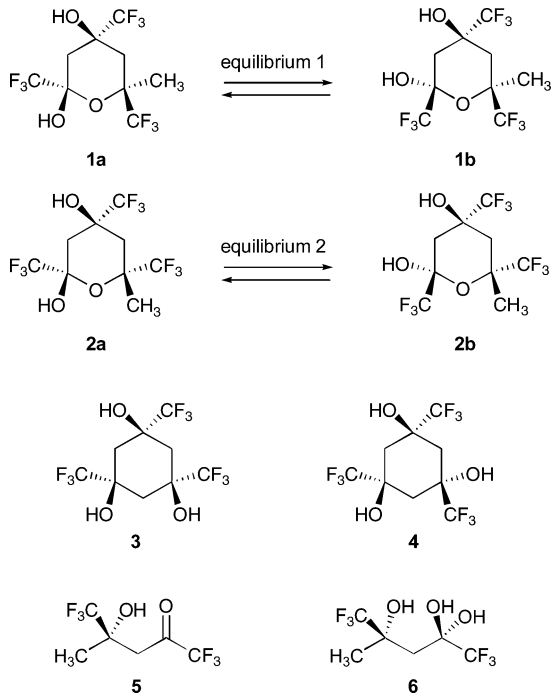

FIGURE 1. Trifluoroacetone trimers and dimers.

calcium hydroxide,[4] lithium hydride,[3] potassium *tert*-butoxide,[5] sodium metal,[2,4,6] and magnesium amalgam.[7] Certain authors claimed the isolation of trimers of different constitution, i.e., *cis*,*cis*- and/or *cis*,*trans*-1,3,5-tris(trifluoromethyl)cyclohexane-1,3,5-triol (**3**, **4**)[4,7] (Figure 1). Use of sodium amide or sodium ethoxide proved instead to favor dimeric products of trifluoroacetone, ketone **5**, and hydrate **6**[8,9] (Figure 1). By contrast, plain acetone only gives an unstable cyclic trimer in the presence of 2,2′-bipyridylcycloocta-1,5-dienenickel(0) and oxygen.[10]

The tetrahydro-2*H*-pyran-2,4-diol derivatives **1a**,**b** and **2a**,**b** present structural similarities with fluorinated carbohydrates, an emerging class of carbohydrate analogues (see ref 11 and references therein): they possess several trifluoromethyl groups attached to the ring system but also a hemiketal moiety which allows epimerization at the anomeric center. As a consequence, compounds **1a** and **2a** are in equilibrium with compounds **1b** and **2b** (equilibria 1 and 2, Figure 1). Even though this behavior renders **1** and **2** less attractive for some applications than would tris(trifluoromethyl)cyclohexanetriols **3** and **4**, they were recently introduced in novel acrylate polymers for lithography applications.[5] A simpler fluorinated alcohol, hexafluoroisopropanol (HFIP), has been thoroughly investigated for its capacity to accelerate particular reaction paths and thus render certain reactions more selective.[12,13]

In our search for novel di- and tridentate concave alkoxy ligands with unique properties in reactivity such as *cis*,*cis*-2,4,6-tris(trifluoromethyl)tetrahydropyran-2,4,6-triol **3**,[14] we decided to investigate the potential of trifluoroacetone trimerization.

Results and Discussion

Crystallographic Studies. We first aimed at assigning the correct structure to the four fluorinated tetrahydropyran-2,4-diol derivatives **1a**,**b** and **2a**,**b**, previously only detected by ^{19}F NMR[2] and characterized by ^{1}H NMR for the major diastereoisomer.[5] We thus repeated the experiment using diethylamine as reported by Dhingra et al.:[2] acidic aqueous workup furnished a white crystalline solid containing the four diastereomers **1a**,**b** and **2a**,**b**; ^{19}F NMR in methanol-d_4 showed the reported set of peaks. Surprisingly, the use of dichloromethane-d_2 in place of methanol-d_4 greatly simplified the spectrum (Figure 2); only two of the four signal sets were detected in a 7:4 ratio, favoring the interpretation that the anomeric equilibria were completely displaced. This result suggested that chromatographic isolation of each isomer using dichloromethane might be feasible. Indeed, flash chromatography on silicagel with a dichloromethane/pentane gradient quantitatively separated the mixture and subsequent crystallization in cyclohexane furnished the solid-state structures of both isomers by X-ray diffraction analysis. Structure **1a** was found to correspond to the less polar diastereoisomer (CH_2Cl_2, $R_f = 0.16$, Figure 3) while structure **2a** was assigned to the more polar species (CH_2Cl_2, $R_f = 0.08$, Figure 3). In both structures, the hydroxyl groups show the 1,3-*cis*-diaxial orientation which makes **1a**/**2a** potentially interesting for the application in coordination chemistry. This preference for one of the two possible chair conformations may be explained with the anomeric effect, illustrated by the slight shortening of the C−O bond distance ($d_{C2-O2} = 1.400(2)$ Å vs $d_{C4-O3} = 1.410(2)$ Å in **1a**; $d_{C2-O2} = 1.401(1)$ Å vs $d_{C4-O3} = 1.424(2)$ Å in **2a**) and intramolecular hydrogen-bonding ($d_{O2-O3} = 2.786(3)$ Å in **1a**; $d_{O2-O3} = 2.758(2)$ Å in **2a**). The major structural difference between the two compounds lies in the slight deformation of the chair conformation present in **1a** (O(1)−C(7)−C(6) 114.6(1)° vs O(1)−C(7)−C(6) 112.4(1)° in **2a**) caused by the axial position of the bulkier trifluoromethyl group.

Subsequently, we determined the exact structure of the initial 1:1 adduct between diethylamine and the trifluoroacetone trimers, formed along the trimerization procedure reported by Dhingra.[2] Switching from acetone-d_6, proposed by the authors, to deuterochloroform greatly favored the formation of $Et_2NH\cdot$**1a** over $Et_2NH\cdot$**1b** and $Et_2NH\cdot$**2a** over $Et_2NH\cdot$**2b** (in a similar 95:5 ratio). Indeed, recrystallization from this solvent furnished medium-quality single crystals suitable for X-ray analysis. These crystals contained two adducts, $Et_2NH\cdot$**1a** and $Et_2NH\cdot$**2a**, in an approximate 1:3 ratio, thus proving the absence of any N/O acetal formation unlike previously reported for diethylamine and 2-hydroxytetrahydropyran.[15] In order to improve the quality of the X-ray structure we deliberately prepared the diethylammonium adduct from isolated diastereomer **2a** and we obtained high-quality single crystals leading to the structure shown in Figure 4 that allowed us to determine the salt character of the

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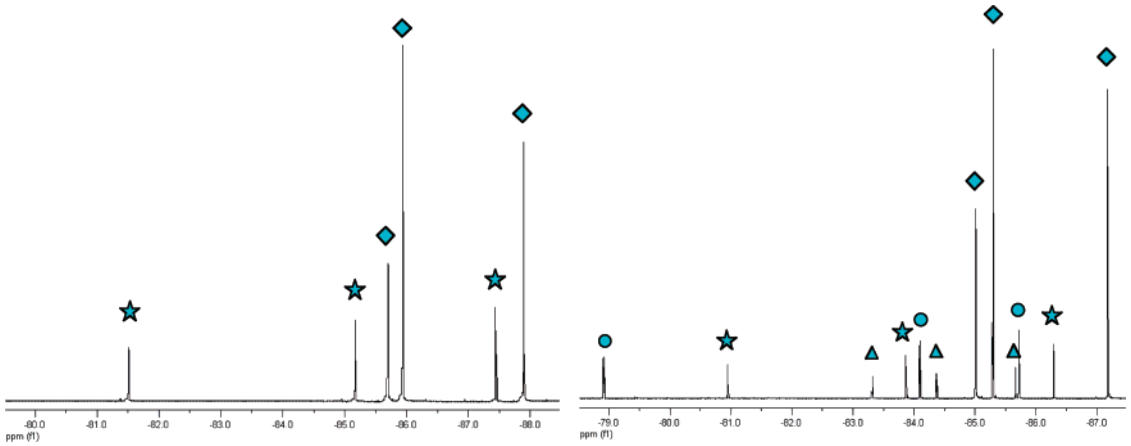

FIGURE 2. ^{19}F NMR spectra at 468 MHz of the product mixture resulting from trifluoroacetone trimerization: (a) dichloromethane-d_2, (b) methanol-d_4; ★ = **1a**, ○ = **1b**, ◊ = **2a**, △ = **2b**.

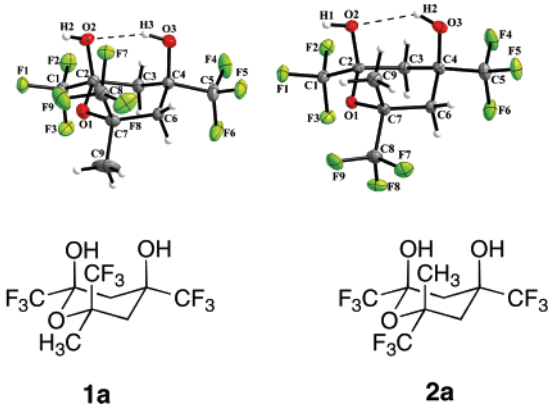

FIGURE 3. X-ray crystal structures (30% probability thermal ellipsoids): (a) (2*S*,4*S*,6*S*)-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2,4-diols **1a** and (b) (2*S*,4*S*,6*R*)-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2,4-diols **2a**.

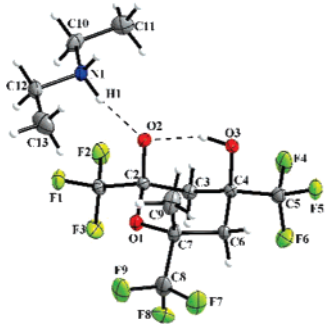

FIGURE 4. X-ray crystal structures (30% probability thermal ellipsoids) of the diethylammonium (±)-(2*S*,4*S*,6*R*)-4-hydroxy-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2-olate salt (Et_2NH·**2a**).

adduct. The deprotonation actually takes place at the hemiketal moiety of **1a** and **2a**, resulting in the formation of 4-hydroxy-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2-olates. The stability of these salts is quite impressive since a 1-h period in the presence of 10% HCl is required to liberate the trifluoroacetone trimers, as already mentioned by Dhingra.[2] The intramolecular hydrogen-bond between O2 and O3 (d_{O2-O3} = 2.467(3) Å) likely enhances the stability of these salts. The solubility of **1a**,**b** in water (approximately 65 mg/10 mL at 30 °C) was sufficient to evaluate the acidity of the hemiketal function. The pK_a constant was determined to be 9.4 ± 0.2 at 30 °C by means of titration with 1 N NaOH. This value, roughly 3 orders of magnitude lower than the pK_a of carbohydrate hemiacetals (12.4) (ref 16 and references therein), is in agreement with the general effect of α-trifluoromethyl groups, which increase the Bronsted acidity of alcohols. For instance, the pK_a of hexafluoroisopropanol (HFIP) is 9.3 while that of 2-propanol is 16.1.[17] The elevated acidity of **1** and **2** favors the formation of an ammonium salt over that of an N/O acetal, a fact that should be heeded when working with carbohydrates bearing trifluoromethylcarbonyl groups.

Solvent Effects. In view of the crucial effect of dichloromethane-d_2 on the anomeric equilibria 1 and 2 (Figure 2), we carried out NMR studies in solvents of varying acidity, basicity and polarity. Compounds **1a** and **2a** were independently dissolved in the corresponding deuterated solvent, and successive ^{19}F NMR spectra were acquired at 20 °C until complete equilibration of the system. Results are summarized in Table 1. Whereas halogenated solvents totally inhibit the formation of **1b** and **2b**, DMSO-d_6 as well as DMF-d_7 favor their formation. The magnitude of this effect turned out to be much more pronounced in the case of equilibrium 1; in DMSO-d_6, the proportion of **1b** over **1a** reaches 78%, while **2b** does not exceed 19%. Figure 5 presents a plot of the relative proportions of **2a** and **1a** according to the nature of the solvent. As can be seen, the solvent effect is quite similar for the two systems. However, several deviations show that the two equilibria are not exactly influenced in the same manner by all solvents.

Solvation plays a crucial role in equilibrium thermodynamics. As several types of solute−solvent interactions can act simultaneously, this variation of solvation is not always easy to predict. Nevertheless, in a number of cases solvation is the result of one major specific type of interaction.[18] In the following, we propose to rationalize the shift of equilibria 1 and 2 using solvent descriptors. Initially, we tried to associate the observed equilibrium shifts with the physical parameters of the solvents, i.e., the dipole moment μ and the dielectric constant ϵ_r. When

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TABLE 1. Solvent Effect on Equilibria 1 and 2

	relative percentage (%) determined by ^{19}F NMR[a]				selected solvent parameters[d]					
solvent	**1a**	**1b**	**2a**	**2b**	E^N_T[e]	AN[f]	DN[g]	α[h]	β[h]	π^*[h]
$CDCl_3$	100	0	100	0	39.1	23.1	4	0.44	0	0.58
CD_2Cl_2[b]	100	0	100	0	40.7	20.4	1	0.30	0	0.82
C_6D_6	88	12	98	2	34.5	8.2	3	0	0.1	0.59
CD_3CN	62	38	88	12	46.7	18.9	14.1	0.19	0.31	0.75
THF-d_5	51	49	95	5	37.4	8.0	20	0	0.55	0.58
acetone-d_6	50	50	86	14	42.2	12.5	17	0.08	0.48	0.71
DMF-d_7	23	77	82	18	43.8	16.0	26.6	0	0.69	0.88
DMSO-d_6[c]	22	78	81	19	45	19.3	29.8	0	0.76	1
methanol-$d4$	40	60	86	14	55.5	41.5	19	0.93	0.62	0.60
D_2O	50	50	82	18	63.1	54.8	18	1.17	0.18	1.09
pyridine-d_5	44	56	88	12	37.6	14.2	33.1	0	0.64	0.87

[a] Thermodynamic values determined at 20 °C otherwise mentioned (±1−2% estimated error). [b] Spectrum recorded at 18 °C. [c] Extrapolated at 20 °C from linear plot. [d] Referring to the nondeuterated solvents. [e] Reichardt's E^N_T values, from ref 18. [f] Gutmann's acceptor number, from ref 18. [g] Gutmann's extended donor number, from ref 19. [h] Taft and Kamlet's α, β and π^* parameters, from ref 20.

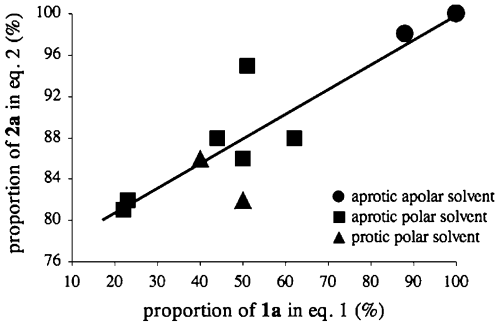

FIGURE 5. Percentage of **2a** in equilibrium 2 as a function of the percentage of **1a** in equilibrium 1 in varying solvents.

it was found that their correlation was unsatisfactory, including by use of the Lippert−Mataga equation,[21−23] we turned to empirical solvent descriptors that were previously proven useful to explain the strong solvent dependence of the ^{13}C NMR analysis of various iodoalkynes.[24] These descriptors include Reichardt's polarity measure, E^N_T, Gutmann's acceptor and donor number systems, AN and DN, Taft−Kamlet's α, β, and π^* solvent model.

We first tested Reichardt's parameter, which is known as an empirical measure of bulk solvent polarity.[18] Interestingly, linear regression analysis showed that the E^N_T scale only slightly correlates with equilibrium 2 and not at all with equilibrium 1 (see the Supporting Information). This is in agreement with the previous analysis using μ and ϵ_r and indicates that polarity is probably not the main factor responsible for the observed equilibrium shifts.

We then turned to Gutmann's acceptor and donor numbers which respectively evaluates the Lewis acidity and basicity of the solvent.[25] The acceptor number AN is derived from the ^{31}P NMR chemical shifts produced by the electrophilic action of acceptor solvents in triethylphosphine oxide, while the donor number is defined as the negative enthalpy of formation of a

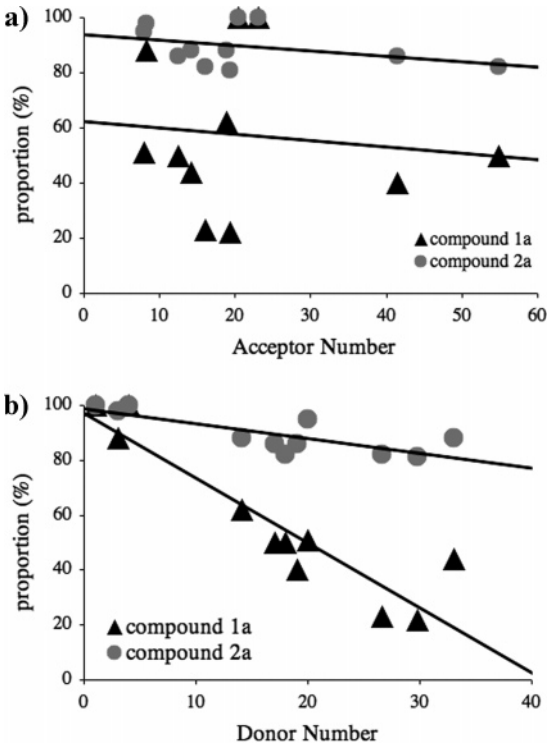

FIGURE 6. Percentage of compounds **1a** and **2a** as a function of Gutmann's parameters: (a) acceptor number and (b) donor number.

1:1 complex between the basic solvent molecule and antimony-(V) chloride in dilute solution, typically in 1,2-dichloroethane. Because of the popularity of the donor number (DN) scale, an extended version, the so-called *extended donor number*, was introduced based on indirect donicity measurements.[19] Whereas no significant correlation was found with the AN scale (Figure 6a), a linear regression demonstrates that the DN scale can be used to predict the equilibria shifts, especially in the case of **1a** ($R^2_{\mathbf{1a}/DN} = 0.85$, $R^2_{\mathbf{1b}/DN} = 0.62$, Figure 6b). If the value for pyridine-d_5 is excluded, the correlation is considerably improved ($R^2_{\mathbf{1a}/DN-\{pyridine\}} = 0.96$, $R^2_{\mathbf{1b}/DN-\{pyridine\}} = 0.76$). Pyridine, which is by far the most Bronsted-basic solvent of the list, may give rise to some specific effect. While Lewis acidity turns out to have no impact on equilibria 1 and 2, the increase in basicity from halogenated solvents to highly electron-pair donating solvents such as DMF or DMSO nicely accounts for the

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formation of diastereoisomers **1b** and **2b**. Preferential solvation of the two latter compounds seems thus to be due to superior interactions with Lewis basic solvents, on a molecular level, according to the DN definition.[25] The most favorable site for such an interaction lies in the vicinity of the hydroxyl groups which can a priori participate in hydrogen-bonding with discret solvent molecules. These hydroxyl groups are indeed very similar to that of trifluoroethanol (TFE) as they all possess one geminal trifluoromethyl moiety. TFE is well-known for its propensity to alter the structure of peptides and proteins.[26] In this case, it has been proved that the presence of fluorine atoms remarkably alters its hydrogen-bonding capability, in comparison to ethanol and water.[27] While TFE is a poor proton acceptor, its proton-donating ability is exceptionally high. This may explain why equilibria 1 and 2 are not sensitive to proton-donor solvents but only to proton-acceptor solvents. In this context, it has recently been shown that hydrogen-bonding by HFIP is responsible for the enormous rate acceleration of the epoxidation of olefins by hydrogen peroxide (up to 10^5-fold compared to that in dioxane).[28]

In order to validate this hypothesis, we decided to use the parameters introduced by Taft and Kamlet in their so-called linear solvation energy relationships (LSER).[20] These authors have developed a solvatochromic comparison method that includes parameters for acidity (α), basicity (β) and dipolarity/polarizability (π^*) effects. Parameter α corresponds to a measure of the solvent hydrogen-bond donor acidity,[29] while β reflects the solvent hydrogen-bond acceptor basicity.[30] As a consequence, α and β may be more accurate than AN and DN in predicting the solvent effect on equilibria if hydrogen bonds are involved. Finally, parameter π^* evaluates the solvent dipolarity/polarizability, i.e., its ability to stabilize a charge or a dipole by virtue of its dielectric constant.[31] In this regard, π^* differs from Reichardt's polarity scale since it will not be affected by any additional Lewis acid−base interactions.[18,32] In fact, no relationship was seen using α, an observation that confirms the previous result obtained with the AN scale (see Supporting Information). In contrast, β was found to remarkably correlate with equilibrium 1, while less significantly with equilibrium 2 ($R^2_{\mathbf{1a}/\beta} = 0.86$, $R^2_{\mathbf{1b}/\beta} = 0.51$). Removal of the D_2O data, for which the β value is relatively less certain according to the authors,[20] considerably improves both correlations ($R^2_{\mathbf{1a}/\beta-\{D2O\}} = 0.97$, $R^2_{\mathbf{1b}/\beta-\{D2O\}} = 0.78$). A rigorous comparison of DN and β scales over the nine best solvents, thus omitting pyridine-d_5 and D_2O data, gives quasi-identical results, which demonstrates that β is not superior to DN for the description of the two systems. Interestingly, parameter π^* fits better with equilibrium 2 than with equilibrium 1, the correlation factors are rather low ($R^2_{\mathbf{1a}/\pi^*} = 0.21$, $R^2_{\mathbf{1b}/\pi^*} = 0.43$). While confirming the impact of basicity on both equilibria, the LSER parameters also show that a polarity term has to be taken into account in the case of equilibrium 2.

A complementary analysis was conducted with Drago's model developed for the description of interactions between Lewis acidic and Lewis basic species.[33] Drago proposed the following four-parameter equation to correlate the standard enthalpy of the reaction of an acceptor A with a donor B to give a neutral 1:1 adduct in an inert solvent:[33]

$$-\Delta H^\circ_{AB} = E_A E_B + C_A C_B \quad (1)$$

The pairs (E_A; C_A) and (E_B; C_B), respectively, correspond to empirical acceptor and donor parameters characteristic of the acceptor and donor species. The E value reflects the propensity of a given molecule to participate in electrostatic interactions, while the C value estimates its tendency to form covalent bonds. As recommended by Drago[34] for the interpretation of spectral and reactivity parameters, we used the following extended version of the initial four-parameter equation

$$\Delta\chi + W = \text{“}E_A\text{”}E_B + \text{“}C_A\text{”}C_B \quad (2)$$

where $\Delta\chi$ corresponds, in our case, to the percentage of compounds **1a** and **2a** dissolved in the solvent, regarded as a base (E_B; C_B) according to Drago's classification. A subsequent parameter W is introduced in order to take into account any supplementary constant contribution, characteristic for our system. In light of the reduced number of values (7 vs 11 previously), the correlation factor can be regarded as quite satisfactory for both fits ($R^2_{\mathbf{1a}} = 0.97$, $R^2_{\mathbf{2a}} = 0.90$). Moreover, the calculated (“E_A”;”C_A”) sets [(−0.866; 0.020) for **1a** and (−0.252; 0.017) for **2a**] demonstrate a strong prevalence for electrostatic interactions over covalent factors: the absolute value of the ratio “C_A”/”E_A” is below 0.10 (0.023 for **1a** and 0.067 for **2a**), which, in the classical case of Lewis acid−base interaction, accounts for strong hardness according to the interpretation by Drago.[33] This reinforces the hypothesis that specific moderate hydrogen-bond interactions play a crucial role in the observed effect of solvent, as this type of bonding was proved to be mostly electrostatic in character.[35] The unusual difference in sign between “C_A” and “E_A” suggests the existence of an opposite factor, less predominant for equilibrium 1. In addition, a series of multivariable equations recommended by Swain ($A_j + B_j$),[36] Taft and Kamlet ($\alpha + \beta + \pi^*$, $\beta + \pi^*$),[20] and Krygowski and Fawcett ($E^N_T + DN$)[37] were tested (see the Supporting Information for details), but no additional elements could be gathered to shed further light on the systems behavior.

The analysis with several empirical parameters demonstrates that solvent effects can be well predicted by the use of basicity scales (DN and β) as well as Drago's Lewis acid−base model. All analyses prove that the better solvation observed for diastereoisomers **1b** and **2b** is the result of preferential hydrogen-bonding with proton-acceptor solvents. The major difference in structure between **1a**, **2a** and **1b**, **2b** arises from the capacity of **1a** and **2a** to form intramolecular hydrogen bonds, thanks to the 1,3-cis relationship between the two axial hydroxyl groups

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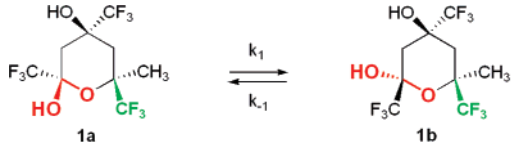

$$x_{\mathbf{1b}}(t) = \frac{[\mathbf{1b}]}{[\mathbf{1a}] + [\mathbf{1b}]}$$

$$x_{\mathbf{1b}eq} = \frac{[\mathbf{1b}]_{eq}}{[\mathbf{1a}]_{eq} + [\mathbf{1b}]_{eq}}$$

FIGURE 7. Kinetic study of partial conversion of **1a** into **1b**: rate constants and molar fractions of **1b** at time t and at equilibrium $t = \infty$.

TABLE 2. Kinetic Parameters of 1a,b Conversion in Methanol-d_4

entry	experimental conditions	k_{obs}/k_{init}
1	1.0×10^{-3} equiv of diethylamine	5.5
2	3.0×10^{-3} equiv of diethylamine	8.2
3	3.5 equiv of acetic acid	1.3×10^{-2}
4	14.5 equiv of acetic acid	7.1×10^{-3}
5	55 equiv of acetic acid	2.7×10^{-3}
6	0.9 equiv of triflic acid	5.9×10^{-4}
7	4.3 equiv of triflic acid	7.6×10^{-4}
8	65 equiv of triflic acid	3.3×10^{-3}

as is seen in the solid state (Figure 3). Intramolecular hydrogen bonding is strongly favored in solvents where no intermolecular hydrogen bonding can compete.[38] By contrast, proton-acceptor solvents preferentially solvate the hydroxyl functions and hence lower the effect of intramolecular hydrogen bonding. Moreover, the hydroxyl groups of **1b** and **2b** are more accessible than those of **1a** and **2a** which results in an additional positive effect on the solvation of **1b** and **2b**. This is supported by several cases of precedence in the carbohydrate literature: Angyal et al. have demonstrated the presence of intramolecular hydrogen bonds for monosaccharides dissolved in DMSO. The authors proposed that this type of interaction firmly contributes to the change of the isomeric distribution when moving from water to DMSO.[39] Another research group interested in the variation of the isomeric equilibrium of caryophyllose monosaccharide in varying solvents invoked the different hydrogen bonding requirements for equatorial and axial hydroxyl groups in order to explain their observations.[40] The weaker solvent effect observed for equilibrium 2 may be explained by the existence of a competitive phenomenon, evidenced by the slight correlation detected with π^*.

Equilibrium Kinetics. A kinetic study of the equilibrium shifts completed our characterization of **1a**,**b** and **2a**,**b**. Indeed, our initial experiments showed that the reaction rate was remarkably dependent on the solvent type. Less than 1 h was sufficient to reach the equilibrium at 77% **1b** in DMF-d_7 starting from pure **1a**, whereas more than 10 days were required to attain the equilibrium at solely 12% **1b** in benzene-d_6. Since trimers **1a/b** typically equilibrated over the course of a few hours in methanol and showed a large solvent effect, we selected this system for further studies. In order to test whether the kinetics followed the same pseudo first-order rate as reported in the case of carbohydrate mutarotation[41] we introduced k_1 and k_{-1}, the rate constants for reactions **1a** → **1b** and **1b** → **1a**, and the molar fractions $x_{\mathbf{1b}}$ at time t ($x_{\mathbf{1b}}(t)$) as well as $x_{\mathbf{1b}}$ at equilibrium ($t = \infty$, $x_{\mathbf{1b}eq}$)(Figure 7). The following rate equation applied to the system **1a**/**1b** allows the rate v of the reaction to be described in two ways:

$$v = k_1[\mathbf{1a}] - k_{-1}[\mathbf{1b}] = \frac{\mathrm{d}[\mathbf{1b}]}{\mathrm{d}t} = -\frac{\mathrm{d}[\mathbf{1a}]}{\mathrm{d}t}$$

Since the sum of concentrations [**1a**] and [**1b**] is constant and equal to the initial concentration, the differential equation may be solved. It is thus possible to describe the time dependence of molar fraction **1b**:

$$x_{\mathbf{1b}}(t) = x_{\mathbf{1b}eq}(1 - \exp{-(k_1 + k_{-1})t})$$

with

$$x_{\mathbf{1b}eq} = \frac{k_1}{k_1 + k_{-1}}$$

By rearrangement, one obtains eq 3:

$$-1\mathrm{n}\,\frac{x_{\mathbf{1b}eq} - x_{\mathbf{1b}}(t)}{x_{\mathbf{1b}eq}} = (k_1 + k_{-1})\,t \qquad (3)$$

This equation correlates well with the kinetic data (see the Supporting Information, p S17):

$$-1\mathrm{n}\,\frac{x_{\mathbf{1b}eq} - x_{\mathbf{1b}}(t)}{x_{\mathbf{1b}eq}} = (8.2 \times 10^{-4})t - (1.3 \times 10^{-2})R^2 = 0.9994$$

which proves that pseudo-first-order kinetics are indeed operative. This allowed us to determine the kinetic parameters ($k_1 = 4.9 \times 10^{-4}$ s^{-1}; $k_{-1} = 3.3 \times 10^{-4}$ s^{-1}) by using the value of $x_{\mathbf{1b}eq}$ determined previously in the case of methanol-d_4 ($x_{\mathbf{1b}eq} = 0.60$, see Table 1).

Since carbohydrate mutarotation is known to be controlled by general acid and base catalysis,[42] we also investigated this influence on the kinetics. The main difference between carbohydrates and compounds **1a**,**b** is found in the presence of trifluoromethyl groups on positions 2 and 7 with respect to the tetrahydropyran ring system (see Figure 4 for labeling). Because of its outstanding properties, fluorine has been widely used in order to modify the physical, chemical, and biological properties of organic compounds.[17] In particular, CF_3 substitution has become a very popular strategy when one wants to efficiently withdraw electron density from a reactive center.[43] In the past, Capon et al. studied the effect of several electron-donating and -withdrawing groups on the mutarotation of 3- and 6-substituted glucose derivatives in water.[41] For all electron-withdrawing groups, the authors observed a concomitant enhancement of hydroxide catalysis and a decrease of hydroxonium catalysis. The two CF_3 moieties in the vicinity of the anomeric center of

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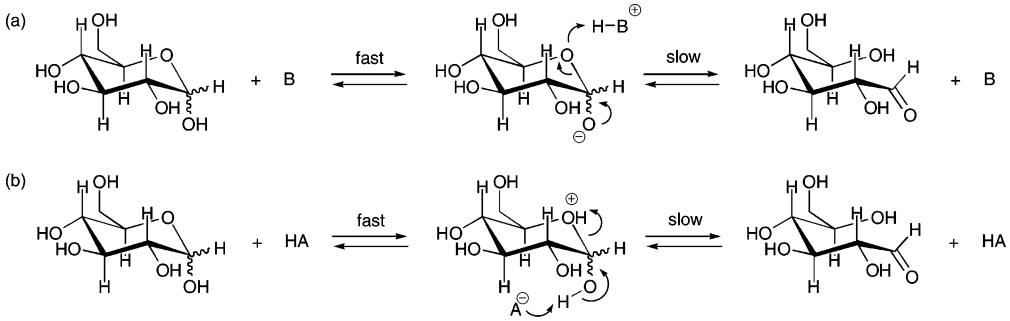
SCHEME 1. Mutarotation of Glucopyranose: Mechanistic Pathways Proposed by Capon[41] to Account for the Observed Catalysis by a General Base (a) and by a General Acid (b), Respectively



1a,**b** might thus alter the base- and acid catalysis in the same manner. We have therefore studied the influence of acidic and basic conditions on the speed of equilibration of system **1a/1b**. Using simple algebra, we have found previously that the kinetic evolution of the molar fraction of **1b** can be expressed by the sum of k_1 and k_{-1} (eq 3). Therefore, following Capon,[41] we denoted by $k = k_1 + k_{-1}$ the experimental kinetic constant. k_{init} (8.2×10^{-4} s^{-1}) corresponds to the constant previously established in the absence of any base or acid, while k_{obs} is used for the new tests. In essence, k_1 and k_{-1} are proportional to k by a factor depending only on $x_{\mathbf{1b}eq}$. For all conditions $x_{\mathbf{1b}eq}$ was found constant and equal to the initial value (0.60, see Table 1). It is thus sufficient to compare k_{obs}, obtained under acidic and basic conditions, with k_{init} to assess the resulting effect.

Results are summarized in Table 2. The quoted range of base and acid concentrations was limited by the rates that can be followed by ^{19}F NMR spectroscopy. Entries 1 and 2 show that reaction rates can be significantly enhanced by trace amounts of diethylamine; this may be indicative of a general base-catalyzed process, similar to that found in mutarotation. However, the presence of acetic acid unexpectedly inhibited establishment of the **1a**,**b** equilibrium (Table 2, entries 3−5), quite in contrast to mutarotation that is accelerated by acetic acid.[44] Overall rate is also significantly reduced in the presence of triflic acid; however, by increasing the triflic acid concentration the rate recovers somewhat (Table 2, entries 6−8).

Two formal mechanistic pathways accounting for the effect of bases and acids on mutarotation reactions are commonly accepted[41] although they do not invoke any solvent participation (see ref 45 for a discussion of the specific effect of water). The first one, under basic conditions, consists in the initial deprotonation of the hemiacetal moiety followed by ring-opening which finally leads to epimerization at the anomeric center (Scheme 1a). The second mechanism describes the initial protonation of the oxygen atom on the tetrahydropyran system by an acid catalyst, followed by the subsequent release of the oxonium ion and ring opening. At that stage, the conjugate base assists the formation of the free carbonyl by deprotonating the anomeric hydroxyl. (Scheme 1b).

We suggest that the mechanism proposed for carbohydrates under basic conditions is still valid in the case of compounds **1a**,**b**. This pathway might be even favored since the CF_3 moiety enhances the acidity of the hemiacetal, as previously demonstrated during formation of the diethylammonium salt. The acid-promoted effect may be explained as a medium effect in light of the large amount of acid used. By contrast, this effect may also be rationalized with the two mechanisms shown in Scheme 1. Indeed, a weak acid such as acetic acid will not notably help in the formation of the oxonium ion, a species that is strongly destabilized by the CF_3 groups.[17] However, the presence of a weak acid will significantly reduce the concentration of 4-hydroxy-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-*2H*-pyran-2-olates required for the base-catalyzed pathway (Scheme 1a), thus causing an apparent inhibition of the equilibration reaction. On the other hand, a strong acid such as triflic acid ($pK_a = -5.9$[46]) will have a notable effect on oxonium formation and will thus favor the acid-catalyzed pathway (Scheme 1b). It is worth mentioning that the base-catalyzed pathway is by far more efficient in increasing the equilibration rate, as previously observed for mutarotation.[47] In any case, weak or even strong acidic conditions can be employed to protect **1a** from epimerization ($T_{1/2}$ =16.5 days with 0.9 eq. triflic acid; Table 2, entry 6) or to block the equilibration at a certain stage.

Tris(trifluoromethyl)cyclohexane-1,3,5-triols. Our increased understanding of the synthetic and analytical chemistry of trifluoroacetone trimers **1a**,**b** and **2a**,**b** encouraged us to re-examine the trimerization conditions which were reported to furnish *cis*,*cis*- and/or *cis*,*trans*-1,3,5-tris(trifluoromethyl)cyclohexane-1,3,5-triol (**3**, **4**) (Figure 1). Smith et al.[4] and Resconich[7] did in fact not offer firm evidence for the formation of **3/4**. When we repeated their experiments using sodium metal in the presence of catalytic amounts of mercury and magnesium amalgam, respectively, ^{19}F NMR analysis in $CDCl_3$ allowed us to determine the main constituents of the crude mixture. In both cases, trimers **1a** and **2a** and also dimer **5**[8,9] (see Figure 1), were found to predominate. Once all of the volatile components removed, trimers **1a** and **2a** remained as the only products of significant abundance. While Resconich reported the isolation of one trimeric species (mp 93−94 °C; M = 345 g·mol^{-1}), assigned to **3/4**, Smith et al. were able to separate three components from the mixture. Two trimers (mp 93 °C; M = 330 g·mol^{-1} and mp 121 °C; M = 328 g·mol^{-1}) were assigned structure **3/4** and a linear one, respectively, while a solid dimeric product (mp 60 °C; M = 242 g·mol^{-1}) was identified as **5**. On the basis of our observations and the literature reports,[8,9] we suggest that the two trimers and the solid dimer correspond to compounds **1a**, **2a**, and **6**, respectively. We recently demonstrated[14] that a previously reported X-ray crystallographic analysis proposing **3** in a Cd_2Cu_2 complex was in fact erroneous.

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In conjunction with the results presented here it must be concluded that the synthetic target **3** remains, for the time being, elusive.

Conclusion

This contribution has presented an extensive study on the equilibrium thermodynamics and kinetics of 6-methyl-2,4,6-tris-(trifluoromethyl)tetrahydro-2*H*-pyran-2,4-diols **1a,b** and **2a,b** in solution. It has also revealed that, contrary to two previous reports,[4,7] trimerization of trifluoroacetone does not lead to the formation of *cis*,*cis*-1,3,5-tris(trifluoromethyl)cyclohexane-1,3,5-triol **3**. The polyfluorinated cyclic diols **1a,b** and **2a,b**, formed instead, present a potential interest for coordination chemistry and catalysis. The remarkable solvent effect of these equilibria as reported here is likely controlled by hydrogen bonding between the hydroxyl groups and hydrogen-acceptor solvents.[13] This work determined the conditions which quantitatively shift both equilibria in favor of **1a** and **2a**. Three X-ray crystallographic analyses put our structural assignments in the chemistry of trifluoroacetone trimers on a firm footing. A complementary kinetic study illustrates that acidic conditions can also be applied to reduce the equilibration rate, thus allowing for operation in a wider range of solvents. The strong deviation of the behavior of CF_3-bearing **1** and **2** from the habitual one found in regular carbohydrates contributes to the growing interest in fluorinated carbohydrates.

Experimental Section

(±)-(2*S*,4*S*,6*S*)-6-Methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2,4-diol 1a and (±)-(2*S*,4*S*,6*R*)-6-Methyl-2,4,6-tris-(trifluoromethyl)tetrahydro-2*H*-pyran-2,4-diol 2a. Procedure adapted from ref 2. Trifluoroacetone (4.96 g, 43.4 mmol) was cannulated into a precooled Schlenk at −10 °C under argon. Slow addition of diethylamine (4.49 mL, 43.4 mmol) resulted in an undetermined white fume which disappeared after a few minutes. The yellow solution was then vigorously stirred for 15 h, while the temperature was slowly raised to ambient. The resulting white slurry, corresponding to the crude diethylammonium 4-hydroxy-6-methyl-2,4,6-tris(trifluoromethyl)tetrahydro-2*H*-pyran-2-olate salts, was dissolved in 100 mL of diethyl ether, and 100 mL of 17% dilute HCl was added. The biphasic system was allowed to react for 2 h under vigorous stirring. After separation of the layers, the aqueous phase was extracted with two portions of 50 mL of diethyl ether. The combined etheral phases were washed with 60 mL of brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield 4.20 g of a light-yellow solid. The crude mixture was then divided into four equal portions, which were successively applied to a prepacked silica gel column (FlashSmart Pack by AIT; Quality: Silica BP Sup; 50 g). For each run, flash chromatography purification was carried out using 600 mL of a 6:1 dichloromethane/pentane mixture followed by 1 L of dichloromethane at a flow rate of 30 mL/min. Subsequently, 1.28 g of compound **1a** (white cristalline solid; 3.80 mmol; 26%) and 2.26 g of compound **2a** (cristalline solid; 6.72 mmol; 46.5%) were isolated. X-ray quality monocrystals of the diethylammonium salt were obtained by recrystallization of the white slurry from above in boiling $CHCl_3$, whereas hot cyclohexane was employed to afford monocrystals of **1a** and **2a**.

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Supporting Information Available: ^1H, ^{13}C, and ^{19}F NMR spectra of compounds **1a**, **2a**, their respective ammonium salts as well as statistical analyses for the determination of the kinetic and thermodynamic data (including their NMR protocols), and CIF files for compounds **1a**, **2a**, and Et_2NH·**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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