Acidity Measurements from Protonation of Aromatics. Protonation of Hexamethylbenzene by Trifluoromethanesulfonic Acid and Its Use To Relate Acidities of Strong Superacids to Acidities of Acids Included in the Traditional Hammett Scale†,[1]

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Abstract: The degree of protonation of hexamethylbenzene (**1**) can be determined from the chemical shifts of its carbon-13 signals for the aromatic and methyl carbons, respectively, at temperatures of 45–65 °C. Complete protonation occurs for a 0.5 molar solution in trifluoromethanesulfonic acid (acid to hydrocarbon ratio of 22:1). Treatment of **1** with an equivalent amount or a small excess (2–3:1 molar) of the acid in a nonbasic solvent (sulfur dioxide–chloroform or sulfuryl chloride fluoride–chloroform) results in partial protonation. At a 3:1 acid-to-base ratio hexamethylbenzene is protonated by trifluoromethanesulfonic acid somewhat less than benzene is protonated by hexafluorotantalic acid in HF (30:1 HF–TaF_5). Since the two bases are closely related structurally and hexamethylbenzene is a base stronger than benzene by a factor of 6×10^{10}, it is concluded that the protonating ability (acid strength) toward carbon bases of the 30:1 HF–TaF_5 mixture is greater than that of trifluoromethanesulfonic acid (H_0 −14.2) by at least the same factor. As established before, HBr–$AlBr_3$ and HF–SbF_5 superacid systems are even stronger.

Some years ago we initiated a study of relative acidities of superacids based on the measurement by ^{13}C NMR spectroscopy of the degree of protonation of aromatic hydrocarbons.[3] The approach had been determined by the following considerations.

(1) The traditional Hammett acidity scale,[4] extended for very high acidities by Gillespie,[5] could not be used for the strongest superacids because of lack of sufficiently weak indicator bases.

(2) For superacid composites containing a solid Lewis acid the solubility of the latter in the Brønsted acid is so low that only acidity of mixtures close to the pure Brønsted acid can be measured. By contrast, superacid catalysts contain a much larger proportion of Lewis acid,[7] solubilized by interaction with the hydrocarbon substrates which generate carbocations.[8]

(3) Hammett indicator measurements[4,5] as well as newer methods[9-12] are based on protonation of oxygen bases. Since the relative acidities are determined by the nature of the indicator base,[4b] development of methods using carbon bases as indicators[13] seemed to us worthwhile.[8,14]

(4) UV–visible spectroscopy, typical for Hammett acidity studies, is inapplicable to many acid catalyst systems of practical importance, which are often dark-colored and occasionally opaque. Measurements based on NMR spectroscopy[9-12,15,16] or voltammetry[12] have no such limitation.

It was for the above reasons that the acidity of aluminum halide composites had never been determined, despite their importance as acid catalysts. By using benzene as the indicator base (eq 1) we established the acidity order HF–SbF_5 and HBr–$AlBr_3$ > HF–TaF_5.[14] The high strength of the hydrogen bromide–aluminum bromide system has invalidated an entire scheme of classification of superacids.[17]

$$C_6H_6 + AH \rightleftarrows C_6H_7^+ + A^- \quad (1)$$

To calculate the acidity function H_0[4] from eq 1, the activity coefficients of the protonated and unprotonated aromatic at the concentrations used in the ^{13}C NMR measurements (0.2–0.5 M) should be determined. For practical purposes, quantitative relationships can be established from the comparison of the degree of protonation in two acids. If the degree of protonation in two acids is similar, the activity coefficients should not differ my much, if at all. The change in the ratio of protonated to unprotonated base is then a true measure of acidity difference. Acids differing widely in acidity can be compared by a different approach: if two structurally similar bases dissolved in the same concentration in two different acids are protonated to the same extent, one could

† Dedicated to the memory of Victor Gold.

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Table I. ^{13}C NMR Chemical Shifts for Hexamethylbenzene Protonated in Superacids

			chemical shifts[a]							
no.	acid	temp, °C	C-1	C-2,6	C-3,5	C-4	Me-1	Me-2,6	Me-3,5	Me-4
1	4:1 FSO_3H–SbF_5[b,c]	−60	56.01	192.29	138.47	190.49	19.73	22.25	13.55	22.25
2	1:1 HF-SbF_5[b,d]	−80	57.7	193.8	139.5	191.9	20.5	23.3	14.5	23.3
3	TFMSA[b,e]	−65	*f*	193.88	139[g]	191.39	20.77	22.79	14.41	22.79[h]
4	4:1 FSO_3H–SbF[b,c]	*i*	151.34						18.93	
5	1:1 HF–SbF_5[b,d]	*i*	152.7						19.9	
6	TFMSA	*i*	151.30[j]–152.26[k]						19.66	
7	4:1 FSO_3H–SbF_5[b,c]	0	• • •						18.7	
8[l]	TFMSA	−2	• • •						18.93[m]	
9[l]	TFMSA	+45	151.9[n]						19.09[o]	

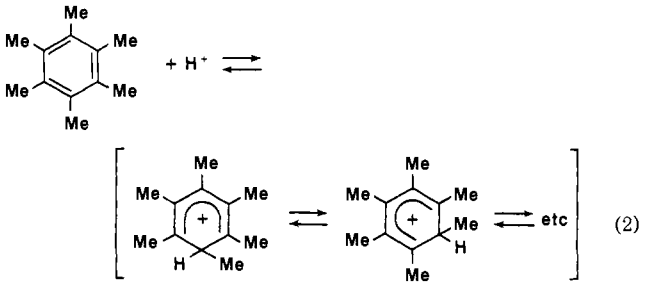
[a] From external (coaxial) TMS. [b] Containing SO_2FCl. [c] SbF_5:HMB 3.3 (molar), 1.5 vol SO_2FCl:vol of acid; spectrum run at 25.2 MHz. [d] The ratios acid/HMB and solvent/acid were not reported (ref 28b). [e] Composition of the sample given in the text; spectrum run at 22.65 MHz. [f] Covered by the CD_2Cl_2 multiplet. [g] Not resolved from the TFMSA signal at δ 139.43. [h] Other signals: 139.43, 125.38, 111.40, 97.35 (TFMSA); 57.03, 55.80, 54.56, 53.39, 52.16 (CD_2Cl_2). [i] Averaged spectrum, calculated from the chemical shifts at low temperature. [j] Assuming δ (C-1) = 56 (entry 1). [k] Assuming δ (C-1) = 58 (entry 2). [l] 0.5 mmol HMB in 1 mL of acid, no solvent; spectrum run at 25.2 MHz. [m] Other signals: 136.46, 123.92, 111.37, 98.82 (TFMSA); 78.18, 76.92, 75.65 ($CDCl_3$). [n] Broad signal. [o] Other signals: 136.82, 124.25, 111.70, 99.13 (TFMSA); 78.20, 76.94, 75.66 ($CDCl_3$).

state that the relative protonating ability (R.P.A.) of the acids is the inverse of the ratio between the basicity of the indicators (the logarithm of that ratio can be used).

We report here on measurements of the protonation equilibrium of hexamethylbenzene (HMB, **1**) in trifluoromethanesulfonic acid (TFMSA) which allow the estimation of the protonating ability of the HF–TaF_5 superacid system relative to TFMSA. Since the Hammett acidity of the latter, $H_0 = -14.2$, is known,[18] a direct correlation of acidic strength of media with widely different ranges of acidity becomes possible. TFMSA[19] has a good thermal stability, it is not easily reduced by organic compounds, as sulfuric and fluorosulfuric acid are, and is not a sulfonating agent. As the probe base, the closest analogue to benzene was a methylated benzene.

It has been reported that benzene and toluene are fully protonated in TFMSA.[20] Such a result meant that mesitylene, 10^9 times stronger a base than benzene,[21] must be fully protonated in aqueous 60% hydrofluoric acid ($H_0 = -6$). In reality mesitylene was not fully protonated even in hydrogen fluoride solutions used to determine its relative basicity.[21] In our earlier work, benzene was only 55% protonated when dissolved (ca. 0.6 molal) in a 1.7 molal solution of TaF_5 in HF,[14] even though a solution as dilute as 0.025 molal (0.6%) of TaF_5 in HF has $H_0 = -18.85$.[22] Therefore, we reinvestigated the behavior of benzene and toluene in TFMSA and found that no protonation occurred.[23] We give below a full description of those experiments as well.

Hexamethylbenzene, 6×10^{10} times more basic than benzene, was appropriate for work in TFMSA. It had been found by UV–visible spectroscopy that 10^{-6} mol/L of HMB is half-protonated in 90.5% sulfuric acid but slowly decomposes upon standing.[13,24] HMB was one of the compounds investigated in the first publication of an NMR study of protonation of aromatics.[25] The protium[26-28] and ^{13}C NMR[28] spectra of protonated HMB (**2**) and of other Pfeiffer–Wizinger complexes[8,29] derived from **1** were reported.[26a,30]



(2)

For acidity comparisons the protonation equilibrium of eq 2 was studied as a function of the acid-to-hydrocarbon ratio with TFMSA as the acid, in nonacidic–nonbasic solvents,[31] and in TFMSA as both acid and solvent. The position of the equilibrium (%**2** of the total **1** + **2**) was determined by ^{13}C NMR spectroscopy.[14]

Results and Discussion

A. Study of Benzene and Toluene in TFMSA. Two types of tests were conducted. First, we determined the distribution ratio (eq 3)[21] of benzene and toluene between pentane and TFMSA at −20 °C

$$\bar{P} = (m_A + m_{AH})/m_A' \qquad (3)$$

where m_{AH} and m_A represent the molal concentration in the acid layer of protonated and unprotonated aromatic, respectively, and m_A' is the molal concentration of aromatic in the pentane layer.

Fully protonated benzene is quantitatively extracted in a superacid.[32] Also, if benzene were protonated to any extent, toluene, a base 1250 times stronger,[21] should show a much greater degree of protonation and a much larger distribution ratio. Instead, we measured similar distribution values: 0.26 for toluene and 0.42 for benzene studied separately, 0.28 and 0.14, respectively, in a competition experiment. These findings indicate no protonation at all for benzene and no sizable protonation for toluene in TFMSA.

Next, we determined the ^{13}C chemical shifts for the more basic compound, toluene, in TFMSA containing 1.5% of the anhydride to remove any traces of water. The NMR spectrum was run at 27 °C, where the hydrogen atoms of the protonated aromatic exchange rapidly.[33] The spectrum of a 0.2 M solution of toluene

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in TFMSA solution exhibited signals at δ 138 (C-1, not resolved from the TFMSA signal at 138.77), 128.48 (C-2,6), 128.16 (C-3,5), 124.15 (C-4), and 19.25 (C-α). These chemical shifts matched closely the spectrum of toluene in deuterochloroform (C-1 137.6, C-2,6 129.1, C-3,5 128.3, C-4 125.4, C-α 21.5 ppm) or trifluoroacetic acid and were completely different from the values for the fully protonated molecule in $HF–SbF_5$ or $HF–TaF_5$ (C-1 202.5, C-2,6 ca. 125, C-3,5 177, C-4 ca. 65, C-α ca. 28). The experimental data rule out any significant extent of protonation of toluene in TFMSA.[34]

B. Protonation of Hexamethylbenzene. For evaluation of acidities[14] the equilibria of eq 2 should be fast enough to result in a ^{13}C NMR spectrum fully averaged between those of **1**, **2a**, **2b**, etc., exhibiting one signal for the aromatic carbons and one signal for the methyl carbons. The degree of protonation is determined by interpolation of the chemical shift of either signal between the chemical shifts of the corresponding signals for **1** and (averaged) **2**.

The ^1H NMR spectrum of **2** was reported both in the region of slow exchange (−60 to −85 °C) and at 0 °C, where a fully averaged methyl signal was seen.[25-27] The carbon chemical shifts in three superacids are shown in Table I. Since the variation in the ^{13}C NMR spectrum of **2** with temperature had not been reported, we examined first the protonation of **1** in 4:1 $FSO_3H–SbF_5$ solution, with SO_2FCl as cosolvent. The spectrum at −60 °C corresponds closely to the spectrum in $HF–SbF_5$.[28b] From the low-temperature spectra one can calculate the chemical shifts for the averaged signals of **2** in each acid. The two values in each pair differ by 1.0–1.4 ppm, possibly due to solvent effects.

Warming the solution in $FSO_3H–SbF_5$ to 0 °C gave the averaged signal of the methyl carbons (Table I, entry 7) situated near the calculated position, but the signals for the ring carbons were broadened into the base line.

Hexamethylbenzene (**1**) was soluble in TFMSA. A solution of 0.5 mmol of **1** in 1 mL of TFMSA was yellow at low temperature but became brown at room temperature. To run the carbon NMR spectrum at −65 °C 0.3 mL of SO_2FCl was added to the sample. The spectrum was clearly that of the protonated material (**2**). Since one peak was superimposed on the signal of TFMSA at 139.43 ppm and another peak (ca. 57 ppm) on the multiplet of the NMR lock solvent, CD_2Cl_2, the chemical shift for the averaged aromatic carbon signal could be calculated only approximately. The low-temperature spectrum does not show any unprotonated HMB (**1**, δ 131–132). Therefore, HMB is fully protonated to **2** by TFMSA at a molar ratio of 22:1.

Upon heating, the methyl carbon signal became fully averaged at 0 °C, just as for the sample in $FSO_3H–SbF_5$. The averaged aromatic signal was seen only at 45 °C, at which temperature it was still broad.

For acidity comparisons HMB dissolved (0.3–0.5 M) in a 75:25 mixture of sulfur dioxide or SO_2FCl, and chloroform was treated with variable amounts of TFMSA at 50–65 °C. The chemical shifts of the signals for the aromatic and methyl carbons were measured from external (coaxial) TMS. Chloroform added to the solvent was a secondary chemical shift standard (δ 77.10 ± 0.07). The carbon-13 chemical shifts for unprotonated hexamethylbenzene, determined in the same solvent mixtures and at the same concentration (0.5 mmol/mL), were 133.18 and 15.80 ($SO_2–CHCl_3$) and 131.54 and 15.60 ($SO_2FCl–CHCl_3$).

The degree of protonation of HMB (%**2** in the mixture of **1** + **2**) was obtained by interpolating the chemical shift found in each case between the value for **1** in the same solvent (SO_2 or SO_2FCl) and the value for **2** from Table I, entry 9. The interpolation was done both for the aromatic and for the methyl carbon signals. The average of the two results is represented in Figure 1 as a function of the ratio TFMSA/**1** introduced in the sample. The difference between each pair of results is shown as an error bar.

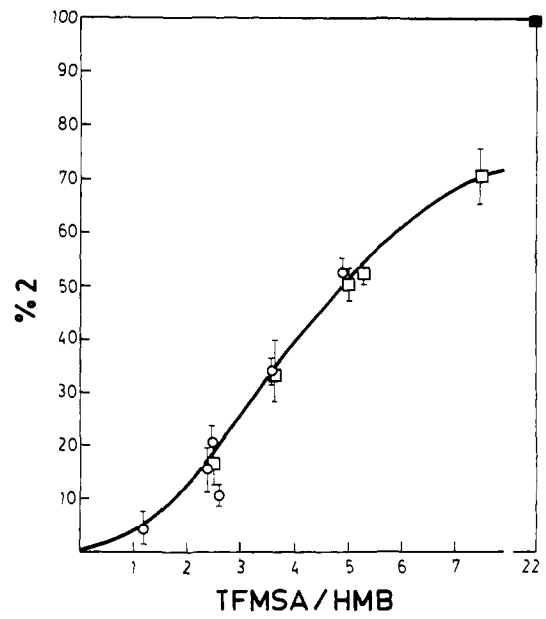

Figure 1. Degree of protonation of hexamethylbenzene (HMB, **1**) as a function of the excess of TFMSA: (□), in sulfur dioxide at 60 °C and (○), in sulfuryl chloride fluoride at 50 °C.

Inspection of Figure 1 shows no significant difference between the percentages of **2** in the two solvents, for the same ratio of acid to **1**. Because of the low degree of protonation, the point for 1.2 mol of TFMSA per mol of **1** carries a high level of uncertainty.

If hexamethylbenzene were protonated to an extent of 50–55% for a 3:1 excess of TFMSA, the protonating power of 30:1 $HF–TaF_5$ relative to TFMSA in SO_2 or SO_2FCl with chloroform as cosolvent would be about 6×10^{10}. Actually, from Figure 1 one finds that about 25% of **1** is converted to **2** at this ratio of TFMSA to 1, so it appears that R.P.A. for 3:1 $HF–TaF_5$ is more than 11 logarithmic units over that of TFMSA in the solvents studied.

The Hammett acidity measurements of Gillespie stopped at 0.6% TaF_5 in HF (167:1 $HF–TaF_5$, H_0 −18.85).[22] In the Hammett indicator method the acidity appears to level off at that amount of TaF_5. For aromatic carbon bases, we find that the effective acidity continues to increase significantly for further increases in the Lewis acid concentration. An increase in acidity with the amount of Lewis acid added and no leveling off were also observed in protonation of oxygen bases studied by various ^1H NMR techniques.[10,11]

We can combine our present results with the findings published earlier on the protonation of benzene[14] and rank the superacids according to their relative protonating ability toward aromatics, as follows:[35] $HF–TaF_5$ (30:1) is stronger than TFMSA by a factor of about 10^{11}. $HF–TaF_5$ (4:1) is stronger than 30:1 $HF–TaF_5$ by a factor of 1.5–2 (based on benzene protonation in the two media at $TaF_5/C_6H_6 = 1.7$). $HBr–AlBr_3$ (4:1) is stronger than 30:1 $HF–TaF_5$ by a factor of 10 (from benzene protonation at Lewis acid/C_6H_6 = 1.7). If the measured chemical shift difference found for benzene in 30:1 $HF–SbF_5$ (144.8) relative to 1:1 $HF–SbF_5$ (145.7) means incomplete benzene protonation in the former ($SbF_5/C_6H_6 = 2.85$), rather than a medium effect, the 30:1 system is somewhat weaker than 4:1 $HBr–AlBr_3$. Unfortunately, the two systems could not be compared more extensively, because benzene formed a polymer in the SbF_5-based system at lower excess of the fluoride.[14] Polymerization was probably initiated by one-electron transfers between the Lewis acid and unprotonated benzene. For systems more concentrated than 30:1, other workers

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(35) We emphasize that the comparison between TFMSA and the strong superacids is dependent upon the relative basicity of **1** and of benzene measured in ref 21 and considered reliable.

found that the acid strength of HF–SbF_5 solutions toward oxygen bases increases markedly with the increase in SbF_5 concentrations up to the 1:1 mixture.[9b,10b]

Experimental Section

General Methods. Sample preparation was done under dry nitrogen, in a drybox. A.R. grade chemicals were used as purchased. GLC analyses were performed on a 1.8 m × 3 mm o.d. column, with 10% methyl silicone SP2100 on Supelcoport. Carbon-13 NMR spectra were run at 22.65 MHz on a JEOL FX-90Q instrument. All glassware was dried in the oven at 120 °C and transferred while hot to the antechamber of the drybox, which was quickly evacuated.

Distribution Experiments. The hydrocarbons were dried on 4A molecular sieves in the drybox. A mixture of 9:1 (v:v) pentane and heptane (integration standard) was used as inert solvent. Benzene, toluene, and mixtures of the two were dissolved in the pentane–heptane mixture in concentrations of 0.4–0.6 M. TFMSA (1 mL) was introduced into a round-bottomed flask, which was then fitted with a stopcock, covered with a rubber septum, and cooled in a −90 °C bath. A volume of the hydrocarbon solution measured to give a TFMSA to aromatics ratio of 10–25 was added from a syringe through the rubber septum, after which the stopcock was closed, and the mixture was stirred at −20 °C for equilibration (30 min). Samples were taken with a syringe through the septum and added to pentane (1.0 mL) in a vial over a pellet of NaOH. The change in the heptane-to-aromatic ratio was determined by GLC at 45 °C. In a blank experiment the pentane–heptane solution was stirred with acid as described above, and then the acid layer was quenched in water and extracted with pentane. No heptane was found in the extract.

NMR Measurements. The samples were prepared as described previously.[14] The order of addition of reagents was aromatic, acid, and solvent (if any) mixed in the drybox at liquid nitrogen temperature, except for SO_2, which was passed through a tube of P_2O_5, liquified, measured, and added on the vacuum line. All tubes were sealed on the vacuum line and stored in dry ice until the spectra were recorded.

Metal-Stabilized Rare Tautomers of Nucleobases. 2.[1] 2-Oxo-4-hydroxo Form of Uracil: Crystal Structures and Solution Behavior of Two Platinum(II) Complexes Containing Iminol Tautomers of 1-Methyluracil†

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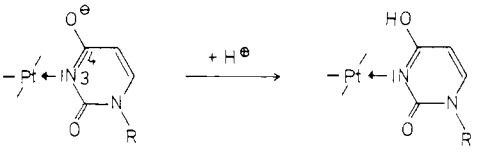
Abstract: A model for a metal-assisted tautomerization of the pyrimidine model nucleobase 1-methyluracil is presented which, by analogy, could account for mutagenic AT → GC or GC → AT transition in DNA. It involves initial metal binding to the N3 site of a thymine anion, followed by protonation of the exocyclic O4′ oxygen, and liberation of the rare 2-oxo-4-hydroxo tautomer which could then mispair with guanine. Three Pt(II) complexes, *cis*-$[(NH_3)_2Pt(1\text{-MeU})(1\text{-MeUH})]NO_3\cdot 2H_2O$ (**1**), *cis*-$[(NH_3)_2Pt(1\text{-MeUH})_2](NO_3)_2\cdot 3H_2O$ (**2**), and *cis*-$[(NH_3)_2Pt(1\text{-MeUH})_2][PtCl_6]\cdot 2H_2O$ (**3**) containing neutral 1-MeUH ligands in the 2-oxo-4-hydroxo tautomeric forms, have been prepared, and the crystal structures of **1** and **3** have been determined. Raman and ^1H NMR spectroscopies have been used to establish relevant acid–base equilibria and the protonation states of the uracil ligands in **1** and **3**. Both complexes crystallize in space group $P2_1/n$ with cell parameters a = 16.181 (3) Å (**1**) and 16.019 (7) Å (**3**), b = 8.340 (1) Å (**1**) and 12.415 (6) Å (**3**), c = 13.744 (2) Å (**1**) and 12.513 (6) Å (**3**), β = 97.61 (3)° (**1**) and 103.10 (6)° (**3**), V = 1838.4 Å^3 (**1**) and 2423.7 Å^3 (**3**), and Z = 4 (**1** and **3**). In **1**, the two 1-methyluracil ligands are oriented head-to-head, with the O4′ position of one ligand protonated and hydrogen bonded (2.52 Å) to O4′ of the anionic 1-MeU ligand. In **3**, the two rings are arranged head-to-tail. C4–O4′ distances in the 2-oxo-4-hydroxo tautomers [1.287 (7) Å, ring b of **1**; 1.302 (17) Å and 1.313 (19) Å in **3**] are only moderately longer than those in the free 2,4-dioxo tautomer yet clearly longer than the C2–O2′ bond lengths in **1** and **3**. On the basis of the X-ray results, a geometry of the hypothetical *free* 2-oxo-4-hydroxo tautomer of 1-MeUH is estimated. With respect to the normal 2,4-dioxo tautomer, the rare tautomer is expected to display major differences in internal ring angles C2 (larger by 3–4°), N3 (smaller by 8–9°), and C4 (larger by 7–8°).

The rare tautomeric forms of the naturally occurring nucleobases are of substantial interest with respect to the mechanism of spontaneous mutations, with respect to the fidelity of base pairing in nucleic acids and base mispairing, respectively,[3] and also for theoretical aspects concerning relative stabilities of tautomers.[4] While there is no doubt that under physiological conditions the normal tautomers (keto forms of pyrimidine bases, amino forms of purines) predominate to >99.99%, it is well-known that electronic excitation,[5] solvent properties,[6] and chemical modification of the nucleobase may change the tautomer equilibrium. For example, 1-methyluracil (1-MeUH), as demonstrated by spectroscopy, structural studies, and quantum-mechanical calculation,[7–9] exists almost exclusively in its diketo form I (Figure 1), exceeding the keto, iminol tautomer II by a factor of 4×10^3 to 4×10^4,[10,11] but the 5-bromo derivative contains form II in a 10-fold higher amount.[10]

Scheme I



As has previously been shown by us using spectroscopic methods, it is possible to stabilize a rare tautomer form of 1-

† Dedicated to Prof. Friedo Huber.

(1) For part 1, see Lippert, B.; Schöllhorn, H.; Thewalt, U. *J. Am. Chem. Soc.* **1986**, *108*, 6616.

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