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A ^{13}C NMR Study of the 1:1 Hydrogen Bond between Trifluoroacetic Acid and Aromatic Ethers in Deuteriochloroform

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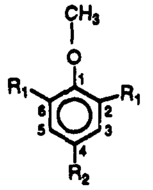
From the measured values of the equilibrium constants and ^{13}C NMR shift changes for 1:1 hydrogen bonding of trifluoroacetic acid with 2-alkyl- and 2,6-dialkylanisoles and 7-alkyl-2,3-dihydrobenzofurans in deuteriochloroform, conclusions are drawn concerning the stereochemistries of the hydrogen bonded complexes. The data indicate that hydrogen bonding of the planar 2-alkylanisoles may involve rotation of the methoxy group about the Ar–OCH_3 bond, the rotational angles ranging from 13° (anisole) to 43° (*tert*-butylanisole). The values of log K_1 correlate roughly with the torsional potential for methoxy group rotation in anisole, recently obtained by means of quantum mechanics, and with the angle-dependent electron densities at the methoxy oxygens that have been calculated for these *o*-alkylanisoles. The equilibrium constants for hydrogen bonding of the 2,6-dialkylanisoles also follow the predicted order of increasing methoxy oxygen electronic charge. The results for the rotationally rigid 2,3-dihydrobenzofurans are compatible with preferential involvement of the oxygen sp^2 lone electron pair in hydrogen bond formation.

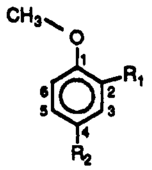
Much current research concerns the angular orientation of a proton donor about the acceptor oxygen in intermolecular X–H···O hydrogen bonds. It has now been established by means of rotational spectroscopy[1] that, in the hydrogen bonding of sp^3-hybridized O< acceptors, such as ether or water, in the gaseous state, there is some tendency for a proton donor to align with the axes conventionally associated with the oxygen lone pair orbitals. This angular bias is evidently quite weak because it is readily masked in nongaseous phases by medium effects, such as the lattice forces within solids. Thus searches of the crystallographic literature for the stereochemistries of intermolecular O–H···O< units reveal no preference of proton donors for oxygen tetrahedral lone pair directions, although most of the hydrogen bonds surveyed do tend to lie within the plane of the two oxygen lone pair orbitals.[2] These observations are consistent with molecular orbital calculations[3] which predict a rather flat potential energy surface for the motion of the proton donor within the lone pair plane.

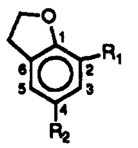
In contrast, hydrogen bonding of sp^2-hybridized oxygens seems to be more stereospecific since a tendency for the hydrogen bonds to carbonyl groups to lie near the oxygen lone pair axes has been noted for both solid[2,4] and gaseous[1] complexes. More importantly, this apparent preference by proton donors for the oxygen sp^2 lone pair implies that the nonbonding rather than the π-bonded electron pair is the better H-bond acceptor.[1a]

In light of these results a study of the hydrogen bonding of anisole should be of special interest. The sp^2-hybridized methoxy oxygen of this molecule is carbonyl-like to the extent that its p electrons are π-bonded through methoxy–aryl resonance. However, unlike its carbonyl counterpart, the oxygen p lone pair is still largely nonbonding. Moreover, by lacking s character, it should be an intrinsically better electron donor in hydrogen bond formation than the competing nonbonded sp^2 lone pair.[5,6] Thus one cannot predict, as one can in the case of the carbonyl group,[1a] which of the nonequivalent oxygen electron pairs might be favored in the hydrogen-bonding process.

This study was undertaken to see whether ^{13}C NMR spectroscopy could reveal a preference for one or the other of these pairs in the hydrogen bonding of anisole. To this end intermolecular hydrogen bonding between trifluoroacetic acid (hereafter TFA) and anisoles **1**, **2**, and **3**[7] in deuteriochloroform was examined in terms of the equilibrium constants and changes in ^{13}C chemical shifts of the bases that are associated with formation of the 1:1 complexes.







1a: $R_1 = R_2 = H$
b: $R_1 = CH_3$; $R_2 = H$
b′: $R_1 = R_2 = CH_3$
c: $R_1 = C_2H_5$; $R_2 = H$
d: $R_1 = i\text{-}C_3H_7$; $R_2 = H$
e: $R_1 = t\text{-}C_4H_9$; $R_2 = H$

2a: $R_1 = R_2 = H$
a′: $R_1 = H$; $R_2 = CH_3$
a″: $R_1 = H$; $R_2 = t\text{-}C_4H_9$
b: $R_1 = CH_3$; $R_2 = H$
b′: $R_1 = R_2 = CH_3$
c: $R_1 = C_2H_5$; $R_2 = H$
d: $R_1 = i\text{-}C_3H_7$; $R_2 = H$
e: $R_1 = t\text{-}C_4H_9$; $R_2 = H$

3a: $R_1 = R_2 = H$
b: $R_1 = CH_3$; $R_2 = H$
b′: $R_1 = R_2 = CH_3$
c: $R_1 = C_2H_5$; $R_2 = H$
d: $R_1 = i\text{-}C_3H_7$; $R_2 = H$
e: $R_1 = t\text{-}C_4H_9$; $R_2 = H$

Because **1**, **2**, and **3** represent diverse environments at the hydrogen bonding site, it was hoped that, at the same time, this study might give insight into the stereoelectronic factors that are of importance in the formation of intermolecular hydrogen bonds between proton donors and aromatic ether oxygens.

Although an earlier paper[8] reported on hydrogen bonding of TFA with **2a**, **2b**, and **2c**, the changes in the ^{13}C NMR shifts cited there were incorrect, having been adjusted for solvent effects by using an erroneous literature value[9] for the dielectric constant of TFA. These shifts have now been remeasured and corrected for medium effects

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(1) (a) Legon, A. C.; Millen, D. J. *Acc. Chem. Res.* **1987**, *20*, 39 and references therein. (b) Szczesniak, M. M.; Scheiner, S.; Bouteiller, Y. *J. Chem. Phys.* **1984**, *81*, 5024.

(2) (a) Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320 and references therein. (b) Vedani, A.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 7653. (c) Murray-Rust, C. P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018.

(3) Schuster, P. In *The Hydrogen Bond, Recent Developments in Theory and Experiment*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; p 130.

(4) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761.

(5) Sherry, D., in ref 3, p 1199.

(6) Epiotis, N. D.; Cherry, W. R.; Shark, S.; Yates, R. L.; Bernardi, F. B. In *Structural Theory of Organic Chemistry* (*Top. Curr. Chem.* **1977**, *70*). Springer-Verlag: New York, 1977; p 156.

(7) The conventional numbering of ring carbons has been changed to correspond to the numbering of structurally related anisoles **1** and **2**.

(8) Schuster, I. I. *J. Org. Chem.* **1985**, *50*, 1656.

(9) Simons, J. H.; Lorentzen, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1426.

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Table I. Association Constants[a] and ^{13}C NMR Shift Changes[b] for 1:1 Hydrogen Bonding of Anisoles 1, 2, and 2,3-Dihydrobenzofurans 3 with Trifluoroacetic Acid in Deuteriochloroform

compd	K_1	ϕ,[c] deg	ΔC_4[d]	$\Delta^\circ C_4$[e]	$\Delta^\circ{}_1C_1$	$\Delta^\circ{}_1C_2$	$\Delta^\circ{}_1C_6$	$\Delta^\circ{}_1OCH_3$[f]
1b	5.024		2.263	2.104	−3.555	−0.142	−0.142	0.972
1c	7.563		2.309	2.149	−3.900	−0.263	−0.263	0.986
1d	11.900		2.423	2.416	−3.966	0.131	0.131	0.685
1e	2.383		2.047	2.041	−3.097	0.037	0.037	0.620
9-OCH_3[g]	2.554		2.350[h]	2.148[i]	−3.758[j]	−0.307[k]	−0.307[k]	0.514
2a	2.324	13.2	2.763	2.763	−2.912	0.936	0.936	1.752
2a′	3.843[l]	14.3	3.892	3.020[m]	−3.049	1.273	1.273	1.867
2a″	2.549[l]		3.845	2.841[n]	−3.298	1.224	1.224	1.978
2b′	1.347	37.9	5.315	4.364[o]	−2.562	1.383	6.394	4.394
2b	1.203	35.2	3.848	3.768	−2.617	1.141	5.837	4.091
2c	1.007	36.7	3.910	3.830	−2.509	1.384	6.258	4.665
2d	0.681	40.2	4.251	4.242	−1.946	2.734	6.949	4.837
2e	0.590	42.7	3.182	3.180	0.015	3.115	6.387	4.163
3a	(250 K)[p] 8.247		2.572	2.492	−4.031	0.551	−0.806	0.543
	(263 K)[p] 5.769		2.607	2.527	−3.944	0.596	−0.710	0.568
	(280 K)[p] 4.659		2.567	2.487	−4.023	0.427	−0.828	0.624
	(301 K)[p] 3.279		2.566	2.486	−3.913	0.491	−0.793	0.674
3b	1.837		2.587	2.427	−3.373	0.565	−0.127	0.526
3b′	2.505		3.642	2.610	−2.946	0.109[q]	−0.666[q]	0.774[q]
3d	1.619		2.674	2.858	−3.632	0.692	−0.145	0.723
3e	1.352		1.592	1.499	−1.514	1.089	0.979	0.885

[a] In L/mol at 301 K unless noted otherwise. [b] In parts per million. Positive value signify downfield shift changes. [c] The angle between the Ar–O–CH_3 and aromatic planes in the 1:1 complex with TFA. [d] The shift of C4 of the anisole in neat TFA minus the shift of anisole in neat $CDCl_3$. [e] The experimental shift difference corrected for the electronic effects of the alkyl group, in TFA and in $CDCl_3$ (see Table V of supplementary material). [f] Or $\Delta^\circ{}_1(OCH_2)$. [g] 9-Methoxyanthracene. [h] The experimental change in shift carbon 10. [i] $\Delta^\circ{}_1C_{10}$. [j] $\Delta^\circ{}_1C_9$. [k] $\Delta^\circ{}_1C_{11}$, C_{12}. [l] The monitoring resonance was that of C2,6. [m] The value of $\Delta^\circ{}_1C_4$ is 3.355 ppm. [n] The value of $\Delta^\circ{}_1C_4$ is 3.384 ppm. [o] The value of $\Delta^\circ{}_1C_4$ is 4.114 ppm. [p] The temperature at which the titration was carried out. [q] The shift changes are the experimental, SCS-corrected values. The SCS of the ethyl group was used for the electronic effect of CH_2CH_2O.

using the proper solvent parameter.[10]

Results

On titrating anisoles **1**, **2**, and **3** with TFA in deuteriochloroform, large displacements of their ^{13}C NMR signals are observed due to the formation of the 1:1 and 1:*n* hydrogen-bonded complexes, B·A and B·A_n (eq 1). B, A, and

$$B + A \underset{}{\overset{K_1}{\rightleftharpoons}} B{\cdot}A \qquad (1a)$$

$$B + A_n \underset{}{\overset{K_n}{\rightleftharpoons}} B{\cdot}A_n \qquad (1b)$$

A_n of eq 1 represent, respectively, molecules of "free" base weakly hydrogen bonded with $CDCl_3$, TFA monomer, and acid polymer. By tracking the chemical shift of one of the ^{13}C resonances of the anisole in the course of a titration, the progressively changing mole fraction, f, of the anisole in complexed forms B·A plus B·A_n is obtained by means of eq 2. Here $\delta^\circ{}_B$ and δ, respectively, are the chemical

$$f = (\delta - \delta^\circ{}_B)/\Delta C = \Delta\delta/\Delta C \qquad (2)$$

shifts of the monitoring resonance of the anisole in neat deuteriochloroform and in deuteriochloroform plus TFA, and ΔC is the observed change in the chemical shift of that resonance produced by a change of solvent from neat $CDCl_3$ to neat TFA at the same base concentration. The ^{13}C resonance chosen to monitor the extent of acid–base complexing during each titration was, whenever possible, that of a CH carbon para to the methoxy group undergoing hydrogen-bond formation. Unlike the resonances of quaternary carbons and of carbons near the hydrogen bonding site, such a resonance, though sensitive to the formation of the hydrogen bond, is not otherwise affected by changes in the medium or in the degree of aggregation of TFA in the hydrogen bonded complex.[8]

From the change in f as a function of the changing stoichiometric acid/base ratio during the titration, values of the equilibrium constants K_1 and K_n (eq 1) were obtained as previously described,[11] as well as values of f_1, the progressively changing mole fraction of base, 1:1 hydrogen bonded with TFA as B·A. Equation 3 relates the change in the experimental shift of the ith carbon of base, $\Delta\delta_i$, to f_1 and f in the course of the titration. Multiple regressional

$$\Delta\delta_i/f = f_1(\Delta^\circ{}_1C_i - \Delta^\circ{}_nC_i)/f + \beta\Delta S/f + \Delta^\circ{}_nC_i \qquad (3)$$

analysis of eq 3 provides values of $\Delta^\circ{}_1C_i$ and $\Delta^\circ{}_nC_i$, the ^{13}C chemical shifts of the base in the hydrogen bonded complexes B·A and B·A_n, respectively, extrapolated to neat deuteriochloroform and relative to the shift of the free base in that same solvent. ΔS in eq 3 reflects the change in the reaction field of the medium as the titration progresses. The value of S used for each solution was obtained from the weighted average of the dielectric constants of the solution components as previously described[8] ($S = (\epsilon - 1)/(2\epsilon + 1)$).

Table I summarizes the values obtained for K_1 and for $\Delta^\circ{}_1C_i$[12] of selected carbon resonances in the hydrogen bonding of anisoles **1**, **2**, and **3** with TFA. The table also lists the experimental shift changes of the para carbon resonances of the bases (usually ΔC of eq 2), together with $\Delta^\circ C_4$, the shift changes corrected for the electronic effects of the alkyl substituents.[13]

Discussion

The largest values of K_1 measured here are those associated with 1:1 hydrogen bonding of TFA with the 2,6-dialkylanisoles **1** (see Table I). In these crowded molecules nonbonded interactions between the OCH_3 group and the two proximate ortho substituents have forced the methoxyl methyl from its usual location within the aromatic plane,

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(10) Harris, F. E.; O'Konski, C. T. *J. Am. Chem. Soc.* **1954**, *76*, 4317.

(11) Davis, P.; Schuster, I. I. *J. Soln. Chem.* **1984**, *13*, 167.

(12) Values of K_n and of $\Delta_1{}^\circ C_i$ are not included here because repetitive titrations of randomly selected anisoles with TFA showed these parameters to be excessively sensitive to experimental error.

(13) The substituent electronic effect (SCS) of an alkyl group at C_i of the ether is the shift of C_i in the corresponding alkylbenzene relative to the shift of benzene in the same solvent. These SCS are summarized in Table V of supplementary material.

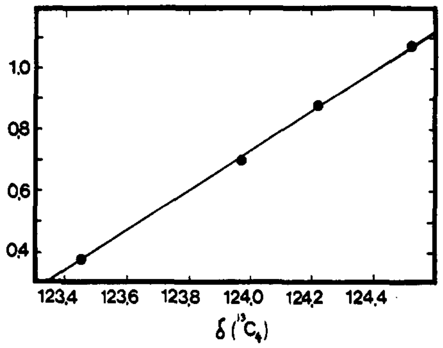

Figure 1. log K_1 for 1:1 hydrogen bonding of trifluoroacetic acid with anisoles **1** as function of δC4, the ^{13}C chemical shift of the para carbon of **1** dissolved in deuteriochloroform, in ppm and corrected for the electronic effects[13] of the two *o*-alkyl substituents; $r = 0.9998$.

as in the monosubstituted ethers **2**, into a plane that is approximately perpendicular to the benzene ring.[14,15] This 90° rotation of the O–CH_3 bond about the Ar–OCH_3 axis, **2** → **1**, causes an approximately 40% reduction in methoxy–aryl resonance.[14] The accompanying increase in electronic charge at the acceptor oxygen is expected to favor hydrogen-bond formation, and this is confirmed by the values of the equilibrium constants for hydrogen bonding of **1** being larger than those of planar anisoles **2**.

Unexpectedly, however, K_1 is not the same for all **1** though these anisoles have identical out-of-plane methoxy group conformations. This result may be attributed to differences in repulsion between the lone pair electrons of the methoxy oxygens and bonding electrons of the proximate ortho substituents. We have recently demonstrated[14] that such nonbonded interactions in **1** increase the mesomeric release of electronic charge from the methoxy oxygen to the benzene ring. The extent of this resonance-promoting effect of the *o*-alkyls, R, was shown to increase in the order: R = isopropyl < ethyl < methyl ≪ *tert*-butyl, as gauged by the increasingly upfield para carbon shifts of the anisoles dissolved in deuteriochloroform.[16] The values of K_1 for hydrogen bonding of anisoles **1** with TFA are now found to *decrease* in that same order, following the progressive, sterically induced depletion of electron density at the methoxy oxygens of the uncomplexed ethers. The trend is quite quantitative, as illustrated in Figure 1 by the excellent fit of data in the correlation between log K_1 and the SCS-corrected[13] para carbon shifts of the free anisoles **1** in deuteriochloroform (correlation coefficient, 0.9998).

Because of steric constraints, most configurations of the 1:1 complex between TFA and **1** are expected to have the hydrogen bond oriented near the intersection of the C–O–CH_3 plane and that associated with the two oxygen sp^3 lone pairs. If, as is probable, hydrogen bonding occurs without altering the conformation of the methoxy group, then the size of the time-averaged TFA-induced shift changes of the aromatic carbons of **1** will be solely a function of how large a change is produced in methoxy–aryl resonance and in the electrostatic field at OCH_3 by hydrogen-bond formation. This, in turn, will depend on the strength of the interaction. The largest of the ^{13}C chemical shift changes of **1**, those of the ipso and para carbons, correlate with log K_1:[17]

$$\log K_1 = 1.8643\Delta C_4 - 3.4562 \quad (r = 0.990) \qquad (4a)$$

$$\log K_1 = -0.7287\Delta^{\circ}{}_1C_1 - 2.8868 \quad (r = 0.979) \qquad (4b)$$

Thus it is the charge density at the acceptor methoxy oxygen, rather than steric hindrance to donor–acceptor docking, which determines the strength of the 1:1 hydrogen bond between TFA and these crowded anisoles.

Unlike **1**, the monosubstituted anisoles **2** and 2,3-dihydrobenzofurans **3**[7] have ArOCH moieties which are approximately coplanar with the aromatic rings.[14,15,18] Moreover, their *o*-alkyl substituent seems to have no resonance-perturbing effect on the proximate ether oxygen, as indicated by uniform values of the para carbon shifts of these ethers dissolved in deuteriochloroform (**2a–e**, 120.516 ± 0.070 ppm;[19] **3a–e**, 120.367 ± 0.043 ppm). The charge densities and, hence, the electron-donor strengths of the acceptor oxygens are, therefore, identical within each series and also nearly the same for **2** and **3**.

Because the orientations of the *tert*-butyl groups in crystalline 4-CO_2H-substituted **2e** and **1e**,[14] and in a structure related to **3e**,[18] are all approximately the same, it is reasonable to suppose that each of the other *o*-alkyls of correspondingly substituted **2** and **3** also have like conformations and are oriented on average as in the *p*-anisic acids corresponding to anisoles **1**. In these acids the methyl, isopropyl, and *tert*-butyl substituents ortho to the OCH_3 group each have two of the three nonaromatic bonds to the α-carbon staggered with respect to the benzene ring, with the third in the aromatic plane. In the case of methyl and *tert*-butyl, this in-plane bond (CH and C–CH_3, respectively) is directed away from the OCH_3 group. When R is isopropyl, it is the methine CH bond which lies in the aromatic plane, as is usual for this substituent in aromatic systems,[20] and it projects toward OCH_3.[21]

The C2–C1–O angle of **3** is about 125° due to strain of the five-membered ring.[18] That same angle in **2** is compressed to an average 115°[15] (117.7° when R = *tert*-butyl[14]) because of interference between H6 and the methoxyl CH_3. Thus **2** and **3** differ significantly only in that the acceptor oxygen of **3** is more accessible than that of **2** in the vicinity of its sp^2 lone pair axis, and that in **2** the ArOCH moiety possesses rotational mobility.

Despite the many structural similarities of **2** and **3**, the changes in ^{13}C NMR shifts and values of K_1 produced by 1:1 complexing of each with TFA are markedly different (see Table I). Thus the values of K_1 for hydrogen bonding of **3** are consistently larger than those for hydrogen

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(14) Schuster, I. I.; Parvez, M.; Freyer, A. J. *J. Org. Chem.* **1988**, *53*, 5819.

(15) (a) Anderson, G. M. III; Kollman, P. A.; Domelsmith, L. N.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2344. (b) Breen, P. J.; Berstein, E. R.; Secor, H. V.; Seeman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 1958. (c) Hummel, W.; Huml, K.; Bürgi, H.-B. *Helv. Chim. Acta* **1988**, *71*, 1291.

(16) This order is reproduced by PRDDO-MO calculations of the oxygen electronic charge of **2** in which the O–CH_3 bond is rotated about Ar–OCH_3 axis by 110–130°. See ref 38.

(17) 9-Methoxyanthracene, with its in-plane C1–H and C8–H bonds projecting toward the methoxy group, structurally resembles **1d**. It is then not surprising that the shift changes of its ^{13}C resonances for 1:1 hydrogen bonding with TFA are approximately like those of **1c** and **1d**. The value of K_1 for complexing is, however, smaller than that for hydrogen bonding of these anisoles.

(18) Wong, R. Y.; Jurd, L. *Aust. J. Chem.* **1984**, *37*, 2593.

(19) The ^{17}O chemical shifts of **2a**, **2b**, and **2e**, 48.0, 46.2, and 48.8 ppm, respectively, are also nearly constant. The small difference of ca. 2 ppm corresponds to a difference in electronic charge at the methoxy oxygen of less than 0.001e. Wysocki, M. A.; Jardon, P. W.; Mains, G. J.; Eisenbraun, E. J. *Magn. Reson. Chem.* **1987**, *25*, 231.

(20) (a) Arnett, E. M.; Bollinger, J. M. *J. Am. Chem. Soc.* **1964**, *86*, 4729. (b) Hopff, H. *Chimia* **1963**, *18*, 140. (c) Hopff, H.; Gati, A. *Helv. Chim. Acta* **1965**, *48*, 509.

(21) Theoretical and experimental data on the ethyl substituent in aromatic systems show a preference for the perpendicular over the planar conformation by 2.2 and 1.3 kcal/mol (Hehre, W. J.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 1496. Bruckwedde, F. G.; Moskow, M.; Scott, R. B. *J. Chem. Phys.* **1945**, *13*, 547). In either conformation the spatial distribution of methylene bonds will be quite similar to that of the CH bonds of the methyl substituent in the vicinity of the hydrogen bonding methoxy oxygen.

Table II. ^{13}C NMR Shift Changes[a,b] of the Alkyl Carbons for Hydrogen Bonding of Trifluoroacetic Acid and 2,2,2-Trifluroethanol with 1, 2, 3, and 4′

	CH_3		C_2H_5		*i*-C_3H_7		*t*-C_4H_9	
compd	$\Delta\delta CH_3$	$\Delta\delta CH_3$[c,d,e]	$\Delta\delta CH_2$	$\Delta\delta CH_3$	$\Delta\delta CH$	$\Delta\delta CH_3$	$\Delta\delta C$	$\Delta\delta CH_3$
TFA								
1	0.077	0.159 (−0.038)	−0.261	0.108	0.055	0.188	0.309	0.621
2	−0.106	−0.130 (−0.379)	−0.518	0.427	−0.481	0.751	0.042	0.699
3	0.283	0.353 (0.233)			−0.998	0.444	0.093	0.546
4′		0.291 (0.104)						
TFE								
1	0.050	0.098 (−0.039)	−0.264	−0.115	−0.149	0.157	–[f]	
2	0.036	−0.004 (−0.069)	−0.060	0.053	−0.173	0.186	0.079	0.218
3	0.155	0.200 (0.100)			−0.411	0.153	0.084	0.213
4′		0.251 (0.115)						

[a] In parts per million. Positive values denote deshielding on hydrogen bonding with TFA and TFE. [b] Experimental shift changes, corrected for medium effects (see Table V). [c] The *o*-methyl substituent of *o,p*-polymethyl ethers **1b′**, **2b′**, **3b′**, and **4b′**. [d] The TFA-induced shift changes of the *p*-CH_3 substituent (corrected for medium effects) are (in ppm) 0.197 (**1b′**), 0.132 (**2a′**), 0.249 (**2b′**), 0.120 (**3b′**), 0.145 (**4a′**), and 0.187 (**4b′**). The corresponding TFE-induced shift changes are 0.137 (**1b′**), 0.041 (**2a′**), 0.065 (**2b′**), 0.100 (**3b′**), 0.070 (**4a′**), and 0.136 (*4b′*). [e] The *o*-CH_3 shift changes, corrected for medium effects and for the change in the electronic effect of the benzene ring (substraction of the *p*-CH_3 shift change), are shown in parentheses. [f] The anisole was not soluble in TFA.

bonding of correspondingly substituted **2**. Anisoles **2**, on the other hand, experience considerably greater deshielding of most of their carbon resonances, some of the TFA-induced shift changes of **2** and **3** differing by as much as 6 ppm! Whereas hydrogen bonding produces nearly identical downfield shifts of the para carbon resonances of dihydrobenzofuran **3** having H, CH_3, and *i*-C_3H_7 as the ortho substituent (2.609 ± 0.060 ppm), the para carbon shift changes of correspondingly substituted **2** range from 2.76 to 4.25 ppm.

These differences in the consequences of hydrogen bonding anisoles **2** and cyclic ethers **3** suggest that in the absence of significant steric effects the distribution of the 1:1 complexes between in-plane ArOCH moieties and TFA, which are configurationally averaged on the NMR time scale, may be weighted in favor of those structures in which the proton donor lies in the vicinity of the oxygen sp^2 lone pair. Were TFA to prefer the region of the ether p lone pair and its surrounding space then the magnitudes of K_1 and the size of the time-averaged para carbon shift changes would be about the same for hydrogen bonding of identically substituted **2** and **3**, since the stereochemical features of these ethers in the region above the aromatic plane are nearly the same. Hydrogen bonding of unsubstituted cyclic ether **3a** and *o*-isopropyl-substituted **3d** would then also give like values of K_1 because the methine CH bond of **3d**, projecting toward OCH_2 in the molecular plane, should hinder as little the approach of a proton donor from above that plane as does the in-plane C2–H bond of unsubstituted **3a**. In fact, though, K_1 for hydrogen bonding of **3a** is about 2.4 times the value for **3d**. Indeed, the equilibrium constants for 1:1 hydrogen bonding of dihydrobenzofurans **3**, decreasing in the sequence R = H > methyl > isopropyl > *tert*-butyl, follow an order which could reasonably be attributed to substantial contributions from hydrogen bonded structures which are progressively destabilized through internal repulsions between the ortho substituent and a molecule of TFA, oriented near the oxygen sp^2 lone pair axis.

It has recently been shown that the magnitude and direction of alkyl carbon shift changes produced by dipolar electric fields depend on the proximity of the electrical dipole and on its orientation with respect to the direction of the bonds involving the alkyl carbon atom.[22-24] Significant differences are observed between the TFA-induced *o*-alkyl shift changes of ethers **1** and **3** (and **2**) although the orientation of each substituent relative to the benzene plane and donor oxygen is nearly identical in these molecules. So, for example, the resonance of the isopropyl methine carbon is shifted 0.998 ppm *upfield* in the hydrogen bonding of **3d** but *downfield* by 0.055 ppm for hydrogen bonding of **1d**. The corresponding shift changes of the isopropyl methyls are 0.444 and 0.188 ppm downfield. Differences of similar magnitude are noted for the shift changes of the remaining *o*-alkyls of **1** and **3** (see Table II). These results suggest that the average position of the OH dipole of TFA, relative to that of the *o*-alkyl substituent, must be different in hydrogen bonded **1** and **3**. Since in complexes of **1** the proton donor must, on steric grounds, lie above the oxygen and aromatic plane, the sizable differences between the alkyl shift changes of **1** and **3** imply that TFA in hydrogen bonded **3** may lie in an area different from that of the oxygen p lone pair in a significant number of configurations.[25] These results then also are compatible with a tendency on the part of the proton donor to seek the oxygen sp^2 lone pair in the hydrogen bonding of the planar cyclic ethers **3**.

Values of ΔH and ΔS of −10.9 kJ/mol and −26.4 J/mol deg, respectively, for hydrogen bonding of **3a** with TFA, were obtained from the correlation of log K_1 with $1/T$ measured at four temperatures (correlation coefficient, 0.993, see Table I). These represent the thermochemical changes associated with transforming **3a**, weakly hydrogen bonded with $CDCl_3$, into its 1:1 complex with TFA in deuteriochloroform. The change in enthalpy is close to the experimental (13.8 kJ/mol)[26] and calculated (9.12 kJ/mol)[27] values for the energy of the intramolecular hydrogen bond in 2-methoxybenzoic acid, which is also believed to

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(22) (a) Schneider, H.-J.; Buchheit, U.; Becker, N.; Schmidt, G.; Siehl, U. *J. Am. Chem. Soc.* **1985**, *107*, 7027. (b) Schneider, H.-J.; Freitag, W. *J. Am. Chem. Soc.* **1977**, *99*, 8363.

(23) Seidman, K.; Maciel, G. E. *J. Am. Chem. Soc.* **1977**, *99*, 3254.

(24) Batchelor, J. G.; Feeney, J.; Roberts, G. C. K. *J. Magn. Reson.* **1975**, *20*, 19.

(25) The differences in the TFA-induced *o*-alkyl carbon shift changes of **1** and **3** cannot simply be attributed to the different ArOCH conformations and methoxy oxygen hybridizations of **1** and **3** giving rise to different changes in the through-bond electronic effect of the benzene ring on the alkyl resonances. The magnitude of such differences in π electronic effects of hydrogen bond formation on R amount to less than 0.1 ppm, as gauged by the shift changes of the *p*-CH_3 resonances of **1b′** and **3b′** (see Table II, footnote d):

$$\Delta p\text{-}CH_3(\mathbf{1b'}) - \Delta p\text{-}CH_3(\mathbf{3b'}) = 0.197 - 0.120 = 0.077 \text{ ppm}$$

(26) Davies, M.; Griffiths, D. M. L. *J. Chem. Soc.* **1955**, 132.

(27) Jaccard, G.; Carrupt, P.-A.; Lauterwein, J. *Magn. Reson. Chem.* **1988**, *26*, 239.

involve the in-plane sp^2 lone pair of the methoxy oxygen acceptor.

Hydrogen bonding by TFA not only deshields the ^{13}C resonances of anisoles **2** more than it does those of **3**, but this deshielding is greatest for hydrogen bonding of those anisoles **2** in which there is an alkyl substituent at C2. For example, $\Delta°C_4$ is up to 1.5 ppm larger for hydrogen bonding of **2b–e** than for anisole itself. The average of the downfield displacements of the two ortho carbon resonances, $\Delta°_1C_2$ and $\Delta°_1C_6$, is 3.5–4.8 ppm for hydrogen bonding of **2b–e** compared to only 0.9–1.3 ppm for hydrogen bonding of ortho-unsubstituted **2a**, **2a′**, and **2a″**. The shift changes of the methoxy carbons of ortho-substituted **2** exceed those of the unsubstituted ethers by 2–3 ppm. On the other hand, the TFA-induced *upfield* movement of the *ipso* carbon resonance is smaller for **2b–e** and **2b′** than for **2a**, **2a′**, and **2a″** by 0.4–2.6 ppm. These are surprising results when one considers that the methoxy group conformations and electronic charges at the donor methoxy oxygens are identical for all **2** in neutral solvents. Noteworthy also is the sizable *difference* in the magnitudes of the downfield shift changes of substituted **2b–e** and **2b′** ($\Delta°_1C_2$ = 1–3 ppm; $\Delta°_1C_6$ = 6–7 ppm).

Such diverse chemical shift behavior in the hydrogen bonding of the ortho-substituted and -unsubstituted planar anisoles **2** could be due to a difference in the configurationally averaged position of the proton donor, nearer the in-plane methoxy oxygen sp^2 lone pair orbital in hydrogen bonded **2a**, **2a′**, and **2a″** but closer to the more accessible p-type orbital in TFA complexes of the sterically more conjested *o*-alkyl ethers **2b–e** and **2b′**. This interpretation is based on the supposition that for configurations in which the proton donor lies progressively nearer the oxygen p-type orbital, there may be increasingly greater depletion of π electronic charge at the aromatic conjugated carbons C2, C4, and C6, and hence more downfield movements of their resonances, because of progressively greater involvement of the mesomerically active oxygen lone electron pair in the hydrogen bonding process. Attractive nonbonded interactions could, moreover, account for the large difference between the downfield movements of the ortho carbon resonances that are observed in the hydrogen bonding of ortho-substituted **2**. Following the reasoning of Epiotis,[28] the p orbitals of C1 and C6, the methoxy oxygen p lone pair orbital, and an orbital of π symmetry of the methoxyl methyl group proximate to C6 in planar ethers **2** constitute a cyclic Huckel array of overlapping orbitals which is aromatic ($4n + 2$ electrons), and hence stabilizing, when C1–C6 is doubly bonded. Therefore, in **2** the C1–C6 bond order will exceed that of C1–C2.[29] Carbon 6 will be more strongly conjugated than C2 with the OCH_3 group and experience greater deshielding of its resonance as negative charge becomes localized at the ether oxygen, or is transferred to TFA, on hydrogen-bond formation.

However, and equally likely explanation is that steric hindrance by the ortho substituents of **2** causes the in-plane methoxy group to rotate about the Ar–OCH_3 bond in the process of hydrogen bonding. Such a rotation, by itself, will reduce the π electronic charge at the conjugated aromatic carbons, producing downfield shifts of their resonances, because it results in less favorable orbital overlap between OCH_3 and the aromatic ring. Subsequent hydrogen bonding of the rotated methoxy group by TFA then produces further shift changes, additionally downfield in the case of the para carbons for which the effects of reduced methoxy–aryl resonance and changing electric fields at OCH_3 due to hydrogen-bond formation are both deshielding, and upfield for C1 because the field effect predominates and is shielding at the *ipso* carbon.[24]

Repulsions[30] between the C6–H bonding electrons and those of the proximate in-plane methoxyl CH_3 of the planar, uncomplexed anisoles **2** in neutral solvents give rise to exceptional shielding[31] of the C6 and OCH_3 carbon resonances (δ steric effect).[32] This effect vanishes on hydrogen bonding of ortho-substituted **2** if TFA causes the methoxyl methyl to rotate out from the molecular plane. The additional downfield movements of the C6 and OCH_3 carbon resonances which result then account for the observed C2/C6 shift change differential and for the larger downfield shifts of the OCH_3 resonances that are observed in the hydrogen bonding of the ortho-substituted anisoles of series **2**.[33]

Table I gives estimates of θ, the angle through which the OCH_3 group is then rotated away from coplanarity with the aromatic ring in the hydrogen bonded complexes of **2a–e** with TFA. These values were obtained by interpolation (eq 5)[34] using the para carbon shifts of identically ortho-substituted anisoles **1**,[35] **2**, and **3**,[36,37] measured in

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[28] Bernardi, F.; Epiotis, N. D.; Yates, R. L.; Schlegel, H. B. *J. Am. Chem. Soc.* **1985**, *107*, 818.

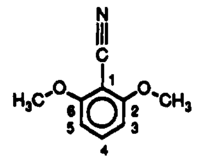
[29] L. I. Kruse has used this argument to rationalize the magnitudes of conformational preferences in a series of aromatic ethers. Kruse, L. I.; DeBrosse, C. W.; Kruse, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 5435.

[30] For a different interpretation of ortho carbon shifts of aromatic ethers, based on electric field effects of the ether oxygen electric dipole, see: Clayden, N. J. *Magn. Reson. Chem.* **1989**, *27*, 692.

[31] This shielding effect on the C6 resonance has also been noted in solid state NMR measurements. Saito, H.; Yokoi, M.; Aida, M.; Kodama, M.; Oda, T.; Sato, Y. *Magn. Reson. Chem.* **1988**, *26*, 155.

[32] Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

[33] The data for planar 2,6-dimethoxybenzonitrile with a stronger electron donor than OCH_3 ortho to the two methoxy groups (K_1 = 3.19 L/mol, C_6H_5CN, ref 8) show that neither rotation nor hydrogen bonding of the methoxy groups is occurring in the titration of this molecule with TFA. Thus the downfield shift change of C3 and C5, ortho and para to OCH_3, is only 0.10 ppm compared to 6–7 ppm (ortho) and 3–4 ppm (para) for hydrogen bonding of **2**. The shift changes of the methoxy carbons of the nitrile are also 5–10 times smaller than those of **2** and **3**. That CN rather than OCH_3 is being hydrogen bonded here is indicated by the shift changes of C1 and C2,6, 2.59 ppm *upfield* and 0.77 ppm *downfield*, respectively. (It is the aromatic, quarternary carbon holding the group undergoing hydrogen bond formation which experiences the largest upfield change of shift (refs 8 and 24)). Although the CN substituent will hinder the approach of TFA to the methoxy oxygens along the sp^2 lone pair axis, no such hindrance would be involved in the hydrogen bonding of the oxygen p lone pair. That hydrogen bonding of OCH_3 is not taking place is thus further proof that the oxygen p lone pair is not a particularly strong electron donor. The methoxy groups nonetheless participate in the hydrogen-bonding process through electron donation to CN via methoxy–aryl conjugation, as indicated by the value of K_1 for the dimethoxynitrile, which is more than twice that for hydrogen bonding of benzonitrile itself.



$\Delta°_1 C_1$	−2.592	$\Delta°_1 C_4$	2.140
$\Delta°_1 C_{2,6}$	0.771	$\Delta°_1 OCH_3$	0.334
$\Delta°_1 C_{3,5}$	0.101	$\Delta°_1 CN$	−0.833

K_1 = 6.72 L/mol

[34] The values of θ in hydrogen-bonded *p*-CH_3-substituted **2a′** and **2b′** were obtained by comparing the hydrogen-bonding shift changes of the *i*th carbon of **2a′** and **2b′** with those of correspondingly substituted **2a** and **2b**. Calculations of θ using C_i = C2, C4, C6, and OCH_3 gave similar values which were averaged. It is this average value of θ which is given in Table I.

$$(\Delta°_1C_i/\sin^2 \theta)_{2a,2b} = (\Delta°_1C_i/\sin^2 \theta')_{2a',2b'}$$

[35] The SCS-corrected shift of **1d** was used for the para carbon chemical shift of anisole with a perpendicular OCH_3 group (**1a**).

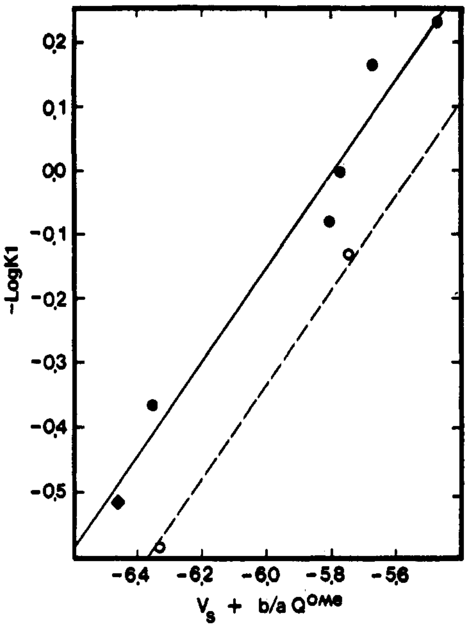


Figure 2. The dependence of $-\log K_1$ for 1:1 hydrogen bonding of trifluoroacetic acid with *o*-alkylanisoles **2a–e** (●), cyclic ether **3a** (◆), and *p*-methylanisoles **2a′** and **2b′** (○) on the potential function for methoxy group rotation, V_S(kJ/mol), and on the methoxy oxygen electronic charge, Q^{OMe} (see eq 8a, 8b); $r = 0.984$.

neat TFA and corrected for the electronic effects of the alkyl substituents.[13]

$$\sin^2\theta = [(\delta C4(2) - \delta C4(3))/(\delta C4(1) - \delta C4(3))]_{TFA} \qquad (5)$$

The change in free energy for formation of the 1:1 complex between TFA and **2** in deuteriochloroform is given by $-\log K_1$. The corresponding change in enthalpy will be the sum of two terms, the enthalpy change for rotation of the methoxy group in the absence of medium effects and that for subsequent hydrogen bonding of the rotated OCH_3:

$$\Delta H = \Delta H^{ROT} + \Delta H^{HB} \qquad (6)$$

Because the potential energy of anisoles **2** is unaffected by the presence of the *o*-substituents for $\theta < 75°$,[38] one can use for ΔH^{ROT} of all **2** the potential function of methoxy group rotation in anisole itself, calculated recently by Schaefer[39,40] using the 6-31G basis set with geometry optimization and inclusion of polarization functions:

$$V(\theta),\ \text{kJ/mol} = 6.07V_S$$

$$V_s = \sin^2\theta + 0.4415156\sin^2 2\theta \qquad (7)$$

If ΔH^{HB} for hydrogen bonding of **2** depends mainly on Q^{OMe}, the amount of electronic charge at the acceptor oxygen, as in the hydrogen bonding of **1**, if, in addition,

Table III. Residual Shifts,[a] ΔC_i^{RES}, of Anisoles 2 and Shift Changes, $\Delta°_1C_i$, of 3,4-Dihydro-2*H*-1-benzopyrans 4′ for 1:1 Hydrogen Bonding with Trifluoroacetic Acid

compd	ΔC_1	ΔC_2	ΔC_6	ΔC_4
2a[b]	−2.854	0.556	0.556	2.557
2a′[b]	−2.953	0.828	0.828	2.772
4a′[c,d]	−3.471	0.530 (0.785)[e]	1.039	2.484
2b[b]	−2.138	−0.298	2.063	2.563
2b′[b]	−1.974	−0.197	2.279	2.960
4b′[c,f]	−2.193	0.394	2.169	2.655
2c[b]	−2.282	−0.173	2.371	2.484
2d[b]	−1.815	0.818	2.515	2.615
2e[b]	−1.861	0.507	2.098	1.849

[a] In parts per million. Positive values denote downfield shift changes. [b] Residual shift. [c] Hydrogen bonding shift, $\Delta°_1C_1$ (see Table I). [d] $K_1 = 2.078$ L/mol, based on C4 as the monitoring resonance. [e] The average of ΔC_2 and ΔC_6. [f] $K_1 = 1.262$ L/mol, using average values of f (eq 2), obtained from the shift changes of C4 and C6.

ΔS is insensitive to R and θ, then $\log K_1$ will be a linear function of V_S and Q^{OMe} if the interaction of TFA with **2** does, indeed, involve rotation of the OCH_3 group. Using

$$-\log K_1 = aV_S + bQ^{OMe} + c \qquad (8a)$$

the data for **2a–e** and **3a** and the angle-dependent values of Q^{OMe} recently derived for **2** by PRDDO-MO calculations,[38] one obtains eq 8b from 8a by multiple regressional analysis.[41] The plot of eq 8 shown in Figure 2, though

$$-\log K_1 = 0.73317V_S + 22.42958Q^{OMe} + 4.24587 \qquad (8b)$$

based on some simplifying assumptions, is clearly linear (correlation coefficient, 0.984). The slope of the correlation line gives 4.23 kJ/mol (= 0.73317 × 2.303 × 8.314 × 301/1000) for the energy difference between anisole having in-plane and perpendicular methoxy group conformations. That this value compares well with 6.07 kJ/mol obtained by Schaefer using quantum mechanics further strengthens the case for TFA-induced methoxy group rotation in **2**.

The data for *p*-methyl-substituted **2a′** and **2b′** fall on a separate correlation line of similar slope (see Figure 2) corresponding to values of ΔH which are more negative than those for hydrogen bonding of the para-unsubstituted anisoles **2** by about 1 kJ/mol. A difference in enthalpy change of about 0.8 kJ/mol is also found in the hydrogen bonding of the *p*-methyl-substituted and unsubstituted cyclic ethers **3b′** and **3b**.[42] These energy differences may be attributed to a small increase in electronic charge at the acceptor methoxy oxygens of the para-substituted ethers which results from hyperconjugative electron donation by the *p*-methyl substituent and which increases the potential of the oxygen to hydrogen bond.

One can estimate the contribution of OCH_3 group rotation, ΔC_i^{ROT}, to the total shift change, $\Delta°_1C_i$, of each carbon of anisoles **2** from $\sin^2\theta$ and the SCS-corrected[13] shifts of the carbon resonance in correspondingly substituted anisoles **1** and **2** in deuteriochloroform, in which the methoxy group is either orthogonal to (**1**), or in the plane of (**2**) the benzene ring. Subtracting ΔC_i^{ROT} from $\Delta°_1C_i$

$$\Delta C_i^{ROT} = \sin^2\theta\,(\delta C_i(1) - \delta C_i(2))_{CDCl_3} \qquad (9)$$

leaves a residual shift change, ΔC_i^{RES}, which measures the sensitivity of the NMR shift to hydrogen bonding, by TFA, of the rotated methoxy group. Table III summarizes these

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(36) The para carbon shifts of **3**, corrected for the electronic effects of the alkyl substituents at C2, were also corrected for the effect of strain of the heterocyclic ring by the addition of 0.3389 ppm:

$$\delta(^{13}C(\mathbf{2a}))_{CDCl_3} - \delta(^{13}C(\mathbf{3a}))_{CDCl_3} = 120.5878 - 120.2489\ \text{ppm} = 0.3389\ \text{ppm}$$

(37) The corrected shift of **3b** was used to approximate the para carbon shift of **3c**, a molecule which was not synthesized.

(38) Jardon, P. W.; Vickery, E. H.; Pahler, L. I.; Pourahmady, N.; Mains, G. J.; Eisenbraun, E. J. *J. Org. Chem.* **1984**, *49*, 2130.

(39) Schaefer, T.; Sebastian, R. *Can. J. Chem.* **1989**, *67*, 1148.

(40) Similar potentials for methoxy group rotation of anisole, in which there are also two local minima, have been derived by others. See Klessinger, M.; Zywietz, A. *J. Molec. Struct.* **1982**, *90*, 341 and references therein.

(41) Q^{OMe} is a negative term.

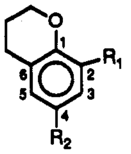
(42) The data for ortho-substituted cyclic ethers **3b–e** and **3b′** do not fall on either correlation line. The lower than expected values of $\log K_1$ associated with hydrogen bonding of these ethers probably arises from destabilization of the hydrogen-bonded complexes, as discussed.

Table IV. ^{13}C NMR Shift Changes[a] for Hydrogen Bonding of Anisoles 1 and 2, 2,3-Dihydrobenzofurans 3,[b] and 3,4-Dihydro-2*H*-1-benzopyrans 4′[b] with 2,2,2-Trifluoroethanol

compd	ΔC4	ΔC1	ΔC2	ΔC6	ΔOCH
1b′	1.086	−0.862	−0.431	−0.431	0.028
1b	1.201	−0.787	−0.259	−0.259	0.064
1c	1.055	−0.976	−0.377	−0.377	0.155
1d	1.166	−1.079	−0.250	−0.250	0.127
2a	0.987	0.056	0.404	0.404	0.013
2a′	1.014	−0.044	0.462	0.462	0.077
2a″	1.070	0.034	0.513	0.513	0.101
2b′	1.182	0.330	0.225	2.042	0.579
2b	0.964	0.436	0.182	1.695	0.336
2c	0.863	0.454	0.231	1.580	0.334
2d	0.884	0.395	0.339	1.603	0.433
2e	0.449	0.654	0.358	1.067	−0.175
3a	1.070	−0.731	−0.107	−0.181	0.536
3b′	0.899	−0.575	−0.320	−0.171	0.421
3b	0.888	−0.557	−0.277	−0.084	0.412
3d	0.839	−0.398	−0.057	−0.009	0.363
3e	0.316	0.233	0.023	0.164	0.135
4a′	1.058	−0.476	−0.335	0.308	0.706
4b′	0.700	0.003	−0.446	0.416	0.514

[a] In parts per million. Positive values denote downfield shift changes. These shift changes have been corrected for the SCS of the alkyl substituent (see Table V, supplementary material). [b] The SCS of the ethyl group was used for the SCS of the cyclic $(CH_2)_nO$ fragments ($n = 2, 3$).

residual shifts for the aromatic carbons C2, C4, C6, and C1 of **2**. Also listed are the values of $\Delta^{\circ}{}_{1}C_i$ for hydrogen bonding of 3,4-dihydro-2*H*-1-benzopyrans[7] **4a′** and **4b′**, heterocyclic ethers which, having partially rotated, though conformationally locked OCH moieties[43] and skewed Ar–OCH bonds,[44] resemble hypothetical uncomplexed anisoles **2** in which methoxy group rotation has taken place. According to the data of Table III ΔC_i^{RES} (**2a**, **2a′**) ~ $\Delta^{\circ}{}_{1}C_i$ (**4a′**) and ΔC_i^{RES} (**2b**, **2b′**) ~ $\Delta^{\circ}{}_{1}C_i$ (**4b′**). In fact, the residual shifts of all ortho-unsubstituted **2** resemble the shift changes of ortho-unsubstituted **4a′**, and there is a similar correspondence between most of the residual and hydrogen bonding shifts of all the ortho-substituted anisoles **2** and cyclic ethers **4b′**. Thus these residual shifts, and therefore also the shift changes due to rotation, ΔC_i^{ROT}, on which they are based, are of a sign and magnitude compatible with TFA-induced methoxy group rotation taking place in the hydrogen bonding of **2**.[45,46]



4a′: $R_1 = H$; $R_2 = CH_3$
b′: $R_1 = R_2 = CH_3$

Hydrogen Bonding of 1, 2, 3, and 4′ by 2,2,2-Trifluoroethanol. For comparison Table IV lists the changes in ^{13}C NMR shifts of **1**, **2**, **3**, and **4′** that are produced by a change of solvent from neat deuteriochloroform to neat 2,2,2-trifluoroethanol (hereafter TFE), the shifts of the ethers in each solvent having been corrected for the electronic effects of the alkyl substituent.[13]

On average, hydrogen bonding of the ethers by TFE results in shift changes which are much smaller than those for hydrogen bonding by the stronger proton donor TFA. Moreover, the TFA- and TFE-induced changes in shift do not correlate. Therefore the energies of the hydrogen bonds, the mix of charge transfer, electric field, and mesomeric effects of hydrogen bond formation, and perhaps the stereochemistries of the hydrogen-bonded complexes differ for hydrogen bonding of the ethers by each of these proton donors.

The amount of deshielding of the para carbon resonances of ortho-unsubstituted **2a**, **2a′**, **2a″**, **3a**, and **4a′** on hydrogen bonding with TFE is nearly the same and is somewhat greater than that for hydrogen bonding of the corresponding *o*-alkyl-substituted ethers. Hydrogen bonding of TFE with **2** probably does not now involve rotation of the methoxy group because the size of the downfield shift changes of C4 is the same for identically ortho-substituted **2** and **3**. Accordingly, the shift changes of OCH_3 for hydrogen bonding of **2b–e** and **2b′** with TFE are now also approximately the same as those of the OCH_2 moieties in the hydrogen bonding of correspondingly substituted **3b–e** and **3b′**. Except for ΔC4, the changes in shift of ortho-unsubstituted **2a**, **2a′**, and **2a″** are again noticably smaller than those for hydrogen bonding of the ortho-substituted molecules. This could be due to different average positions of TFE in the hydrogen-bonded complexes—nearer the oxygen sp^2 lone pair orbital for hydrogen bonded **2a**, **2a′**, and **2a″**, but closer to the oxygen p orbital axis above the benzene ring in complexes of **2b–e** and **2b′** as discussed above for hydrogen bonding of these molecules by TFA. This conclusion has some support in the greater similarity between the *o*-alkyl carbon shift changes of correspondingly substituted **1** and **2** than between those of **2** and **3** (see Table II).

Experimental Section

Aromatic Ethers. Anisoles **1** and **2** were either commercial materials or were synthesized by routine methods as described previously.[14] The cyclic ether **3a** was commercially available and **3b′**, **4a′**, and **4b′** were generously donated by Professor Charles Bradsher of Duke University, Durham, NC. The remaining alkyl-substituted members of series **3** were obtained by following the general outline of his procedure.[47] This involved brominating the appropriate 2-alkylphenol, treating the sodium salt of the 2-alkyl-4,6-dibromophenol produced with excess 1,2-dibromoethane, and cyclizing the resulting (aryloxy)ethyl bromide by means of *n*-butyllithium to give 7-alkyl-5-bromo-2,3-dihydrobenzofuran. The bromine was then removed by further addition of *n*-butyllithium and subsequent quenching with methanol. The

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(43) The rotational angle of O–CH about the Ar–O bond in the crystal structure of a compound related to **4b′** is about 16.9° (Burton, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472). There is some evidence that for the compound in solution this angle might be appreciably larger still (Doba, T.; Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 6506).

(44) The C6–C1–O angle in the structure related to **4b′** (ref 43) is 122.3°. The C2–C1–O angle is 115.1° (Gabe, E. J., private communication. See also Burton, G. W.; LePage, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791).

(45) Rotation of the OCH_3 of **2** increases the accessibility by TFA of the oxygen sp^2 lone pair by a concomitant widening of the C2–C1–O angle (Schaefer, T., private communication). From a survey of the crystallographic literature Bürgi has proposed the relation:

$$\phi(\text{C2–C1–O}) = 120 + 4.63 \cos \theta$$

where θ is the rotational angle of the methoxy group.

(46) The changes in *o*-alkyl carbon shifts of **2** produced by hydrogen bonding of these anisoles do not resemble those for hydrogen bonding of **3** (see Table II). This is so even when these shift changes are corrected for the differential TFA-induced changes in the through-bond electronic effects of the aromatic ring as in the case of the *o*-CH_3 shift changes (corrected by subtraction of the *p*-CH_3 shift change; see Table II, values in parentheses and footnote *d*). Thus there is a difference in the through-space electric field effect of TFA on the *o*-alkyl resonances of **2** and **3** and this can be attributed to a difference in the orientation of TFA with respect to the *o*-alkyl substituent in the hydrogen bonded complexes of **2** and **3**. These results accord with TFA lying within the molecular plane near the oxygen sp^2 lone pair orbital in complexes with **3** but above that plane in the hydrogen bonding of the rotated methoxy groups of *o*-alkylanisoles **2**.

(47) Bradsher, C. K.; Reames, D. *J. Org. Chem.* **1981**, *46*, 1384.

procedure for the preparation of **3d** described below is typical for the syntheses of all **3**.

o-Isopropylphenol (0.05 mol), dissolved in aqueous ethanol, was treated with a slight molar excess of aqueous Br_2–KBr (6.4 mL of Br_2, 30 g of KBr, 200 mL of water) at room temperature. The solution was stirred for 1 h before an equal volume of water was added, and the dibromophenol was extracted with several portions of ether. The extracts were successively washed with 5% $NaHCO_3$, water, and saturated aqueous NH_4Cl and then dried over anhydrous $MgSO_4$. The ether was removed using a rotary evaporator, and the residue was dissolved in 7 mL of water containing 1.9 g of NaOH. This solution was added slowly and without external heating to a well-stirred mixture of 1,2-dibromoethane (0.063 mol, 5.5 mL) plus water (26 mL). The solution was then refluxed for 6 h, cooled, and extracted with ether. The extracts were washed sequentially with water and saturated NH_4Cl and then dried over anhydrous $MgSO_4$. The ether was removed at room temperature using a rotary evaporator, and the remainder was fractionated under reduced pressure. The first distillate was mostly unreacted dibromoethane. The fraction boiling at 134 °C (ca. 15.5 Torr) was 2,4-dibromo-6-isopropylphenoxyethyl bromide which solidified on cooling. It was identified by its ^{13}C NMR spectrum.

To 15 mmol of this material, dissolved in 100 mL of dry tetrahydrofuran plus 25 mL of cyclohexane (both solvents distilled from sodium benzophenone ketyl) in a dry nitrogen atmosphere at −100 °C (methanol–liquid nitrogen bath), was slowly added with stirring 17 mmol of *n*-butyllithium (2.5 M in hexane) at such a rate that the temperature did not rise by more than 5 °C. Stirring was continued at −100 °C for another 30 min before an additional 17-mmol portion of *n*-butyllithium in hexane was added. Following this, the reaction mixture was stirred for 1 h at −100 °C. Then it was quenched by slowly adding 30 mmol of methanol in 20 mL of THF. Stirring was continued for another 30 min, and then the mixture was allowed to come to room temperature. It was poured into 150 mL of water, the layers were separated, and the aqueous phase was extracted three times with 150 mL of ether. The ether extracts and organic layer were combined, dried over anhydrous $MgSO_4$, concentrated to a smaller volume at room temperature using a rotary evaporator, and fractionally distilled from CaH_2 under reduced pressure. The first fraction was residual THF; the second, 7-isopropyl-2,3-dihydrobenzofuran **3d**, bp 79–81 °C (15 Torr), was identified by its ^{13}C NMR spectrum.

NMR Measurements. A series of ^{13}C NMR spectra of 0.5 M solutions of the anisoles in $CDCl_3$, titrated with successive portions of TFA, were recorded at 301 ± 2 K on a Bruker WN-250 (5-mm tubes) spectrometer, operating at 62.9 MHz. The peaks of the base were referenced to internal cyclohexane (1%, v/v) because of the reported sensitivity of the ^{13}C chemical shift of Me_4Si to medium and temperature effects.[48] The conversion to the TMS scale is $\delta(^{13}C(Me_4Si)) = \delta(^{13}C(C_6H_{12})) + 26.92$ ppm.

Peak assignments were based on coupled spectra, the attached proton test, and comparisons with peak assignments in similar systems.

Variable-Temperature Titrations of 3a. Four sets of ^{13}C NMR spectra were obtained by titrating **3a**, 0.5 M in $CDCl_3$ containing 1% (v/v) each of Me_4Si and C_6H_{12}, with successive portions of TFA at 250, 263, 280, and 301 K. The peaks of **3a** were referenced to the internal C_6H_{12}. The chemical shift of Me_4Si, relative to C_6H_{12} in deuteriochloroform solutions of **3a** containing no TFA, varied linearly with temperature: $\delta^T(^{13}C(Me_4Si)) = -0.00469T + 1.37856$ ppm (correlation coefficient, 0.998). In each titration of **3a** the shift of Me_4Si relative to C_6H_{12} moved upfield with increasing stoichiometric acid:base ratio. Plots of these shifts versus the acid:base ratio at the four temperatures were parallel curves with a vertical separation of ca. $0.00469\Delta T$. Thus, after the addition of each aliquot of TFA in the titration of **3a**, return of the sample to the proper temperature could be monitored by observing the position of the Me_4Si signal.

The chemical shift of the para carbon of **3a**, 0.5 M in TFA containing 1% (v/v) C_6H_{12} plus 5% (v/v) Me_4Si, was measured relative to internal C_6H_{12} at six temperatures giving the correlation: $\delta^{TFA}C4(\mathbf{3a}) = -0.00329T + 123.7842$ ppm (correlation coefficient, 0.992). This relation was used to obtain the para carbon shift change associated with fully hydrogen bonding **3a** in neat TFA (ΔC in eq 2) at each of the four temperatures at which the titration was carried out.

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Supplementary Material Available: Substituent chemical shifts of the alkyl groups of arenes in deuteriochloroform, TFA, and TFE (Table V) and ^{13}C NMR shifts of cyclic ethers **3** and **4′** in deuteriochloroform and in TFA (Tables VI and VII) (the corresponding chemical shifts for **1** and **2** have been deposited previously[14]) (3 pages). Ordering information is given on any current masthead page.

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[48] Ziessow, D.; Carroll, M. *Ber. Bunsenges.* **1972**, *76*, 61.

Isotactic Polymethoxy-1-alkenes from Blue-Green Algae. Synthesis and Absolute Stereochemistry

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Novel isotactic polymethoxy-1-alkenes **1**–**4** were isolated from tolytoxin-producing blue-green algae belonging to the family Scytonemataceae. *Scytonema mirabile* produced **1** and **2**, whereas **3** and **4** were isolated from *S. burmanicum*. The gross structures and relative stereochemistries were determined by mass and NMR spectral analyses. The absolute configurations of **1**–**4** were established by direct comparison with optically active synthetic samples.

Isotactic polymethoxy-1-alkenes were first found in a field-collected sample of tolytoxin-producing blue-green alga *Tolypothrix conglutinata* var. *colorata* Ghose from Fanning Island.[1] Recently, however, we have been able

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