Substituent Control of Intramolecular Hydrogen Bonding in Formyl-Protonated o-Anisaldehydes: A Stable Ion and Semiempirical MO Investigation

Kenneth K. Laali,*[1a,b] Gerald F. Koser,*[1a,c] Sundar Subramanyam,[1a] and David A. Forsyth*[1d]

Department of Chemistry, Kent State University, Kent, Ohio 44242, Department of Chemistry, University of Akron, Akron, Ohio 44325, and Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

Received October 14, 1992

o-Anisaldehyde and its 5-Br, 5-F, 5-CF_3, 5-CN, 5-NO_2, and 5-COMe derivatives are protonated at the formyl group in 1:1 SbF_5–FSO_3H/SO_2 (or SO_2ClF) to give persistent carboxonium ions as mixtures of *Z* and *E* geometrical isomers. The cyano, nitro, and acetyl substituents are also protonated, leading to dications and additional geometrical isomers in the nitro and acetyl cases. The carboxonium ions are predominantly in the *Z*,syn configuration, but with increased amounts of the *E*,anti configuration with increased electron withdrawal by the substituents. With 5-NO_2H^+, *E* isomers become more abundant than *Z*. The formyl protonated 2-(trifluoromethoxy)benzaldehyde shows a strong preference for the *E* configuration. The preference for the *Z*,syn form is attributed to intramolecular hydrogen bonding that becomes less favorable as electron density is withdrawn from the methoxyl oxygen. The log *Z*/*E* values correlate with differences in energy content of the isomers predicted in AM1 calculations, and the chemical shift of the hydroxyl proton of the carboxonium group correlates well with predicted charge on the proton.

Introduction

Protonated carbonyl compounds (mesomeric carboxonium or hydroxycarbenium ions) are intermediates in a vast number of acid-catalyzed organic transformations. Although intramolecular hydrogen bonding in neutral carbonyl compounds has been studied extensively, and detailed kinetic, structural, and spectroscopic data are available,[2] little is known about intramolecular H-bonding in long-lived carboxonium ions. Issues pertaining to their relative energies, configurational preferences, basicity requirement of the lone pair donor, and whether remote substituents might be used to influence isomer content are largely unexplored.

The pioneering work of Olah and co-workers on NMR studies of persistent species in superacid media included a host of O-protonated aldehydes and ketones.[3] These and other NMR studies[4–6] of hydroxycarbenium ions demonstrated that sufficient π-bond character is retained such that *E* and *Z* geometrical isomers can be observed. In protonated aldehydes, the vicinal $HCOH^+$ coupling provides a diagnostic tool for identifying the isomers, with trans coupling roughly twice the magnitude of cis coupling.

Sommer et al.[7,8] have shown that, in protonated α-halo aldehydes and ketones, an intramolecular H-bond is formed between the α-halogen atom and the $C{=}OH^+$ group. Formation of a H-bond in a five-membered ring changes the equilibrium composition in favor of the H-bonded *Z* isomer as opposed to the *E* isomer which is predominant in O-protonated acetaldehyde (*Z*/*E* = 0.25).[3,4] In the H-bonded *Z* isomers, the $C{=}OH^+$ NMR signals are upfield relative to the same signal in the *E* isomers. On the other hand, Emsley et al.[9] observed an unusually deshielded proton (δ 21.44) involved in an intramolecular H-bond for a protonated β-diketone in HBr/CF_2Br_2.

Benzaldehyde and *p*-anisaldehyde are fully protonated in FSO_3H or CF_3SO_3H and give the *E* configuration about the carboxonium C=O bond. In addition, π-delocalization approximately doubles the Ph–CO rotational barrier over that of the free base, so that isomerism about this bond can be readily observed by NMR also.[10] Protonations of *o*-anisaldehyde and *o*-hydroxybenzaldehyde have been briefly studied.[11] Just one $HC{=}OH^+$ signal showing trans coupling for the *Z* isomer was observed in protonated *o*-anisaldehyde. For protonated *o*-hydroxybenzaldehyde, about 10% of the *E* isomer was also present. The preferred *Z* configuration of the protonated carbonyl group was attributed to intramolecular H-bonding in these two cases.

We report herein an experimental and theoretical study of the influence of substituents at C5 (para to methoxy) on *Z*/*E* isomer ratios, and hence on the stability of the intramolecular H-bond, in C=O protonated *o*-anisaldehydes. Four isomers are possible in these carboxonium ions, as shown in Chart I. The relative stabilities of the isomeric carboxonium ions were also probed by semiempirical AM1 calculations.

(1) (a) Kent State University. (b) To receive correspondence. (c) Senior Scholar on sabbatical leave from University of Akron at Kent State (Spring 1991). (d) Northeastern University.

(2) For a comprehensive review, see: Hibbert, F.; Emsley, J. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: 1990; Vol. 26, pp 255–379.

(3) (a) Olah, G. A.; O'Brien, D. H.; Calin, M. *J. Am. Chem. Soc.* **1967**, *89*, 3582. (b) Olah, G. A.; Calin, M.; O'Brien, D. H. *J. Am. Chem. Soc.* **1967**, *89*, 3586. (c) Olah, G. A.; White, A. M.; O'Brien, D. H. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: 1973; Vol. IV, Chapter 31. (d) Olah, G. A.; White, A. M.; O'Brien, D. H. *Chem. Rev.* **1970**, *70*, 561.

(4) Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 676.

(5) (a) Ramsey, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058. (b) Brouwer, D. M. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 879.

(6) (a) Childs, R. F.; Lund, E. F.; Marshall, A. G.; Morrisey, W. J.; Rogerson, C. V. *J. Am. Chem. Soc.* **1976**, *98*, 5924. (b) Forsyth, D. A.; Osterman, V. M.; DeMember, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 818.

(7) Thil, L.; Riehl, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 591.

(8) Sommer, J.; Jost, R.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* **1980**, *4*, 185.

(9) Clark, D. R.; Emsley, J.; Hibbert, F. *J. Chem. Soc., Chem. Commun.* **1988**, 1252.

(10) Jost, R.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1971**, 879.

(11) Kotkowska-Machnik, Z.; Zakrzewski, J. *Org. Magn. Reson.* **1981**, *15*, 319.

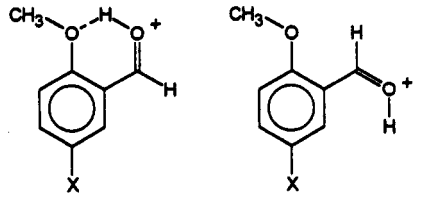
0022-3263/93/1958-1385$04.00/0

Table I. ^{1}H NMR Chemical Shifts[a] and Coupling Constants[b] of Protonated *o*-Anisaldehydes in 1:1 SbF_5–FSO_3H/SO_2

cation	temp, °C	HCO*H*$^+$	*H*COH$^+$	OCH_3	H6	H4	H3	other
1	−70	exch[c]	9.30 (s)	4.38 (s)	8.12 (d, 7.0)	8.35 (br t)	7.40 (m)	7.40 [H5] (m)
3	−70	14.18 (d, 15.8)	9.32 (d, 15.1)	4.35 (s)	8.19 (d, 2.6)	8.33 (dd, 8.9, 2.1)	7.39 (d, 9.2)	
4	−70	12.25	9.7	4.1	*d*	*d*	7.25	
5	−60	14.40 (br)	9.32 (s)	4.38 (s)	7.79 (m)	8.15 (m)	7.50 (m)	
5-F, E	−60	12.3	9.75	4.20	*d*	*d*	*d*	
6	−70	14.16 (d, 16.4)	9.33 (d, 16.4)	4.31 (s)	8.31 (br s)	8.32 (d, 9.1)	7.50 (d, 9.0)	
7	−70	12.41 (d, 7.9)	9.74 (d, 8.3)	4.06 (s)	8.76 (br s)	8.23 (d, 9.2)	7.33 (d, 9.2)	
8	−60	14.51 (d, 16.9)	9.69 (d, 17.0)	4.58 (s)	9.09 (d, <2)	8.84 (dd, 9.2, <2)	7.84 (d, 9.33)	12.2 [CNH$^+$]
9	−60	13.70 (d, 8.4)	10.04 (d, 8.4)	4.36 (s)	9.19 (br s)	8.71 (dd, 9.2, <2)	7.67 (d, 9.4)	12.0 [CNH$^+$]
11	−70	14.55 (d, 17.2)	9.76 (d, 17.4)	4.66 (s)	9.4–9.9	8.8–9.3	7.88 (d, 9.8)	16.2–16.4[e] [NO_2H^+]
10	−70	14.27 (d, 8.0)	10.14 (d, 8.2)	4.47 (s)	9.4–9.9	8.8–9.3	7.74 (m)	15.6–15.9[f] [NO_2H^+]
11	−45	14.58 (d, 17.3)	9.79 (d, 17.3)	4.70 (s)	9.67 (br s)	9.20 (d, 9.8)	7.92 (d, 9.9)	[NO_2H^+] exch
10	−45	14.43 (d, 8.6)	10.18 (d, 8.4)	4.53 (s)	9.73 (br s)	9.05 (d, 9.8)	7.78 (d, 10.0)	[NO_2H^+] exch
12	−70	14.34, 14.46 (d, 16.8; d, 17.0)	9.68, 9.72 (d, 16.7; d, 16.7)	4.64 (s)	9.3–9.6	9.0–9.2	7.83 (d, 9.8)	13.80, 13.74 [C(Me)O*H*$^+$] 3.47 [C(*Me*)OH$^+$]
13	−70	13.60, 13.72 (d, 8.7; d, 8.7)	10.09 (d, 9.0)	4.43 (s)	9.3–9.6	9.0–9.2	7.68 (d, 9.7)	13.44, 13.36 [C(Me)O*H*$^+$] 3.41 [C(*Me*)OH$^+$]
OCF_3[g]	−70	13.42 (d, 8.4)	10.06 (d, 8.4)		8.58 (d, 8.0)	8.46 (t, 8.0)	7.69 (t, 8.0)	7.74 [H5] (t, 8.0)

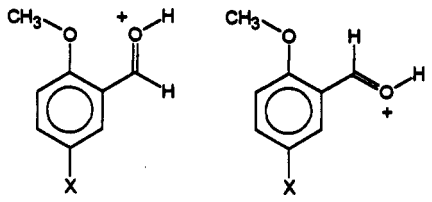
[a] δ_H in ppm from TMS, reference $CHDCl_2$ (5.32). [b] Coupling constants in parentheses, in hertz; if none given, signal is too weak or too complex. [c] Exchanging. [d] Obscured by overlap and/or too small. [e] Two broad peaks; see text. [f] Four peaks; see text. [g] Protonated 2-(trifluoromethoxy)benzaldehyde, *E*, anti.

Chart I



Z,syn

Z,anti



E,syn

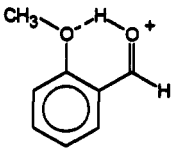
E,anti

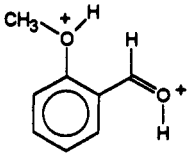
The carboxonium ions in the NMR study reported here were produced by protonation, with 1:1 SbF_5–FSO_3H, of *o*-anisaldehyde (2-methoxybenzaldehyde) and its 5-bromo, 5-fluoro, 5-trifluoromethyl, 5-cyano, 5-nitro, and 5-acetyl derivatives. The latter three substituents are also protonated in this medium, leading to dications and to additional geometrical isomers in the 5-nitro and 5-acetyl cases. In addition, the protonation of 2-(trifluoromethoxy)-benzaldehyde was studied.

Results

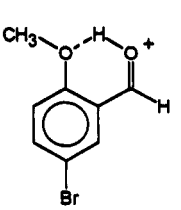
(a) Superacid Protonation. The ^{1}H NMR spectra resulting from the protonation of *o*-anisaldehydes by 1:1 SbF_5–FSO_3H in SO_2 are summarized in Table I. The assignments of *Z* and *E* isomers are based principally on vicinal coupling in the carboxonium group. However, it is also noted that the chemical shift of the HCO*H*$^+$ resonance in the *Z*,syn, intramolecularly H-bonded structures varies in a narrow range (δ 14.15–14.55), while the HCO*H*$^+$ shift in the *E*,anti isomers is much more substituent dependent (δ 12.2–14.3). In the *E* isomers, the more downfield HCO*H*$^+$ shift with increasing electron-withdrawing character of the substituents is very similar to earlier observations on protonated para-substituted benzaldehydes,[10] that are also *E*,anti and which obviously are not intramolecularly H-bonded.

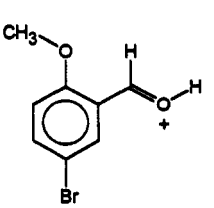
From the protonation of *o*-anisaldehyde, the HCO*H*$^+$ and superacid peaks in the ^{1}H NMR spectrum at −70 °C are very broad and change shape upon raising the temperature to −60 and −50 °C, indicating averaging due to rapid exchange. Thus, a conformationally frozen carboxonium ion was not obtained in 1:1 SbF_5–FSO_3H. Since a previous study with weaker acids found a well-resolved HCO*H*$^+$ signal with trans coupling to the formyl proton,[11] indicating the *Z*,syn isomer, **1**, it is likely that the exchange is promoted by transient protonation of the methoxyl oxygen to form the dication, **2**. This is also consistent with the finding that *p*-anisaldehyde is diprotonated at the high acidity of 1:1 SbF_5–FSO_3H as indicated by NMR titration and barrier measurements, although the proton on the methoxyl oxygen is not visible in the NMR due to rapid exchange with the acid.[12,13]





1 **2**





3 **4**

In contrast, similar protonation of 5-bromo-2-methoxybenzaldehyde gave rise to a distinct HCO*H*$^+$ doublet in

(12) (a) Sommer, J.; Rimmelin, P.; Drakenberg, T. *J. Am. Chem. Soc.* **1976**, *98*, 2671. (b) Sommer, J.; Schwartz, S.; Rimmelin, P.; Canivet, P. *J. Am. Chem. Soc.* **1978**, *100*, 2576.

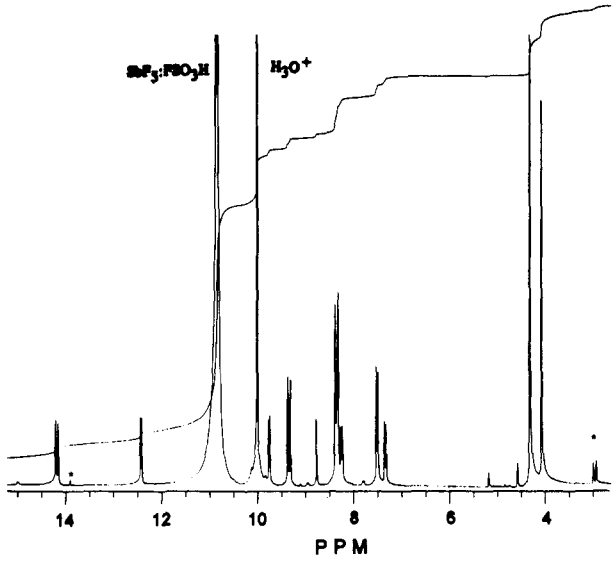


Figure 1. 300-MHz ^{1}H NMR spectrum of initial mixture that resulted from protonation of 5-(trifluoromethyl)-2-methoxybenzaldehyde in 1:1 SbF_5–FSO_3H/SO_2 at −70 °C. The spectrum shows signals for both *Z*,syn and *E*,anti isomers, e.g., at δ 14.16 and 12.41 for HCO*H*$^+$, and a small amount of a possible third isomer (HCO*H*$^+$ at δ 15.0). Peaks marked with an asterisk are due to impurity of protonated acetone.

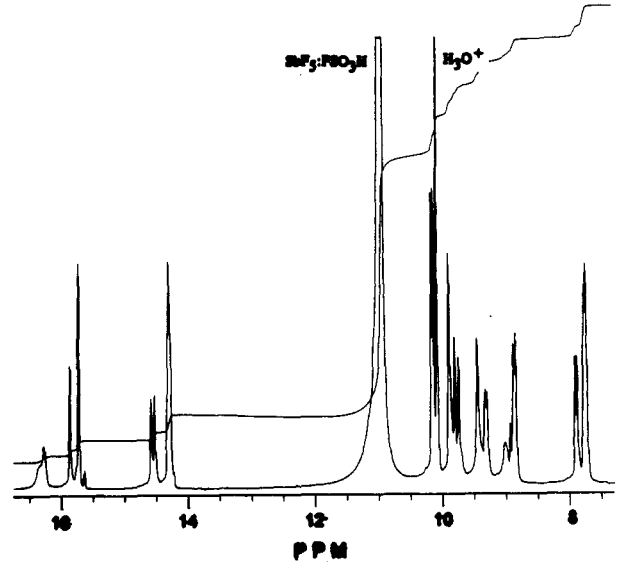
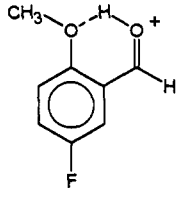


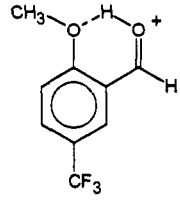
Figure 2. 300-MHz ^{1}H NMR spectra at −70 °C showing mixture of isomers **10** and **11** resulting from diprotonation of 5-nitro-2-methoxybenzaldehyde in SbF_5–FSO_3H/SO_2. Region from δ 15.5 to 16.5 shows multiple NO_2H^+ signals for isomeric protonation of the nitro group. Broadening of signals at δ 16.3 indicates beginning of fast exchange for *Z*,anti isomers.

the ^{1}H NMR spectrum at −70 °C, coupled to the formyl proton. The large ($J > 15$ Hz) *H*CO*H* coupling indicates that this carboxonium ion exists principally as the *Z* isomer, **3**. About 2% of a minor isomer was detected and assigned as the *E*,anti isomer, **4**, by comparison with chemical shifts in the spectra for the 5-trifluoromethyl cation, described below. There was no change in the spectrum between −70 and −50 °C, nor with the less nucleophilic solvent SO_2ClF instead of SO_2.

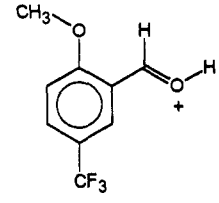
Low-temperature protonation of 5-fluoro-2-methoxybenzaldehyde also gave predominantly the *Z*,syn isomer, **5**. In the ^{1}H spectrum recorded at ca. −60 °C, the HCO*H*$^+$ signal for the *Z* isomer is a broad peak and the *H*COH$^+$ signal is a slightly broadened singlet. The lack of coupling and the broadening can be attributed to exchange of the HCO*H*$^+$ proton with the acid. Very small signals that are likely due to the *E* isomer can be seen at 12.3 and 4.2 ppm. The relative amount of *E* isomer is estimated at about 1%.



5



6

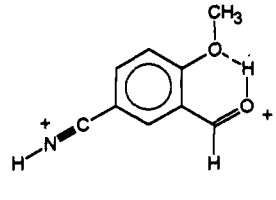


7

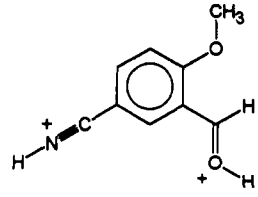
The ^{1}H NMR spectrum (Figure 1) of protonated 5-(trifluoromethyl)-2-methoxybenzaldehyde at −70 °C clearly indicates the presence of both *Z* and *E* isomers, **6** and **7**. The HCO*H*$^+$ and formyl proton signals show a 16.4 Hz coupling for the *Z* isomer and smaller 8 Hz coupling for the *E* isomer. The ring proton (H6) between the CF_3 and carboxonium groups was deshielded by 0.45 ppm in **7** compared with that of **6**. The increased deshielding of H6 is a strong indication of the anti orientation of the carbonyl oxygen relative to OMe in the *E* isomer. In contrast, both H3 and H4 are shielded in the *E* isomer compared with the *Z* isomer. About 3% of a third isomer, unidentified, is represented by small peaks at δ 15.0, 4.6, and in the aromatic region.

The spectrum of **6** and **7** recorded initially at −70 °C indicated a *Z*/*E* ratio of 1.6. A subsequent spectrum, recorded at −53 °C, showed an increase in the ratio to 2.63, and the *Z*/*E* ratio reached a final value of about 10. It seems plausible that the initial ratio indicates kinetic protonation, followed by a relatively slow isomerization.

The ^{1}H NMR spectrum at −60 °C for protonated 5-cyano-2-methoxybenzaldehyde indicates two isomeric carboxonium ions with the *Z* isomer, **8**, predominating over **9** (*Z*/*E* = 2.4). The only mixture showing a preference for the *E* isomer arose from the protonation of 5-nitro-2-methoxybenzaldehyde. The ^{1}H NMR spectrum at −70 °C (Figure 2) indicates the formation of isomeric carboxonium ions, with the *E* isomer predominating (*Z*/*E* = 0.48). However, additional complexity is introduced by isomeric protonation of the nitro group.



8



9

The HCO*H*$^+$ resonance of the *Z* isomer in Figure 2 appears at δ 14.55 as a 17.2-Hz doublet, and the formyl proton as a 17.4-Hz doublet at δ 9.76. For the *E* isomer, the previously noted trend of shielding of the HCO*H*$^+$ (δ ~14.3) and deshielding of the *H*COH$^+$ (δ ~10.1) compared

(13) Jost, R.; Sommer, J. *Rev. Chem. Intermed.* **1988**, *9*, 171.
(14) The HCOH$^+$ signal in monoprotonated *p*-methoxybenzaldehyde is at 193.4 ppm (FSO_3H). A second protonation at OMe (1:1 SbF_5–FSO_3H) shifts this absorption to 205.5 ppm (see ref 12b).

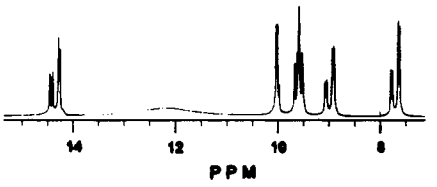
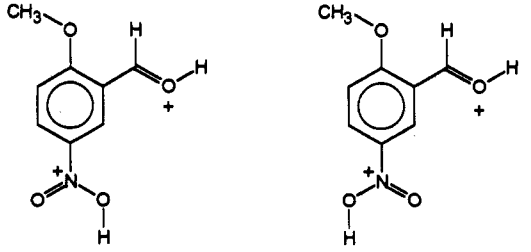
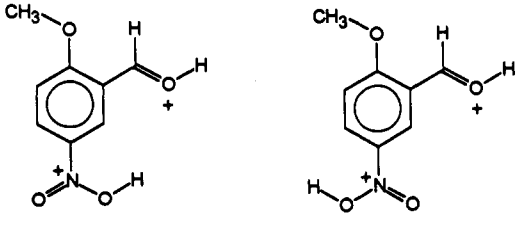


Figure 3. Spectrum of same mixture as in Figure 2, but at −45 °C where exchange of all NO_2H^+ protons with acid protons is fast.

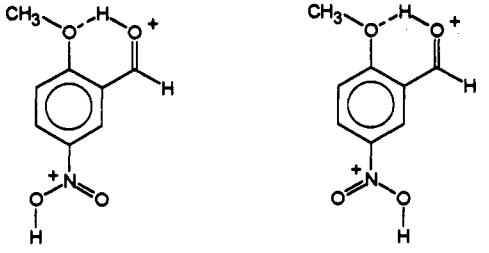
with the *Z* isomer is apparent. However, the HCO*H*$^+$ signal for the *E* isomer is more complex than the simple doublet expected for a single isomer. The reason for the complexity is shown to be isomeric protonation of the nitro group by the occurrence of *four* NO_2H^+ signals near δ 15.7: two major and two minor (Figure 2). Presumably, these correspond to the principal isomeric forms **10a** and **10b**, and lesser forms **10c** and **10d**, all of *E*,anti configuration in the carboxonium group. The *Z* isomer also shows two NO_2H^+ signals at δ ~16.3 for **11a** and **11b**, but these signals are broadened by faster exchange with the acid. (The nitro group would be less basic when the methoxy is H-bonded to the carboxonium group.) The pattern of signals for the aromatic protons is also complex, reflecting the additional isomeric forms.



10a **10b**



10c **10d**

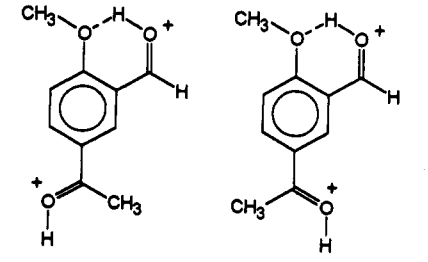


11a **11b**

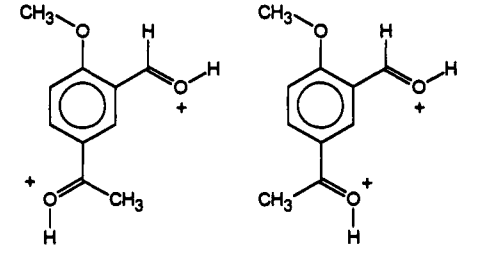
Considerable simplification is seen in a ^1H spectrum taken at −45 °C, Figure 3. The acid and all NO_2H^+ protons are exchanging rapidly, leading to a very broad, averaged signal centered at 12 ppm. The protons of the carboxonium groups are not rapidly exchanging; in fact, their signals are more sharply defined, with a clear doublet now for the HCO*H*$^+$ resonance of the *E* isomer at δ 14.4. The aromatic pattern is simplified, with a single resonance for each proton in the *Z* and *E* isomers. The *Z*/*E* ratio is essentially unchanged, at *Z*/*E* = 0.52.

A ^{13}C NMR spectrum at −60 °C of the **10** and **11** mixture also reflects the *Z* and *E* isomerism of the carboxonium group, isomeric protonation of the nitro group, and intermediate rate of exchange of the NO_2H^+ protons. Signals for the *Z* and *E* forms are apparent, with two distinct methoxy signals at δ_C 64.1 and 62.5 (*Z* and *E*, respectively) and two C2 peaks at 180 and 177 ppm. Clusters of signals, some broad, are present for other ring carbons at δ_C 143–147, 135–138, and 118–122, and for $HCOH^+$ at 203–205.

The ^1H NMR spectrum for protonated 5-acetyl-2-methoxybenzaldehyde at −70 °C shows four isomeric dications generated by protonation of both carbonyls. The ratio of *Z* isomers (**12a** and **12b**) to *E* isomers (**13a** and **13b**) for protonation at the formyl group is estimated at *Z*/*E* = 2.0, based on integration of HCO*H*$^+$ and $C(CH_3)$-O*H*$^+$ signals, or 2.35, based on O*C*H_3 and $C(CH_3)OH^+$ signals. While the assignments (see below) within the category of *Z* or *E* isomer is firmly based on the vicinal couplings in the $HCOH^+$ group, the final assignments of individual isomers are tentative. If the assignments are correct, the approximate composition of the mixture is 42% **12a**, 24% **12b**, 24% **13a**, and 10% **13b**.



12a **12b**



13a **13b**

Two HCO*H*$^+$ doublets for *Z* isomers at 14.34 and 14.46 ppm are present in the spectrum of the dication in ca. 2:1 ratio (**12a** and **12b**). Two HCO*H*$^+$ doublets for *E* isomers also appeared, at 13.60 and 13.72 ppm and in a 3:1 ratio (**13a** and **13b**). Four $C(CH_3)O\mathit{H}^+$ singlets are evident: the largest at δ 13.80 (**12a**), two of nearly equal size at 13.74 and 13.44 (**12b** and **13a**), and the smallest at 13.36 (**13b**). The configuration of $C(CH_3)OH^+$ had no effect on the H3 signals, as only two simple doublets were observed. The remaining ring protons gave a complex pattern between 9 and 9.6 ppm; however, it is this group that allows tentative assignment of the structures. Between δ 9.3 and 9.6 are four broad singlets arising from H6, the largest being in the most upfield position, and the smallest in the most downfield. It is also clear that the largest H4 doublet is most downfield (δ ~9.2). Assuming that the proximal

Table II. AM1 Calculations on Formyl Protonated 5-Substituted o-Anisaldehydes

substituent	isomer	H_f, kcal/mol	OCH_3 charge	COH^+ charge
H	Z,syn	112.32	−0.2435	0.2996
	Z,anti	114.28	−0.2002	0.2760
	E,syn	117.34	−0.1649	0.2828
	E,anti	115.68	−0.2041	0.2902
Br	Z,syn	121.08	−0.2411	0.3007
	Z,anti	122.98	−0.1974	0.2784
	E,syn	125.91	−0.1622	0.2854
	E,anti	124.32	−0.2013	0.2928
F	Z,syn	73.10	−0.2415	0.3020
	Z,anti	74.79	−0.1967	0.2803
	E,syn	77.83	−0.1613	0.2866
	E,anti	76.38	−0.2010	0.2938
CF_3	Z,syn	−35.66	−0.2396	0.3026
	Z,anti	−33.75	−0.1960	0.2811
	E,syn	−31.05	−0.1612	0.2894
	E,anti	−32.63	−0.1996	0.2971
CNH^+	Z,syn	390.66	−0.2208	0.3203
	Z,anti	394.12	−0.1713	0.2868
	E,syn	393.06	−0.1397	0.3217
	E,anti	390.78	−0.1746	0.3294
$C(CH_3)OH^+$	Z,syn	313.93	−0.2180	0.3192
	Z,anti	317.05	−0.1688	0.2896
	E,syn	316.21	−0.1379	0.3223
	E,anti	314.14	−0.1724	0.3294
NO_2H^+	Z,syn	376.23	−0.2145	0.3232
	Z,anti	379.41	−0.1645	0.2941
	E,syn	378.03	−0.1340	0.3293
	E,anti	375.87	−0.1678	0.3370
OCF_3[a]	Z,syn	−41.52	−0.3262	0.3063
	Z,anti	−39.20	−0.2853	0.2811
	E,syn	−36.44	−0.2531	0.2914
	E,anti	−38.20	−0.2872	0.2981

[a] No 5-substituent; 2-(trifluoromethoxy)benzaldehyde.

deshielding effect of the protonated carbonyl bond on an ortho proton is larger than that of the methyl group in $C(CH_3)OH^+$, the most abundant isomer can be assigned as **12a** and the least abundant as **13b**.

The protonation of 2-(trifluoromethoxy)benzaldehyde shows the influence of electron depletion at oxygen by the CF_3 group. The ^1H NMR spectrum at −70 °C exhibits distinctive signals indicative of a carboxonium ion in the *E* configuration. About 1% of a *Z* isomer may be present, as indicated by very small additional peaks (e.g., δ 12.95, d, J = 18 Hz).

(b) AM1 Calculations. The influence of substituents at C5 on the relative stability of possible configurations of formyl-protonated *o*-anisaldehydes was also assessed in a theoretical study with the AM1 semiempirical molecular orbital method.[15] As noted earlier, four types of structures are possible: *Z*,syn, *Z*,anti, *E*,anti, and *E*,syn. AM1 calculations with geometry optimization were performed on each structural type for all of the substituents (5-H, 5-F, 5-Br, 5-CF_3, 5-CNH^+, 5-$C(CH_3)OH^+$, and 5-NO_2H^+) included in the experimental study. The protonated forms of 2-(trifluoromethoxy)benzaldehyde were also examined. The predicted heats of formation, H_f, are summarized in Table II, along with the electronic charges on the methoxyl oxygen and hydroxyl proton ($HCOH^+$). Furthermore, calculations were carried out on the syn and anti forms of the unprotonated *o*-anisaldehydes (protonated substituents were left in protonated form).

For unprotonated *o*-anisaldehydes, the anti form is consistently predicted to be more stable (lower H_f) than the syn form by 2.5–3.3 kcal/mol. In contrast, the syn form with the *Z* configuration was the most stable structure for all but one of the protonated aldehydes. For the set of protonated *o*-anisaldehydes with uncharged substituents, the predicted order of stability from most to least stable is *Z*,syn > *Z*,anti > *E*,anti > *E*,syn, with a 1–3 kcal/mol gap between structures in the sequence. The same order is predicted for protonated 2-(trifluoromethoxy)-benzaldehyde. In changing to the highly electron-withdrawing cationic substituents, the *Z*,syn and *E*,anti structures become nearly equal in energy while the *Z*,anti form becomes the least stable form. The calculations predict that the *E*,anti structure is favored by 0.4 kcal/mol for the 5-NO_2H^+ substituent, the only such case.

The electron density (Mulliken population analysis) on the methoxyl oxygen is higher by 0.04–0.05 for the *Z*,syn form than for the other isomers, with all substituents. Presumably, this reflects polarization of electron density toward the hydroxyl proton in the hydrogen-bonded *Z*,syn cations. The oxygen electron density responds to substituents, being highest for the unsubstituted cation and lowest for 5-NO_2H^+ in all isomers. The electron density on the hydroxyl proton responds similarly, being highest (lowest positive charge) for the unsubstituted cations and lowest for 5-NO_2H^+.

Discussion

Intramolecular hydrogen bonding seems to lower the energy of the *Z* form of protonated *o*-anisaldehydes. Indeed, under stable ion conditions, only the *Z* isomer was reported for protonation of the parent, unsubstituted *o*-anisaldehyde,[11] in contrast to only the *E* isomer for protonated *p*-anisaldehyde.[12] With 5-F and 5-Br substituents, the *Z* form is strongly favored over the *E* form. The *Z* structure is still favored with the 5-CF_3, 5-CNH^+, and 5-$C(CH_3)OH^+$ substituents, although less strongly so. With 5-NO_2H^+, the *E* form becomes more abundant. The *E* form is strongly favored in protonated 2-(trifluoromethoxy)benzaldehyde.

As determined from ^1H NMR spectra of protonated *o*-anisaldehydes, the approximate *Z*/*E* ratios associated with the various substituents are 5-H, ≥100; 5-F, 99; 5-Br, 49; 5-CF_3, 10; 5-CNH^+, 2.4; 5-$C(CH_3)OH^+$, 2.17; and 5-NO_2H^+, 0.48. Thus, a clear trend away from the *Z* form and eventually favoring the *E* form is seen as 5-substituents become increasingly electron-withdrawing. This trend is expected as diminishing the electron-donor character of the methoxyl oxygen would make the methoxyl group less suitable as a H-bond acceptor.

The *Z* configuration is clearly identified by a large (15–18 Hz) trans $HCOH^+$ coupling. That the favored configuration is *Z*,syn, with H-bonding of the hydroxyl proton to the methoxyl oxygen, is consistent with the small variation in chemical shift of the hydroxyl proton with substituents, in contrast with previous reports for para-substituted benzaldehydes having the *E* configuration.[10] The other observed isomer for protonated *o*-anisaldehydes is the *E*,anti structure, indicated by cis $HCOH^+$ coupling (8–10 Hz) and relative deshielding of H6. In the *E*,anti structures, the chemical shift of the hydroxyl proton does vary with substituents.

Predictions from AM1 calculations are in qualitative agreement in several respects with the experiments. Most notably, the *Z*,syn form is predicted to be the favored

(15) Dewar, M. J. S.; Zobisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(16) Olah, G. A.; White, A. M. *J. Am. Chem. Soc.* **1967**, *89*, 3591.
(17) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

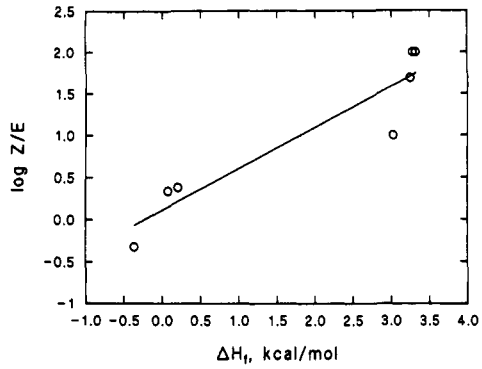


Figure 4. Plot of log Z/E ratio observed in protonated *o*-anisaldehydes vs the difference in heats of formation between Z,syn and E,anti isomers calculated by the AM1 method. Linear relation is log $Z/E = 0.492\Delta H_f + 0.1$, with correlation coefficient = 0.936.

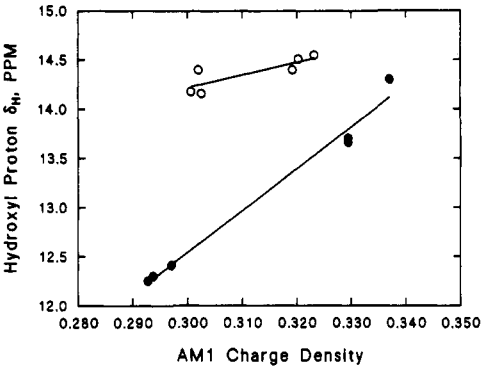


Figure 5. Plot of chemical shift of hydroxyl proton, HCOH^+, vs charge on proton from AM1 calculations. Lower line is for E,anti isomer series: $\delta_H = 42.6q-0.2$, correlation coefficient = 0.992. Upper line is for Z,syn series: $\delta_H = 12.9q-10.4$, correlation coefficient, = 0.832.

isomer except for the 5-NO_2H^+ substituent, where the E,anti form is predicted to be most stable. Quantitative correlation is only fair, as shown in Figure 4, where log Z/E is plotted vs the predicted differences, ΔH_f, in energy content of the Z,syn and E,anti isomers (correlation coefficient = 0.938). The most deviant point is the one for 5-CF_3 that falls well below the correlation line. The AM1 calculations predict little difference in Z/E ratio for the 5-CF_3 cations compared to 5-H or 5-F. The AM1 calculations also fail to predict the change in the Z/E ratio to favor E for protonated 2-(trifluoromethyl)benzaldehyde. Thus, the AM1 calculations may be failing to fully represent the electron-withdrawing character of the trifluoromethyl group.

The AM1 calculations indicate that the anti configuration of the unprotonated *o*-anisaldehydes is favored. The switch in relative stabilities to favor the Z,syn form for the protonated aldehydes is clearly attributable to intramolecular H-bonding in the Z,syn structures. The relative stability of the Z,syn form is reduced by a diminished capacity of the methoxyl oxygen to act as a hydrogen bond acceptor as electron withdrawal from the oxygen by the substituents increases (see Table II).

It is interesting to note that the chemical shift of the hydroxyl proton of the $HCOH^+$ group in the E,anti isomers is well correlated with the electronic charge on the proton in the AM1 calculations. Figure 5 shows a plot of the hydroxyl proton shift vs charge. Also plotted in Figure 5 are the hydroxyl proton chemical shifts of the Z,syn isomers. While the calculations do show a reduced range of electronic charge, the actual variation in chemical shift of this H-bonded proton is even further reduced as clearly seen in a comparison of slopes for the correlation lines of the two types of hydroxyl protons.

In summary, electronic control of intramolecular hydrogen bonding by potent electron-withdrawing substituents at C5 in the persistent carboxonium ions derived from *o*-anisaldehydes has been demonstrated.

Experimental Section

Materials. FSO_3H (Allied) and SbF_5 (Aldrich) were distilled twice under dry nitrogen in an all-glass distillation unit prior to use. Anhydrous SO_2 (Linde) and doubly distilled SO_2ClF (Aldrich) were used as received. FSO_3H–SbF_5 (1:1) was prepared by direct transfer of SbF_5 (27.62 g, 127.4 mmol) under a fast flow of dry nitrogen into a dried Nalgene bottle and by subsequent slow addition of FSO_3H (12.74 g; 1 molar equiv) which had been transferred into a second Nalgene bottle under nitrogen. The mixture was vortexed until homogeneous (*exothermic*!) to give 32.58 g of "magic acid" as a colorless liquid.

All reagents used in syntheses of the 5-substituted *o*-anisaldehydes were high-purity commercial samples. THF and DMF were rigorously dried. $AlCl_3$ (anhydrous; Aldrich) was used as received. 2-(Trifluoromethoxy)benzaldehyde (Maybridge; UK) was used without further purification.

Spectra. The low-temperature NMR spectra of the ion solutions were run on a GN-300 wide-bore instrument. The probe was cooled to the desired temperature while shimming on an acetone-d_6 sample; the cold ion solution was quickly inserted into the cold probe, and the sample was spun for 3–4 min prior to data collection. The ambient NMR spectra of the aldehydes were recorded on the GN-300, and Varian Gemini 200, VXR 300, and EM360 NMR instruments using $CDCl_3$ as solvent and referenced to $CHCl_3$ (δ_H 7.24) or $CDCl_3$ (δ_C 77.00). IR spectra were recorded for Nujol mulls with a Perkin-Elmer 1310 infrared spectrophotometer except for 5-nitro-2-methoxybenzaldehyde which was run as a chloroform solution.

General Procedure for Generation of Ions. To a slurry of the aldehyde (ca. 30 mg) in 0.5 mL of cold SO_2 or SO_2ClF inside a 10-mm NMR tube was added a clear solution of ca. 1–1.3 mL (1.2–1.8 g) of the superacid diluted with ca. 1 mL of SO_2 (or SO_2ClF) with efficient vortex mixing at dry ice/acetone temperature. A cold aliquot of the ion solution was slowly transferred (either via a precooled pipet [liquid SO_2] or directly) into a 5-mm NMR tube immersed in a dry ice/acetone bath, and 6–7 drops of cold CD_2Cl_2 was then added (vortex mixing) as internal standard and lock. The superacid to substrate molar ratios were typically 16–30. For the carbon spectra more concentrated ion solutions were used. In a typical experiment, 122 mg (0.67 mmol) of 5-nitro-2-methoxybenzaldehyde was protonated with 2.21 g of magic acid as above, giving an acid:substrate molar ratio of 10.4.

5-Bromo-2-methoxybenzaldehyde. This compound was prepared from *o*-anisaldehyde (2.6 g, 20 mmol) and Br_2 (1.2 molar equiv) in glacial CH_3COOH. A portion (0.927 g) of the crude product was heated to dissolution in absolute EtOH (ca. 18–20 mL), and the solution was filtered, treated with H_2O (ca. 10 mL), and allowed to stand at rt. The material that separated was isolated (0.776 g) and recrystallized again from absolute EtOH (ca. 20 mL) with H_2O (5 mL), washed with 80% EtOH, and dried in air: pale yellow crystalline solid (0.573 g); mp 113.5–116.5 °C (lit.[18] mp 116–119 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 6.87 (d, J = 8.8 Hz, 1 H), 7.61 (dd, J = 8.9 and 2.6 Hz, 1 H), 7.90 (d, J = 2.6 Hz, 1 H), 10.36 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.87 (OMe), 113.28, 113.65, 125.87 (C-1), 130.79 (C-6), 138.18 (C-4), 160.61 (C-2), 188.25 (C=O); IR (Nujol) 1655 cm^{-1} (C=O).

5-Fluoro-2-methoxybenzaldehyde. A mixture of $BrCH_2$-CH_2Br (0.980 g, 5.22 mmol) and Mg turnings (1.227 g) in Et_2O (70 mL) was stirred at rt. When a black, powdery suspension started to develop (48 min), a solution of 2-bromo-4-fluoroanisole (6.157 g, 30.03 mmol) and $BrCH_2CH_2Br$ (1.986 g, 10.57 mmol) in

(18) Aldrich catalog 1990–1991; p 187.

Et_2O (40 mL) was added dropwise over 16 min (heat evolution). After 9 min at rt and 10 min at reflux, the reaction mixture was placed in an ice bath, and a solution of *N*-formylpiperidine (3.471 g, 30.67 mmol) in Et_2O (40 mL) was slowly (ca. 14 min) introduced. A black gum separated from the solvent. After 21 min at rt, the Et_2O phase was decanted into cold, aqueous HCl (15 mL of concd HCl, 150 mL of H_2O, cracked ice), more Et_2O (100 mL) was added, and the Et_2O layer was isolated. The "plaque" that remained in the reaction vessel was treated with the aqueous HCl layer whereupon it "dissolved", and a yellow oil rose to the surface. The mixture was extracted with Et_2O (200 mL), and the extract and original Et_2O layer (above) were combined, washed (satd $NaHCO_3$, satd NaCl), dried ($MgSO_4$), and concentrated to a yellow oil (4.261 g). The oil (~4 g) was treated with hot hexanes (150 mL). The solution that resulted was decanted away from an insoluble yellow component (10 mL of hexanes used for rinsing) and cooled (dry ice, dry ice/acetone). 2-Methoxy-5-fluorobenzaldehyde separated as an oily, pale yellow solid: yield, 1.999 g (43%). Recrystallization of the crude aldehyde (ca. 1.79 g) from hexanes (150 mL) under similar conditions returned 1.31 g; mp 40.5–45.5 °C. The analytical sample was prepared by further recrystallization of this material (117 mg) from cold (dry ice) hexanes (15 mL); mp 42–43.5 °C (*minor* impurities still present); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 6.93 (dd, J_{HH} = 9.1 Hz, J_{HF} = 3.8 Hz, 1 H), 7.17–7.29 (m, 1 H), 7.48 (dd, J_{HH} = 8.3 Hz, J_{HF} = 3.3 Hz, 1 H), 10.40 (d, J_{HF} = 3.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.04 (s, OMe), 113.09 (d, J_{CF} = 7.1 Hz, C-3), 113.78 (d, J_{CF} = 23.7 Hz, C-6), 122.36 (d, J_{CF} = 23.6 Hz, C-4), 125.26 (d, J_{CF} = 6.0 Hz, C-1), 156.71 (d, J_{CF} = 241.3 Hz, C-5), 158.05 (d, J_{CF} = 1.5 Hz, C-2), 188.60 (s, C=O); IR (Nujol) 1670 cm^{-1} (C=O). Anal. Calcd for $C_8H_7FO_2$: C, 62.34; H, 4.58. Found: C, 62.59; H, 4.60.

A distilled sample of the aldehyde from another prep (wet crystalline solid), when recrystallized from cold (dry ice) hexanes (10 mL), gave white cottony needles; mp 47–48 °C.

2-Methoxy-5-(trifluoromethyl)benzaldehyde. This compound was prepared by the sequential methylation and formylation[19] of *p*-(trifluoromethyl)phenol.

Step 1. A mixture of *p*-(trifluoromethyl)phenol (Aldrich, 4.047 g, 25.0 mmol), iodomethane (4.966 g, 35.0 mmol), and anhydrous K_2CO_3 (3.507 g, 25.4 mmol) in dry acetone (50 mL) was stirred and heated (8 h at reflux, ~12.25 h at rt, 7 h at reflux, 17 h at rt). The mixture was then filtered, to remove potassium salts, and the filtrate was concentrated. The residual liquid/solid mixture was taken up in Et_2O, and the solution was washed (10% NaOH, H_2O), dried ($MgSO_4$), and concentrated to a clean, nearly colorless oil (licorice odor) identified as *p*-(trifluoromethyl)anisole: yield, 3.59 g (81.5%); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 6.8–7.9 (AA'BB' m, 4 H).

Step 2. A solution of *n*-BuLi in hexanes (1.8 mL, 2.5 M) was added under N_2 to a cold (dry ice), stirred solution of *p*-(trifluoromethyl)anisole (0.665 g, 3.77 mmol) in dry THF (10 mL). After 30 min, the solution was placed in an ice bath, and after 1 h more, a solution of *N*-formylpiperidine (0.497 g, 4.39 mmol) in THF (10 mL) was slowly (22 min) introduced. The resulting pale yellow solution was kept for 1 h at rt and treated with chilled 2.5 N HCl (10 mL of concd HCl/40 mL of H_2O). The mixture was extracted with Et_2O (120 mL), and the organic layer was washed [H_2O (100 mL), satd $NaHCO_3$ (100 mL), satd NaCl (100 mL)], dried ($MgSO_4$), and concentrated to an oily, pale yellow crystalline solid (0.732 g). A solution of this material in absolute EtOH (25 mL) was filtered (to remove some particulate matter), treated with H_2O (20 mL), and refrigerated. [Initial storage of the solution at ca. 0 °C gave no crystals. The mixture was then kept at ca. −25 to −30 °C whereupon it froze. When it was allowed to thaw at rt, a solid component remained undissolved. After additional storage at ca. 0 °C, the mixture was filtered.] The fine, white needles that separated were isolated, washed with 50% EtOH, dried in air, and identified as 2-methoxy-5-(trifluoromethyl)benzaldehyde: yield, 0.318 g (41%); mp 84–86 °C. For elemental analysis, the crude aldehyde (from another prep) was recrystallized twice from aqueous ethanol and sublimed in vacuo (~40–60 °C): white crystalline solid; mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.78 (dd, J = 8.8 and 2.5 Hz, 1 H), 8.08 (d, J = 2.4 Hz, 1 H), 10.45 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.99 (OMe), 112.09 (C-3), 123.06 (Q, J_{CF} = 33.6 Hz, C-5), 123.76 (Q, J_{CF} = 271.3 Hz, CF_3), 124.44 (C-1), 125.76 (Q, J_{CF} = 3.9 Hz, C-6), 132.44 (Q, J_{CF} = 3.6 Hz, C-4), 163.65 (C-2), 188.37 (C=O); IR (Nujol) 1670 cm^{-1} (C=O). Anal. Calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 52.86; H, 3.39.

In another experiment, the aldehyde was prepared by treatment of a mixture (~3:1, 2.48 g) of 2-bromo-4-(trifluoromethyl)anisole (7.90 mmol) and *p*-(trifluoromethyl)anisole first with Mg/$BrCH_2CH_2Br$ and then with *N*-formylpiperidine in Et_2O: straw-colored needles, 0.154 g; mp 83.5–86 °C.

2-Methoxy-5-cyanobenzaldehyde. This compound was prepared by the treatment of 2-methoxy-5-bromobenzaldehyde with CuCN in DMF (reflux). A portion (ca. 129 mg) of the crude product was subjected to preparative TLC on alumina (Anspec F-254, type T) with 50:50 (v/v) hexanes/EtOAc. The aldehyde was separated as a pale yellow solid: mp 118–119.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, OMe), 7.08 (d, J = 8.7 Hz), 7.80 (dd, J = 8.7 and 2.1 Hz), 8.10 (d, J = 2.1 Hz), 10.40 (s, CHO); unidentified impurity present; ^{13}C NMR ($CDCl_3$) δ 56.28 (OMe), 104.71 (C-5), 112.74 (C-3), 117.96 (C≡N), 125.13 (C-1), 132.94 (C-6), 138.99 (C-4), 164.12 (C-2), 187.56 (C=O); IR ($CHCl_3$) 1677 (C=O), 2202 cm^{-1} (C≡N).

2-Methoxy-5-nitrobenzaldehyde. Although this compound was prepared by HNO_3/H_2SO_4 nitration of *o*-anisaldehyde, the 3-nitro isomer was the major product. The yield of the 5-nitro compound was optimized by keeping the nitration mixture cold.

A mixture of 70% HNO_3 (22.33 g, 248 mmol of HNO_3) and concd H_2SO_4 (ca. 31 mL), precooled in an ice bath, was added dropwise (2.97 h, *exothermic*) to a stirred, dark red *solution* of *o*-anisaldehyde (20.45 g, 150.2 mmol) in concd H_2SO_4 (50 mL), initially cooled to −9 °C. Care was taken to keep the temperature of the reaction mixture ≤ 4 °C during the addition. The resulting solution was then allowed to warm to 13 °C and poured onto cracked ice whereupon a beige oil separated. The mixture was extracted with CH_2Cl_2 (250 mL), and the organic layer was washed (5% $NaHCO_3$, H_2O), dried ($MgSO_4$), and concentrated to a thick, yellow-orange oil (29.56 g) shown by 60-MHz ^{1}H NMR ($CDCl_3$) analysis to contain a mixture (~60:40) of 3-nitro- and 5-nitro-*o*-anisaldehydes. The oil was taken up in EtOAc (50 mL), and the solution was treated with hexanes (61–62 mL, close to the cloud-point) and refrigerated (~0 °C). The 5-nitro aldehyde separated (7.35 g, 27% yield) as an oily, pale yellow solid. Recrystallization from EtOAc (50 mL)/hexanes (55 mL) with cooling returned a brittle, off-white crystalline solid with a faint yellow hue: yield, 4.317 g; mp 75–79 °C [lit.[20] mp 88 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3 H), 7.11 (d, J = 9.3 Hz, 1 H), 8.40 (dd, J = 9.3 and 2.9 Hz, 1 H), 8.64 (d, J = 2.7 Hz, 1 H), 10.41 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.60 (OMe), 112.33 (C-3), 123.87, 124.14, 130.44 (C-4), 141.08 (C-5), 165.44 (C-2), 187.33 (C=O); IR (Nujol) 1667 cm^{-1} (C=O).

In one experiment, in which the temperature of the nitration mixture rose to 49 °C during the addition, the molar ratio of the 3-nitro and 5-nitro aldehydes was roughly 3.8/1.0.

2-Methoxy-5-acetylbenzaldehyde. Efforts to prepare this compound by the direct acetylation of *o*-anisaldehyde with either $Ac_2O/AlCl_3$ or CH_3CO^+, $SbCl_6^-$ in CH_2Cl_2 were unsuccessful. It was ultimately made from *o*-bromoanisole by acetylation at C-4, protection of the resulting ketone, formylation[19] of the C–Br bond, and deprotection.

Step 1. 3-Bromo-4-methoxyacetophenone (10.76 g) was prepared from *o*-bromoanisole (9.352 g, 50.0 mmol), Ac_2O (6.139 g, 60.1 mmol), and $AlCl_3$ (16.052 g, 120.4 mmol) in CH_2Cl_2. The crude solid (10.303 g) was taken up in absolute/EtOH (75 mL, heating required), and the solution was filtered (10 mL of EtOH for rinsing), treated with H_2O (50 mL), and kept for 15 min at rt and 1 h at ca. 0 °C. The white fibrous needles that separated were isolated, washed with 50% EtOH, and dried in air: 6.303 g; mp 86.5–87.5 °C. The filtrate was allowed to evaporate to dryness, and the residual material was recrystallized in similar fashion from abs EtOH (35 mL) and H_2O (30 mL): 1.487 g; mp

(19) Olah, G. A.; Arvanaghi, M. *Angew. Chem., Int. Ed. Engl.* 1981, *20*, 878.

(20) *Beilstein 8*, 57.

85–87 °C; combined yield of *recrystallized* material, 7.790 g (68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3 H), 3.95 (s, 3 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.90 (dd, J = 8.7, 2.2 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 26.25, 56.42, 111.01, 111.78, 129.43, 131.13, 133.75, 159.49, 195.56.

Step 2. The above ketone (2.316 g, 10.1 mmol) was treated with ethylene glycol (37.6 g) and *p*-TsOH·H_2O (0.309 g) in benzene (130 mL) under reflux, the water being removed with a Dean–Stark trap. Workup gave the ethylene ketal as a yellow oil (2.79 g, ~4 mass % benzene) which was used without further purification. It is noted that a sample of the ketal from another prep crystallized.

Step 3. A solution of *n*-BuLi in hexanes (2.5 M, ca. 3.6 mL) was added under N_2 to a cold (dry ice), stirred solution of 3-bromo-4-methoxyacetophenone ethylene ketal (96 mass %, 2.41 g, 8.47 mmol) in dry THF (12 mL). After 10–15 min, the solution was placed in an ice bath, and after 1 h more, a solution of *N*-formylpiperidine (1.038 g, 9.17 mmol) in THF (12 mL) was slowly (25 min) introduced. The resulting solution was kept for 1.28 h at rt and treated with cold, 2.5 N HCl (20 mL of concd HCl/80 mL of H_2O). The mixture was extracted with Et_2O (200 mL), and the organic layer was washed (H_2O, satd $NaHCO_3$, satd NaCl), dried ($MgSO_4$), and concentrated to an off-white solid, oily in spots; 1.118 g. The crude aldehyde (0.947 g) was taken up in $CHCl_3$ (12 mL), and the solution was treated with Et_2O (25 mL) and allowed to stand at rt (~2–3 h); a crystalline solid separated. After storage at 0 to −3 °C and additional cooling at −25 to −30 °C, the mixture was filtered to give 2-methoxy-5-acetylbenzaldehyde as glistening white needles: yield, 0.4927 g (38% yield, based on portion recrystallized); mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.99 (s, 3 H), 7.05 (d, J = 8.7 Hz, 1 H), 8.20 (dd, J = 8.8 and 2.4 Hz, 1 H), 8.37 (d, J = 2.4 Hz, 1 H), 10.44 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.27 (Me), 56.03 (OMe), 111.80 (C-3), 123.95 (C-1), 129.35, 129.88, 135.59 (C-4), 164.83 (C-2), 188.80 (aldehyde C=O), 196.07 (ketone C=O); IR (Nujol) 1660 cm^{-1} (aldehyde and ketone C=O groups apparently superimposed). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.27; H, 5.50.

Acknowledgment. We thank Kent State University for research support, the Ohio Academic Challenge Program for the funds for the purchase of the GN-300 NMR, and Professor George Olah for his interest in our work and encouragement. We also thank Dr. Dale G. Ray III and Ms. Terri D. Stoner for recording some of the NMR spectra. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research.