Variable Electronic Properties of the $CSNMe_2$ Group

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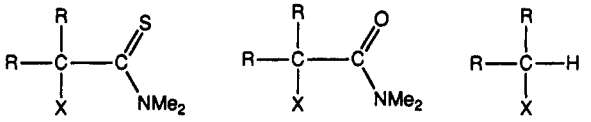
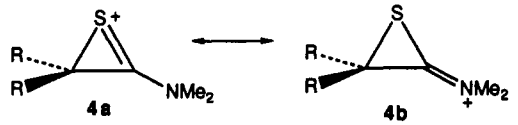
The σ_I value for the $CSNMe_2$ group has been determined and the value of 0.23 indicates that this group is inductively electron withdrawing. The effect of the *p*-$CSNMe_2$ group on the solvolysis rate of cumyl chloride has also been determined and, relative to the *p*-H analogue, this group has a negligible effect on rate. *p*-$CSNMe_2$ substitution slows the hydrolysis rate of substituted benzaldehyde dimethyl acetals. *p*-$CSNMe_2$ substitution enhances the solvolysis rate of $ArCH(OMs)PO(OEt)_2$. These variable rate effects on reactions involving cationic intermediates have been interpreted in terms of variable electronic properties of the $CSNMe_2$ group. This group can be cation stabilizing, electroneutral, or cation destabilizing, depending on the charge demands of specific cations. This is a result of a conjugative interaction of $CSNMe_2$ with a cationic center and resultant delocalization of positive charge onto sulfur. The importance of such conjugation is a function of the amount of transition-state charge developed on the carbon bearing the $CSNMe_2$ group. The electronic effects of the amphielectronic *p*-$CSNMe_2$ group are compared to the more conventional effects of $CONMe_2$ and the *m*-$CSNMe_2$ analogues.

In 1988 we reported on the effect of the thioamide group, $CSNMe_2$, on solvolytic reactions where this group was attached directly to a potential cationic center.[1] This study grew out of our interest in so called "electron deficient" carbocations, where a formally electron-withdrawing group is attached to a cationic center.[2] It was found that systems such as **1** underwent solvolysis at rates far in excess of the amide analogues **2** or the α-H analogues **3**. Two potential reasons were suggested for the rapid rates of reaction of the thioamides **1**. In certain systems, the



1 (X = Leaving Group) **2** **3**

thiocarbonyl group was found to be capable of neighboring group participation, leading to cyclized ions of type **4** and rearranged products. Large rate enhancements resulted from thiocarbonyl participation. The C=O group of **2** was not capable of such neighboring group participation. In other systems **1**, it was proposed that, in the absence of neighboring group participation, the thiocarbonyl group could become involved in extensive mesomeric stabilization of cationic intermediates as represented by **5b**. Such delocalization has also been supported by theoretical studies of Lien and Hopkinson[3]



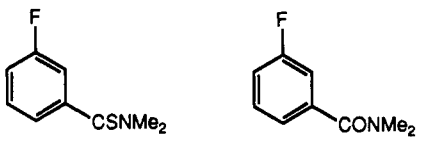
4a **4b**

5a **5b**

In this study we have examined the potential for mesomeric cation stabilization by the thioamide group in more detail. The approach has been to generate aryl-substituted carbocations containing the $CSNMe_2$ group on the aromatic ring. Reported here are the effects of the thioamide group on the rate of formation of such benzylic carbocations.

Results and Discussion

Effect of the $CSNMe_2$ Group on Cumyl Cation Formation Rates. Hammett σ values for the $CSNMe_2$ group have not been previously reported. However σ_I values for the closely related $CSNH_2$ and $CONH_2$ groups have been determined,[4] using the ^{19}F NMR method developed by Taft.[5] These groups, as indicated by identical σ_I values of 0.29, are inductively electron withdrawing. The $CSNMe_2$ group is expected to behave similarly and, indeed, the $CSNMe_2$ group is a very effective carbanion-stabilizing group.[6] We have therefore used ^{19}F NMR data on the *m*-fluoro derivatives **6** and **7** to determine σ_I values for $CSNMe_2$ and $CONMe_2$. The ^{19}F spectra of **6** and **7** show



6 **7**

respective signals at 1.012 and 1.024 ppm downfield from fluorobenzene. These chemical shifts correspond to σ_I values of 0.23 for both $CSNMe_2$ and $CONMe_2$ and indicate that these two groups are slightly less electron withdrawing than the $CSNH_2$ and $CONH_2$ analogues. We next wanted to determine the σ^+ value for the $CSNMe_2$ substituent in order to determine if fundamental differences exist between σ_I and σ^+ values. The requisite substituted cumyl chlorides for determination of σ^+ values[6] (both meta and para isomers) were prepared by starting with the corresponding bromocumyl alcohols **8m** and **8p**. Conversion to the methyl ethers **9m** and **9p** followed by lithium-halogen exchange and reaction with *N,N*-dimethyl thiocarbamoyl chloride gave the methyl ethers **10m** and **10p**. Reaction with HCl in methylene chloride led smoothly to the requisite cumyl chlorides **11m** and **11p**. For comparison purposes, the corresponding amide analogues **12m** and **12p**

(1) Creary, X.; Aldridge, T. E. *J. Org. Chem.* **1988**, *53*, 3888.
(2) For leading references, see: Creary, X.; Mehrsheikh-Mohammadi, M. E.; Eggers, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 2435.
(3) (a) Lien, M. H.; Hopkinson, A. C. *J. Am. Chem. Soc.* **1988**, *110*, 3788. For a report on the generation of **5** (R = aryl) under stable ion conditions, see: (b) Ablenas, F. J.; George, B. E.; Maleki, M.; Jain, R.; Hopkinson, A. C.; Lee-Ruff, E. *Can. J. Chem.* **1987**, *65*, 1800.
(4) Brownlee, R. T. C.; Sadek, M. *Aust. J. Chem.* **1981**, *34*, 1593.
(5) Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Andersen, K. K.; Davis, G. T. *J. Am. Chem. Soc.* **1963**, *85*, 709.
(6) For leading references, see: (a) Schuijl, P. J.; Bos, H. J. T.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 123. (b) Tamura, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631. (c) Tamura, Y.; Harada, T.; Iwamoto, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 5221.
(7) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

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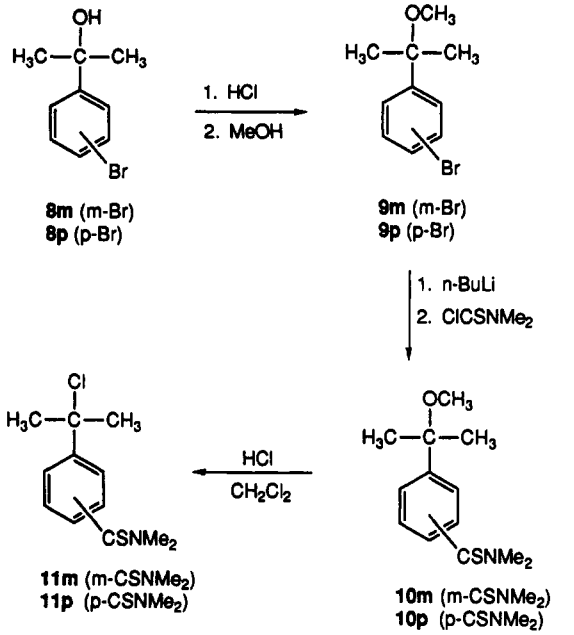
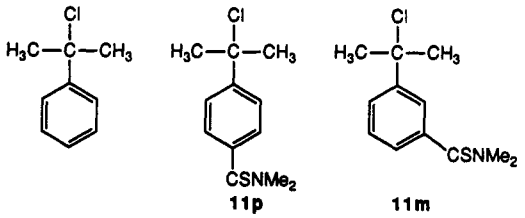
were also prepared by an analogous sequence employing $ClCONMe_2$.



8m (m-Br) **8p** (p-Br) **9m** (m-Br) **9p** (p-Br)

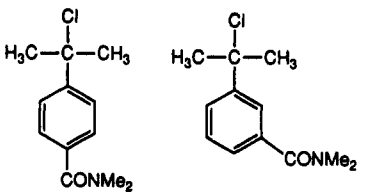
11m (m-$CSNMe_2$) **11p** (p-$CSNMe_2$) **10m** (m-$CSNMe_2$) **10p** (p-$CSNMe_2$)

Rates of solvolysis of the substituted cumyl chlorides were determined in ethanol and these rate data (Table I) were used to determine σ^+ values. The $CONMe_2$ group slows the solvolysis rate in both the meta and para positions. The *m*-$CSNMe_2$ group is also rate retarding, but



11p **11m**

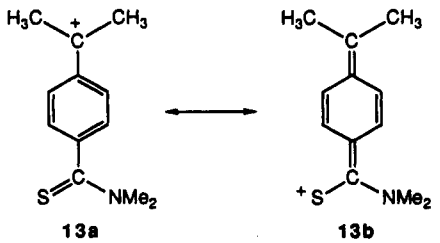
Relative Solvolysis Rate in Ethanol (σ^+)	1.00 (0.00)	1.07 (-0.01)	0.16 (0.17)



12p **12m**

Relative Solvolysis Rate in Ethanol (σ^+)	0.073 (0.24)	0.061 (0.26)

less so than the *m*-$CONMe_2$ analogue. The interesting feature is the behavior of the *p*-$CSNMe_2$-substituted system **11p**, which shows reactivity comparable to the unsubstituted cumyl chloride. It appears that the inductive destabilizing effect of *p*-$CSNMe_2$ is precisely offset by a stabilizing resonance interaction as represented in **13b**. This group is therefore classified as electroneutral with respect to a cumyl cation.



13a **13b**

Table I. Solvolysis Rates in Various Solvents at 25 °C

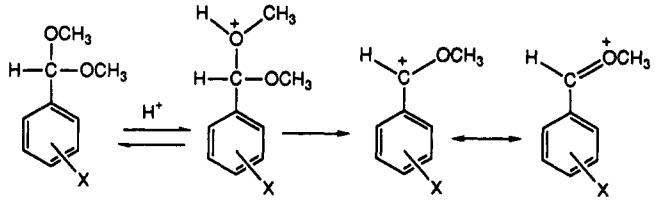
substrate	solvent	k, s^{-1}
$PhC(CH_3)_2Cl$	CH_3OH	5.23×10^{-3}
$PhC(CH_3)_2Cl$	EtOH	3.69×10^{-4}
11p	CH_3OH	4.29×10^{-3}
11p	EtOH	3.96×10^{-4}
11m	EtOH	6.02×10^{-5}
12p	EtOH	2.69×10^{-5}
12m	EtOH	2.25×10^{-5}
$PhCH(OMs)PO(OEt)_2$[a]	HOAc (70 °C)	1.85×10^{-6}
$PhCH(OMs)PO(OEt)_2$[a]	HCO_2H	3.59×10^{-6}
$PhCH(OMs)PO(OEt)_2$[a]	CF_3CH_2OH (80 °C)	1.51×10^{-4}
23p	HOAc (70 °C)	9.49×10^{-5}
23p	HCO_2H	4.14×10^{-5}
23m	CF_3CH_2OH (80 °C)	5.60×10^{-6}
$PhCH(CH_3)Cl$	CH_3OH	1.72×10^{-6}
26p	CH_3OH	2.62×10^{-6}
26m	CH_3OH	2.82×10^{-7}

[a] Data from ref 11.

Table II. Hydrolysis Rates of Benzaldehyde Dimethyl Acetals in 10^{-3} M HCl at 25 °C

substituent	k, s^{-1}
p-H	3.01×10^{-2}
p-$CSNMe_2$ (**19p**)	6.71×10^{-3}
m-$CSNMe_2$ (**19m**)	2.93×10^{-3}
p-Cl	1.01×10^{-2}

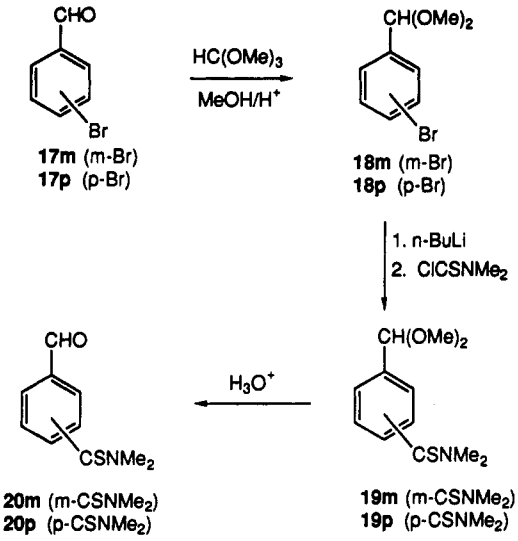
Effect of the $CSNMe_2$ Group on Acetal Hydrolysis Rates. In view of the fact that the $CSNMe_2$ group inductive effect can be "neutralized" under appropriate conditions, we wanted to determine what the effect would be on the rate of formation of a benzylic cation that was greatly stabilized by an additional group, i.e., a directly attached methoxy group. Acetal hydrolysis provides such a test. Hydrolysis of a series of acetal derivatives of substituted benzaldehydes **14** has been investigated and the reaction proceeds via the methoxy-substituted cation **16**.[8] Formation of carbocations such as **16** is generally considered to be rate limiting,[9] although protonation and loss of alcohol may be a concerted process.[10] In any case, substituents that are electron withdrawing slow hydrolysis rates and electron-donor groups enhance rates.[8,10] Simple correlation with neither σ nor σ^+ values are completely satisfactory. This is presumably due to the extensive charge delocalization in **16** involving the methoxy group (i.e. **16b**), which lessens the demand for stabilization by additional aryl substituents.



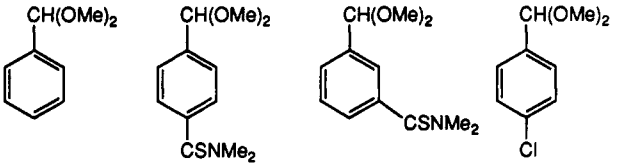
14 **15** **16a** **16b**

We have prepared the acetals **19m** and **19p** by a sequence involving lithium–halogen exchange on the acetals **18**, followed by reaction with *N,N*-dimethylthiocarbamoyl chloride. Hydrolyses of these acetals to the corresponding aldehydes **20m** and **20p** were monitored by ultraviolet spectroscopy and rate constants in 10^{-3} M HCl were de-

(8) Young, P. R.; Bogseth, R. C.; Reitz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268.
(9) (a) Cordes, H.; Bull, H. G. *Chem. Rev* **1974**, *74*, 581. (b) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1.
(10) (a) Capon, B.; Nimmo, K. J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113. (b) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672. (c) Jensen, J. L.; Yamaguchi, K. S. *J. Org. Chem.* **1984**, *49*, 2613.

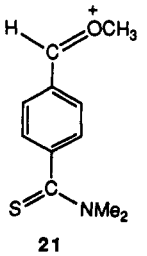


termined. Rate data (Table II) are shown, along with data for related substrates under identical conditions.



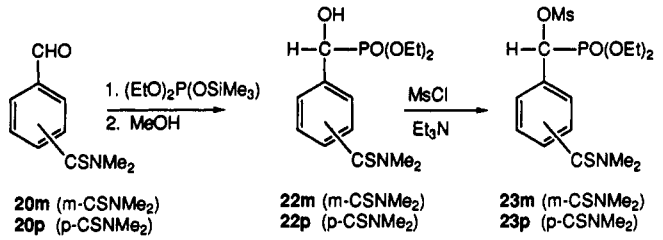
Relative Hydrolysis Rates

The hydrolysis rate of the m-$CSNMe_2$-substituted acetal **19m** is slowed relative to the unsubstituted analogue. This is expected for an electron-withdrawing substituent. The p-$CSNMe_2$ group also *slows the hydrolysis rate of* ***19p***. This indicates that the p-$CSNMe_2$ group is a cation-destabilizing substituent in the acetal hydrolysis reaction, but not as destabilizing as the m-$CSNMe_2$ group. The rate-retarding effect of p-$CSNMe_2$ is slightly greater than that of the p-Cl substituent. It appears that in acetal hydrolysis, the inductive destabilizing effect of p-$CSNME_2$ is not completely offset by a stabilizing resonance interaction. This reflects the decreased demand for C=S mesomeric stabilization in the relatively stable intermediate **21**, where charge is extensively delocalized onto the methoxy group. The p-$CSNMe_2$ group hence exerts less of its mesomeric character (than in the solvolysis reaction leading to cumyl cation **13**) since the demand for such stabilization in **21** is relatively small.

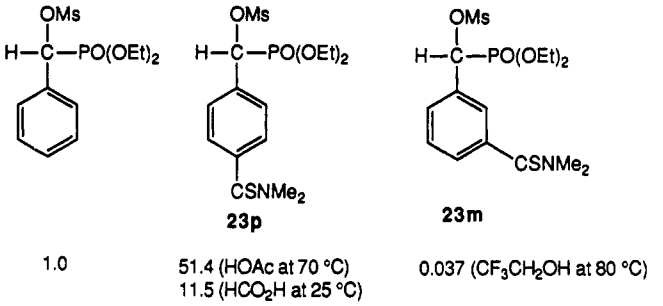


21

Effect of the $CSNMe_2$ Group on an Electron-Deficient Carbocation. The studies on the cumyl chloride **11p** and acetal **19p** have demonstrated the ability of p-$CSNMe_2$ to behave as an electroneutral substituent as well as an electron-withdrawing (destabilizing) group with respect to a developing cationic center. The mesylates **23m** and **23p** were therefore prepared in order to determine the effect of the p-$CSNMe_2$ group on carbocations under conditions of increased electron demand. These mesylates were prepared by condensation of aldehydes **20** with diethyl trimethylsilyl phosphite followed by desilylation. Conversion of the α-hydroxy phosphonates **22m** and **22p** to the mesylates **23m** and **23p** using mesyl chloride and triethylamine was straightforward.

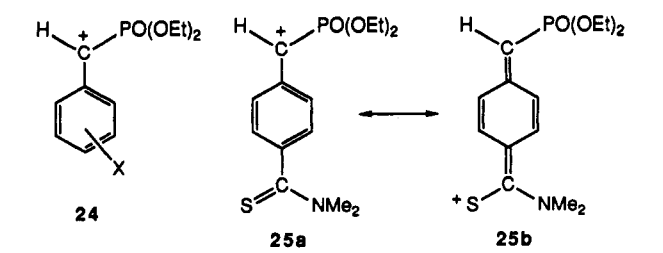


Relative solvolysis rate data are shown. Although **23p** disappeared readily in trifluoroethanol at 70 °C (half-life = 9.6 min), a complex product mixture was formed. Rates of **23p** were therefore determined in acetic and formic acid, where the simple substitution products were formed. Our previous studies[11] have shown that analogues of **23** solvolyze via "electron-deficient" cations **24**, where the electron-withdrawing $PO(OEt)_2$ group is attached directly to the developing cationic center. In the solvolysis of **23m** (which proceeds cleanly in trifluoroethanol), the effect of the m-$CSNMe_2$ group in **23m** is to retard the solvolysis rate relative to the p-H analogue (as is expected for a meta electron-withdrawing substituent). However, the p-



Relative Solvolysis Rates

$CSNMe_2$-substituted system **23p** is *more reactive than the unsubstituted analogue*. This indicates that the p-$CSNMe_2$ group is net stabilizing if the cation carries a directly attached $PO(OEt)_2$ group. This implies that the p-$CSNMe_2$ group in cation **25** is capable of exerting a stabilizing mesomeric effect that is larger than its destabilizing inductive effect. In other words, forms such as **25b** have increased importance due to extensive charge delocalization away from the benzylic and onto the para carbon atom. The σ^+ value of p-$CSNMe_2$ is therefore not a good measure of the cation-stabilizing ability of this group under conditions of high electron demand.



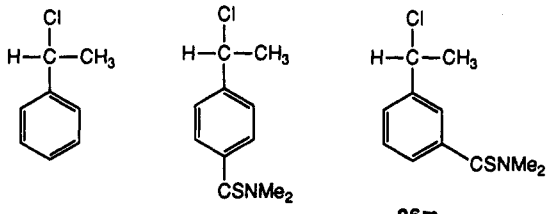
Effect of the $CSNMe_2$ Group on 1-Phenylethyl Cation Formation Rates. As a further test of the electronic nature of the $CSNMe_2$ group, data on a cation of

(11) (a) Creary, X.; Geiger, C. C.; Hilton, K. *J. Am. Chem. Soc.* **1983**, *105*, 2851. (b) Creary, X.; Underiner, T. L. *J. Org. Chem.* **1985**, 2165.

Table III. Effect of *p*- and *m*-$CSNMe_2$ Substituents on Carbocation-Forming Reactions

reaction	*p*/*m* rate ratio
acetal hydrolysis	2.3
cumyl chloride solvolyses	6.6
1-phenylethyl chloride solvolyses	9.3
solvolyses of phosphonates **23**	10^3

"intermediate" stability was desired. The stability of the secondary 1-phenylethyl cation[12] should lie between that of the cumyl cation and the electron-deficient α-phosphoryl cation **24**. The demand for $CSNMe_2$ conjugative stabilization in a para-substituted 1-phenylethyl cation should also be intermediate in magnitude. With this in mind, the chlorides **26p** and **26m** have been prepared and solvolyzed in methanol. The *p*-$CSNMe_2$-substituted system **26p**

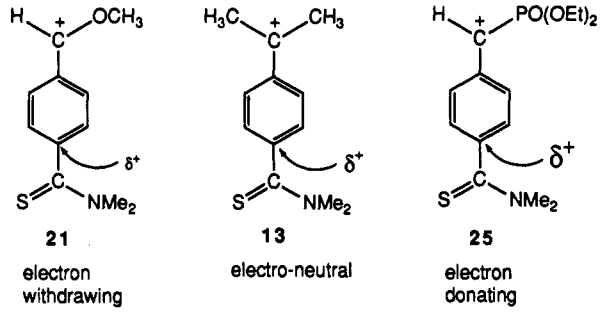


Relative Methanolysis Rates

reacts 1.52 times faster than unsubstituted 1-phenylethyl chloride in methanol. This modest rate increase provides further support for the suggested variable donor ability of the $CSNMe_2$ group. In the cation derived from **26p**, the *p*-$CSNMe_2$ group is apparently behaving as a net electron-donor group, but its donor ability is somewhat less than that in the electron-deficient cation **25a**. This is precisely what is expected for a group with variable stabilizing properties, but contrary to expectations based on a "static" σ^+ value for *p*-$CSNMe_2$. This is further emphasized by Table III, which summarizes p- and *m*-$CSNMe_2$ rate effects.

Conclusions. The effect of the thioamide group, *p*-$CSNMe_2$, on the rate of formation of benzylic-type cationic intermediates is quite variable. This substituent can be cation destabilizing, electroneutral, or stabilizing, depending on demand. The charge developed at the para carbon atom of the benzylic cation determines the electronic properties of this substituent. In the case of cation **21**, where the charge at the para carbon is small, the inductive effect of the $CSNMe_2$ group outweighs the mesomeric effect. In the case of the cation **13**, the charge at the para carbon is intermediate and hence the inductive and mesomeric stabilizing effects balance. In the case of the cation **25**, the charge at the para carbon is largest. Hence increased demand results in an increased stabilizing mesomeric effect and net cation stabilization by the *p*-$CSNMe_2$ group. Molecular orbital calculations have suggested that substituents can change their electronic character in response to changing electronic demand.[13]

The term *amphielectronic* has been used to describe such substituents. While the behavior of *p*-$CSNMe_2$ is reminiscent of the inductive destabilizing effect and the resonance stabilizing effect of the halogens on carbocations, there is an important distinction. The *net* effect of the halogens on benzylic cations can usually be described in terms of static σ^+ values while the behavior of *p*-$CSNMe_2$ is truly amphielectronic.



Experimental Section

NMR spectra were recorded on a General Electric GN 300 spectrometer. Mass spectra were recorded on a Finnigan MAT 8430 high-resolution spectrometer. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ. Tetrahydrofuran was distilled from sodium benzophenone ketyl. All reactions were carried out under a nitrogen atmosphere with magnetic stirring. Chromatographic purifications were carried out on EM Science 230–400-mesh silica gel 60.

Preparation of 3-(*N*,*N*-Dimethylthiocarbamoyl)fluorobenzene (6). A solution of 1.869 g of *m*-fluorobromobenzene in 20 mL of tetrahydrofuran was cooled to −78 °C and 7.0 mL of 1.6 M *n*-BuLi in hexanes was added dropwise to the stirred mixture. After 30 min at −78 °C, the mixture was transferred via a double-ended needle (using nitrogen pressure) to a −78 °C solution of 1.715 g of *N*,*N*-dimethylthiocarbamoyl chloride, $ClCSNMe_2$, in 20 mL of tetrahydrofuran. The mixture was slowly warmed to room temperature and water was added. The mixture was transferred to a separatory funnel with ether and the organic phase was washed with water and saturated NaCl solution and dried over $MgSO_4$. After solvent removal using a rotary evaporator, the residue was chromatographed on 18 g of silica gel. The product **6** (1.609 g; 82%) eluted with 40–60% ether in hexane: ^1H NMR ($CDCl_3$) δ 7.38–7.27 (m, 1 H), 7.09–6.97 (m, 3 H), 3.580 (s, 3 H), 3.158 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.31, 162.33 (d, J = 248 Hz), 145.21 (d, J = 7.4 Hz), 130.12 (d, J = 8.3 Hz), 121.38 (d, J = 2.9 Hz), 115.43 (d, J = 21.2 Hz), 113.18 (d, J = 23.2 Hz), 44.06, 43.13. Anal. Calcd for $C_9H_{10}FNS$: C, 58.99; H, 5.50; N, 7.64. Found: C, 59.24; H, 5.52; N, 7.82.

Preparation of 3-Fluoro-*N*,*N*-dimethylbenzamide (7). The preparation of **7**[14] (60% yield) using *N*,*N*-dimethylcarbamoyl chloride, $ClCONMe_2$, and *m*-fluorophenyllithium, was completely analogous to the preparation of **6**. **7**: ^1H NMR ($CDCl_3$) δ 7.42–7.33 (m, 1 H), 7.22–7.05 (m, 3 H), 3.099 (br s, 3 H), 2.980 (br s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.10 (d, J = 1.7 Hz), 162.50 (d, J = 248 Hz), 138.50 (d, J = 7.0 Hz), 130.17 (d, J = 7.9 Hz), 122.74 (d, J = 2.7 Hz), 116.50 (d, J = 21.2 Hz), 114.34 (d, J = 22.7 Hz), 39.45, 35.38.

Preparation of 2-(4-Bromophenyl)-2-methoxypropane (9p). A mixture of 6.70 g of *p*-bromocumyl alcohol[15] and 3 mL of CH_2Cl_2 was rapidly stirred at room temperature with 40 mL of concentrated hydrochloric acid for 5 h. The mixture was then extracted with CH_2Cl_2 and the organic extract was dried over $MgSO_4$. After filtration, the solvent was removed on a rotary evaporator. The crude 2-(4-bromophenyl)-2-chloropropane was dissolved in 130 mL of absolute methanol at room temperature. After 3 h, 1.3 g of pyridine in 6 mL of methanol was added. After an additional 4 h, another 1.3 g of pyridine in 6 mL of methanol was added.

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After 15 h, the solvent was removed on a rotary evaporator and the residue was taken up into ether and washed with water. The ether extract was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the residue was distilled to give 6.86g (96%) of **9p**, bp 65–67 °C (0.05 mm): ^1H NMR ($CDCl_3$) δ 7.46 and 7.28 (AA'BB' quartet, 4 H), 3.058 (s, 3 H), 1.500 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.16, 131.28, 127.67, 120.77, 76.45, 50.63, 27.82. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72. Found: C, 52.56; H, 5.70.

Preparation of 2-[4-(*N*,*N*-Dimethylthiocarbamoyl)phenyl]-2-methoxypropane (10p). A solution of 2.006 g of the bromide **9p** in 15 mL of tetrahydrofuran was cooled to −78 °C and 5.4 mL of 1.6 M *n*-BuLi in hexanes was added dropwise to the stirred mixture. After 30 min at −78 °C, the mixture was transferred via a double-ended needle (using nitrogen pressure) to a −78 °C solution of 1.299 g of *N*,*N*-dimethylthiocarbamoyl chloride, $ClCSNMe_2$, in 20 mL of tetrahydrofuran. The mixture was slowly warmed to room temperature and water was added. The mixture was transferred to a separatory funnel with ether and the organic phase was washed with water and saturated NaCl solution and dried over $MgSO_4$. After solvent removal on a rotary evaporator, the solid residue was chromatographed on 30 g of silica gel. The product **10p** (1.399 g; 67%), mp 83–85 °C, eluted with 50% ether in hexane: ^1H NMR ($CDCl_3$) δ 7.39 and 7.30 (AA'BB' quartet, 4 H), 3.61 (s, 3 H), 3.20 (s, 3 H), 3.09 (s, 3 H), 1.52 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.35, 146.77, 141.92, 125.80, 125.71, 76.61, 50.70, 44.17, 43.27, 27.84. Anal. Calcd for $C_{13}H_{19}NOS$:C, 65.78; H, 8.07; N, 5.90. Found: C, 65.49; H, 8.29; N, 6.04.

Preparation of 2-[4-(*N*,*N*-Dimethylthiocarbamoyl)phenyl]-2-chloropropane (11p). A solution of 0.175 g of the methyl ether **10p** in 5 mL of CH_2Cl_2 was cooled to 0 °C and HCl gas was bubbled through the solution for about 20 min. At this time NMR analysis of a small portion indicated that the reaction was complete. The solvent was removed on a rotary evaporator and the solid residue was washed with hexanes. The yield of **11p**, mp 84–85 °C, was 0.162 g (91%): ^1H NMR ($CDCl_3$) δ 7.56 and 7.30 (AA'BB' quartet, 4 H), 3.603 (s, 3 H), 3.191 (s, 3 H), 1.977 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 200.68, 146.60, 142.49, 125.70, 125.58, 69.16, 44.20, 43.23, 34.21; exact mass calcd for $C_{12}H_{16}ClNS$ 241.0692, found 241.0689.

Preparation of 2-[4-(*N*,*N*-Dimethylcarbamoyl)phenyl]-2-chloropropane (12p). 2-[4-(*N*,*N*-Dimethylcarbamoyl)-phenyl]-2-methoxypropane was prepared (62% yield) from 2-(4-lithiophenyl)-2-methoxypropane and *N*,*N*-dimethylcarbamoyl chloride, $ClCONMe_2$, using a procedure analogous to the preparation of **10p** described above.

A solution of 0.423 g of 2-[4-(*N*,*N*-dimethylcarbamoyl)-phenyl]-2-methoxypropane in 10 mL of CH_2Cl_2 was cooled to 15 °C and HCl gas was bubbled through the solution for about 2 h. At this time NMR analysis of a small portion indicated that the reaction was approximately 35–40% complete. HCl was then bubbled through the mixture for an additional 6 h at room temperature and additional CH_2Cl_2 was periodically added to replace the evaporated solvent. NMR analysis showed about 90% reaction. The solution was allowed to stand at room temperature for 24 h. The solvent was then removed on a rotary evaporator and the residue solidified on standing at −20 °C. The product was washed with hexanes and collected. The yield of **12p** (which is isolated as the hydrochloride salt), mp 59–73 °C, was 0.451 g (90% based on **12p**·HCl): ^1H NMR ($CDCl_3$) δ 7.64 and 7.44 (AA'BB' quartet, 4 H), 3.107 (s, 6 H), 1.991 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.11, 148.85, 132.24, 127.68, 125.85, 68.95, 38.57, 34.21; exact mass calcd for $C_{12}H_{16}ClNO$ 225.0920, found 225.0918.

Preparation of 4-Bromobenzaldehyde Dimethyl Acetal (18p). A solution of 4.906 g of 4-bromobenzaldehyde, 4.588 g of trimethyl orthoformate, and 7 mL of methanol was treated with 138 mg of *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 24 h. The acid was neutralized by the addition of 1.8 mL of a 0.5 M solution of sodium methoxide in methanol. The solvents were then removed on a rotary evaporator and the residue was distilled to give 5.998 g (98%) of 1-bromobenzaldehyde dimethyl acetal (**18p**),[16] bp 82–83 °C (0.8 mm): ^1H NMR ($CDCl_3$) δ 7.49 and 7.33 (AA'BB quartet, 4 H), 5.356 (s, 1 H), 3.306 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 137.13, 131.33, 128.51, 122.48, 102.29, 52.56.

Benzaldehyde dimethyl acetal[17] and 4-chlorobenzaldehyde dimethyl acetal[5,18] were prepared in an analogous fashion.

Preparation of 4-(*N*,*N*-Dimethylthiocarbamoyl)benzaldehyde Dimethyl Acetal (19p). A solution of 5.72 g of 4-bromobenzaldehyde dimethyl acetal (**18p**) in 70 mL of tetrahydrofuran was cooled to −78 °C and 16.0 mL of 1.6 M *n*-BuLi in hexanes was added dropwise to the stirred mixture. The mixture was stirred at −78 °C for 50 min and then transferred via a double-ended needle (using nitrogen pressure) to a −78 °C solution of 3.54 g of *N*,*N*-dimethylthiocarbamoyl chloride, $ClCSNMe_2$, in 70 mL of tetrahydrofuran. The mixture was slowly warmed to room temperature and water was added. The mixture was transferred to a separatory funnel with ether and the organic phase was washed with water and saturated NaCl solution and dried over $MgSO_4$. After solvent removal on a rotary evaporator, the residue was chromatographed on 50 g of silica gel and the column was eluted with increasing amounts of ether in hexanes. The product **19p** (4.03 g; 70%), mp 57–58 °C, eluted with 50% ether in hexanes: ^1H NMR ($CDCl_3$) δ 7.44 and 7.30 (AA'BB' quartet, 4 H), 5.375 (s, 1 H), 3.603 (s, 3 H), 3.341 (s, 6 H), 3.157 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.83, 143.20, 138.54, 126.70, 125.68, 102.72, 52.84, 44.11, 43.19. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.31; H, 7.22.

Preparation of 4-(*N*,*N*-Dimethylthiocarbamoyl)benzaldehyde (20p). A solution of 3.029 g of 4-(*N*,*N*-dimethylthiocarbamoyl)benzaldehyde dimethyl acetal (**19p**) in 10 mL of tetrahydrofuran was stirred vigorously as 10 mL of 2% H_2SO_4 in water was added dropwise. The mixture was stirred for 3 h at room temperature and then solid Na_2CO_3 was added slowly until CO_2 evolution ceased. The mixture was transferred to a separatory funnel with ether and the organic phase was washed with water and a saturated NaCl solution. The organic extract was dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The crystals that formed were slurried with hexanes and collected. The yield of aldehyde **20p**, mp 72–74 °C, was 2.296 g (94%): ^1H NMR ($CDCl_3$) δ 10.022 (s, 1 H), 7.88 and 7.45 (AA'BB' quartet, 4 H), 3.616 (s, 3 H), 3.167 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.09, 191.34, 148.59, 135.83, 129.89, 126.22, 43.99, 42.92. Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.65; N, 7.25.

Reaction of 4-(*N*,*N*-Dimethylthiocarbamoyl)benzaldehyde (20p) with Diethyl Trimethylsilyl Phosphite. Formation of α-Hydroxy Phosphonate 22p. The preparation of **22p** was analogous to our previously described procedures.[11] A mixture of 0.444 g of aldehyde **20p** and 0.504 g of diethyl trimethylsilyl phosphite in 2 mL of tetrahydrofuran was heated in a sealed tube at 100 °C for 16 h. The contents of the tube were transferred to a flask, using a small amount of ether, and the solvents were removed on a rotary evaporator. The residue was then taken up into 10 mL of 10^{-3} M CF_3CO_2H in methanol and the mixture was kept at room temperature for 22.5 h. The solvent was then removed on a rotary evaporator and the residual oil was stored at −20 °C to induce crystallization. The solid that formed was slurried with two portions of hexanes and collected to yield 0.700 g (92%) of α-hydroxy phosphonate **22p**, mp 95–99 °C: ^1H NMR ($CDCl_3$) δ 7.47 and 7.32 (AA'BB' quartet, 4 H), 5.011 (d, J = 11 Hz, 1 H), 4.09 (m, 4 H), 3.602 (s, 3 H), 3.160 (s, 3 H), 2.49 (br s, 1 H), 1.283 (t, J = 7.4 Hz, 3 H), 1.258 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.93, 142.93, 137.30, 127.04 (d, J = 5.6 Hz), 125.81 (d, J = 1.7 Hz), 70.42 (d, J = 159 Hz), 63.47 (d, J = 7.1 Hz), 63.21 (d, J = 7.3 Hz), 44.16, 43.29, 16.41 (d, J = 5.4 Hz); exact mass calcd for $C_{14}H_{22}NO_4PS$ 331.1007, found 331.1004.

Preparation of Mesylate 23p. A solution of 0.590 g of α-hydroxy phosphonate **22p** and 0.420 g of methanesulfonyl chloride in 10 mL of CH_2Cl_2 was cooled to −78 °C and 0.505 g of triethylamine was added dropwise. The mixture was allowed to warm to 0 °C and the mixture was transferred to a separatory funnel with ether. The mixture was then washed with cold water, a cold dilute HCl solution, and a saturated NaCl solution and then dried over $MgSO_4$. The solvents were removed on a rotary

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evaporator and the residual solid was washed with hexanes. The yield of mesylate **23p**, mp 137–138 °C, was 0.577 g (78%): ^1H NMR ($CDCl_3$) δ 7.51 and 7.36 (AA'BB' quartet, 4 H), 5.755 (d, J = 15.3 Hz, 1 H), 4.16 (m, 4 H), 3.603 (s, 1 H), 3.157 (s, 3 H), 2.970 (s, 3 H), 1.328 (t, J = 7.2 Hz, 3 H), 1.270 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.87, 144.35 (d, J = 2.4 Hz), 132.49, 128.00 (d, J = 5.6 Hz), 126.24 (d, J = 1.2 Hz), 76.87 (d, J = 170 Hz), 64.23 (d, J = 7.1 Hz), 63.90 (d, J = 6.7 Hz), 44.16, 43.21, 39.61, 16.39 (d, J = 6.5 Hz), 16.30 (d, J = 6.2 Hz). Anal. Calcd for $C_{15}H_{24}NO_6PS_2$: C, 44.00; H, 5.91. Found: C, 43.79; H, 6.03.

Preparation of 1-[4-(*N*,*N*-Dimethylthiocarbamoyl)-phenyl]-1-chloroethane (26p). A solution of 0.423 g of aldehyde **20p** in 5 mL of tetrahydrofuran was cooled to −65 °C and 0.73 mL of 3.0 M methylmagnesium bromide in ether (diluted with an additional 2 mL of ether) was added dropwise to the aldehyde solution. The mixture was allowed to warm to room temperature and saturated ammonium chloride solution was then added. The organic extract was dried over $MgSO_4$ and filtered. The solvent was removed on a rotary evaporator to give crude 1-[4-(*N*,*N*-dimethylthiocarbamoyl)phenyl]ethanol, which was used directly in the next step: ^1H NMR ($CDCl_3$) δ 7.33 and 7.26 (AA'BB quartet, 4 H), 4.856 (q, J = 6.6 Hz, 1 H), 3.579 (s, 3 H), 3.165 (s, 3 H), 2.483 (br s, 1 H), 1.451 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.09, 146.40, 142.33, 125.94, 125.37, 69.80, 44.19, 43.27, 25.21.

The crude alcohol prepared above was dissolved in 6 mL of CH_2Cl_2 and the solution was cooled to 0 °C. Gaseous HCl was bubbled into the mixture until the solution was saturated. The solution was warmed in an oil bath at about 35 °C for 1.5 h and $MgSO_4$ was then added. The mixture was filtered and the solvent was removed. ^1H NMR analysis of the residue showed about 10% starting alcohol. Methylene chloride was added (6 mL) and the solution was again saturated with HCl at 0 °C. After 12 h at room temperature, $MgSO_4$ was again added, and the solution was filtered. The solvent was removed on a rotary evaporator and the residue was taken up into ether. The solution was passed through a short column of silica gel and the ether was removed on a rotary evaporator. The chloride **26p** (0.367 g, 74% based on aldehyde **20p**), mp 88–90 °C, was collected: ^1H NMR ($CDCl_3$) δ 7.40 and 7.30 (AA'BB' quartet, 4 H), 5.079 (q, J = 6.9 Hz, 1 H), 3.601 (s, 3 H), 3.184 (s, 3 H), 1.833 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.64, 143.19, 143.16, 126.59, 126.10, 58.14, 44.17, 43.22, 26.51; exact mass calcd for $C_{11}H_{14}ClNS$ 227.0535, found 227.0553.

Preparation of Meta-Substituted Derivatives. All of the meta-substituted compounds described in this paper were prepared by procedures completely analogous to the preparation of the para-substituted compounds. Spectral and analytical data are given as supplementary material.

Solvolyses of 11 and 12 in Ethanol. Titrimetric procedures for determining rates of solvolyses of these chlorides in absolute ethanol (0.025 M in 2,6-lutidine) were identical with those previously described.[19] Endpoints were determined by potentiometric titration of unreacted 2,6-lutidine with 0.01 M $HClO_4$ in ethanol. Maximum standard deviations in duplicate runs were ±2%.

Solvolyses of these substrates in ethanol for at least 10 half-lives gave the ethyl ether substitution products along with small amounts of the corresponding elimination products. As a typical example, a solution of 42.7 mg of **12p** in 15 mL of 0.025 M 2,6-lutidine in ethanol was kept at 25 °C for 8 h and then at 22 °C for 11 h. The ethanol was removed on a rotary evaporator and the residue was taken up into ether and water. The mixture was washed with dilute HCl and saturated NaCl solution and dried over $MgSO_4$. Solvent removal on a rotary evaporator left 43 mg of a mixture of 2-[4-(*N*,*N*-dimethylthiocarbamoyl)phenyl]-2-ethoxypropane and 2-[4-(*N*,*N*-dimethylthiocarbamoyl)phenyl]-propene in a 91:9 ratio as determined by ^1H NMR.

Hydrolyses of Acetals. Kinetics Procedure. Three milliliters of a 10^{-3} M solution of HCl in distilled water were thermally equilibrated in a cuvette at 25.0 °C in a constant-temperature compartment of a UV spectrophotometer. Solutions of the appropriate acetal in acetonitrile (approximately 12 mg/mL) were prepared and the kinetic run was initiated by injecting 5–10 μL of the acetonitrile solution into the 10^{-3} M HCl solution. Increases in absorbance were measured as a function of time. Absorbances at 280 nm were monitored for benzaldehyde dimethyl acetal and *p*-chlorobenzaldehyde dimethyl acetal, while 240 and 257 nm were used for **20m** and **20p**, respectively. Rate constants were calculated by standard least-squares procedures. Maximum standard deviations in duplicate runs were ±1%.

Solvolyses of 23m and 23p. Titrimetric procedure for determining rates of solvolyses of mesylate **23m** in trifluoroethanol (0.025 M in 2,6-lutidine) and mesylate **23p** in acetic acid (0.05 M in sodium acetate) and formic acid (0.05 M in sodium formate) were identical with those previously described.[11] Endpoints were determined by potentiometric titration of unreacted base with 0.01 M $HClO_4$ in acetic acid. Solvolysis of **23p** in 0.025 M 2,6-lutidine in trifluoroethanol at 70 °C was also monitored by ^{31}P NMR. Under these conditions **23p** rapidly disappeared (half-life = 9.6 min). ^{31}P NMR indicated formation of a complex product mixture, which was not further characterized.

Solvolysis of **23m** in 0.025 M 2,6-lutidine in trifluoroethanol for 24 h at 100 °C gave (after trifluoroethanol removal under vacuum and a standard aqueous workup using ether extraction) the corresponding trifluoroethyl ether substitution product as determined by NMR analysis after removal of the ether solvent. Solvolysis of **23p** in 0.05 M sodium acetate in acetic acid at 70 °C for 18 h gave (after a standard aqueous workup and ^1H NMR analysis) the corresponding acetate substitution product (75%). Monitoring the reaction of **23p** in acetic acid by ^{31}P NMR spectroscopy showed that at least four other minor products (not isolated) were formed along with the major acetate product. Solvolysis of **23p** in 0.05 M sodium formate in formic acid at 35 °C for 22 h gave, after a standard aqueous workup, the corresponding formate substitution product.

Solvolyses of 1-Phenyl-1-chloroethanes 26p and 26m in Methanol. Solvolyses of these substrates in methanol containing 0.05 M 2,6-lutidine were monitored by ^1H NMR spectroscopy. The appropriate chloride was dissolved in a 0.05 M solution of 2,6-lutidine in methanol. At periodic time intervals, the methanol solvent was removed from an aliquot on a rotary evaporator and the residue was dissolved in $CDCl_3$ and analyzed by 300-MHz NMR spectroscopy. The area of the doublet at δ 1.83 (which corresponds to the starting chloride) was determined as well as the area of the doublet at δ 1.42 corresponding to the methyl ether solvolysis product. Rate constants were calculated by standard least-squares procedures.

Solvolyses of **26p** and **26m** in 0.025 M 2,6-lutidine in methanol gave only the corresponding methyl ether substitution products, as determined by ^1H NMR spectroscopy.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **11p**, **12p**, **22p**, and **26p** as well as ^1H and ^{13}C NMR spectra and analytical data for compounds **9m**, **10m**, **11m**, **12m**, **19m**, **20m**, **22m**, **23m**, and **26m** (22 pages). Ordering information is given on any current masthead page.

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