Steric Inhibition of Synergistic Radical Stabilizing Effects

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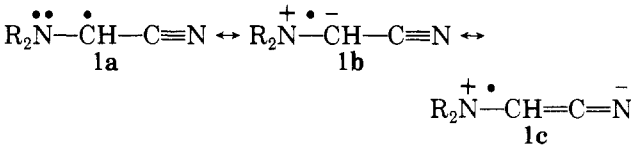
Equilibrium acidities in Me_2SO for 14 α-*N*-morpholinyl-, 6 α-*N*-piperidinyl-, and 7 α-cyclohexylarylacetonitriles and the oxidation potentials of their conjugate bases have been determined. The increased pK_{HA} values by about 2 units observed in these systems, relative to the corresponding arylacetonitriles, is ascribed to the presence of increased steric constraints in the anions. Hammett plots revealed larger ρ values than for arylacetonitriles (6–7 versus 5.5), pointing to an increased negative charge density on the benzylic carbon atoms in the anions. A plot of anion oxidation potentials, $E_{ox}(A^-)$, versus pK_{HA} for the α-*N*-morpholinylarylacetonitriles was linear with a slope near unity, showing that remote substituents for the most part have very little effect on radical stabilities. A 5 and 6 kcal/mol lowering of the BDE of the acidic C–H bond caused by replacing the cyclohexyl group in α-cyclohexylphenylacetonitrile by α-*N*-morpholinyl or *N*-piperidinyl groups, respectively, is attributed to the strong donor properties of these amino functions. The effects are only about one-third as large, however, as similar effects in R_2NCH_2COPh, where the steric effect of Ph is absent and a synergistic effect is believed to be operative.

For more than a decade there has been considerable interest in the question of whether or not functions in radicals of the type donor–Ċ–acceptor act synergistically to provide stabilization greater than expected for the individual effects. This possibility was first suggested by Balaban,[1] who gave several examples of radicals that appeared to be stabilized by what he called "push–pull" resonance of the type shown for the $R_2NĊHCN$ radical (1).



Further examples of such radicals that appeared to possess unusual stability were provided by Katritzky, who coined the name "merostabilization" for the phenomenon.[2] Numerous additional examples were described by Viehe as "captodative effects,"[3] a name that appears to have gained general acceptance. Calculations in 1980 by Schleyer supported the presence of extra stabilization of 3.4 and 12.3 kcal/mol for the $H_2NĊHCN$ and $H_2NĊHBH_2$ radicals, respectively.[4a] More recent calculations by Pasto indicate that the extra stabilization for these radicals is smaller (1.1 and 4.6 kcal/mol, respectively); his calculations suggested, however, that HOĊHCHO and $H_2NĊHCHO$ radicals possess sizable extra stabilizations (4.7 and 8.3 kcal/mol, respectively).[4b] A wide variety of rate and esr data has been interpreted as supporting the existence of captodative effects,[3,5] but, nevertheless, Katritzky reports that considerable skepticism was expressed at the 1986 NATO Conference regarding the existence of any appreciable effect.[2b,6]

In an earlier paper, we used eq 1 to provide a quasi thermodynamic answer to the question of extra stabilization in captodative radicals by estimating stabilization energies (RSEs) in Me_2SO solution of radicals formed from a family of GCH_2COPh substrates by loss of a proton and an electron.[8] When G = MeO or R_2N (R_2N = Me_2N, c-C_4H_8N, or c-$C_5H_{10}N$) the ΔBDEs, relative to that of $PhCOCH_2$-H, were estimated to be 13 ± 2 and 21 ± 2 kcal/mol, respectively. These values are as large as the ΔBDEs of $MeOCH_2$-H and Me_2NCH_2-H, relative to CH_3-H measured in the gas phase,[9] and therefore do not support the presence of a captodative effect, as defined by Viehe.[3,6] The large sizes of these effects were noteworthy, however, in that they implied that the radical stabilization energies (RSEs) for the PhCOĊHOMe and PhCOĊHNR$_2$ radicals were as large as those for the $MeOĊH_2$ and $Me_2NĊH_2$ radicals, respectively, despite the fact that the delocalized $PhCOĊH_2$ radical is about 12 kcal/mol more stabilized than the $ĊH_3$ radical, as judged by ΔBDEs, and should therefore be subject to an appreciable saturation effect. It was argued that one would expect a saturation effect of 4–5 kcal/mol to be present in the PhCOĊHG radicals, and the conclusion was drawn that a synergism of this magnitude was operative between the donor and acceptor groups in these radicals.[8]

$$RSE = \Delta BDE = 1.37\Delta pK_{HA} + 23.1\Delta E_{ox}(A^-) \quad (1)$$

This study has now been extended to acetophenones and arylacetonitriles bearing an additional α-Ph substituent, e.g., PhCOCH(Ph)NR$_2$ and PhCH(Ph)CN. The anions and radicals derived from these substrates are expected

(1) (a) Balaban, A. T. *Rev. Roumanian Chem.* **1971**, *16*, 725. (b) Neguita, N.; Baican, R.; Balaban, A. T. *Tetrahedron Lett.* **1973**, 1877–1878. (c) Balaban, A. T.; Istratoiu, R. *Tetrahedron Lett.* **1973**, 1879–1880.

(2) (a) Baldock, R. W.; Hudson, P.; Katritzky, A. R.; Soti, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1422–1427. (b) Katritzky, A. R.; Zerner, M. C.; Karelson, M. M. *J. Am. Chem. Soc.* **1986**, *108*, 7213–7214.

(3) (a) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917–932. (b) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148–154.

(4) (a) Crans, D.; Clark, T.; Schleyer, P. R. *Tetrahedron Lett.* **1980**, *21*, 3681–3684. (b) Pasto, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 8164–8175.

(5) See ref 4b for a summary and evaluation of these effects.

(6) A referee states that this view is not reflected by the NATO Conference book,[7] but perusal of the papers contained in this book fails to reveal any clearcut thermodynamic evidence for captodative effects as defined by Viehe, Janousek, Merényi, and Stella,[3] i.e., "in the case of two substitutents of opposite polarity, A and D, the sum of the overall effect on radical stabilization is greater than the sum of the individual substituent effects. In other words, the two substituents act in unison; they potentialize one another. This is what we call the captodative effect." It seems likely to us, as will be brought out in this paper, that saturation and steric effects will generally overshadow captodative effects as so defined. We therefore prefer the term *synergistic effects*, to describe these interactions.

(7) *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; D. Reidel Publishing Co.: Dordrecht, Holland, 1986; NATO ASI Series C, Vol. 189.

(8) Bordwell, F. G.; Lynch, T. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558–7562.

(9) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493–532.

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Table I. Equilibrium Acidities of Ring-Substituted α-*N*-Morpholinylarylacetonitriles in Me_2SO at 25 °C

substituent	pK_a[a]	HIn[b]	runs[n]	assigned pK_a[o]
4-$N(CH_3)_2$	25.72 ± 0.07	TP2H[c]	3	25.7
	25.62	HBl[d]	1	
4-OCH_3	24.41	TNH[e]	1	24.4
	24.42	T-BUFH[f]	1	
4-CH_3	23.44 ± 0.03	FH[g]	2	23.4
3,4-(-OCH_2O-)	23.36 ± 0.01	FH[g]	2	23.4
	23.48	MFH[h]	1	
3-CH_3	22.63 ± 0.01	FH[g]	2	22.6
	22.65 ± 0.01	MFH[h]	2	
4-F	22.61 ± 0.01	FH[g]	2	22.6
	22.56 ± 0.01	MFH[g]	2	
H	22.38 ± 0.01	FH[g]	4	22.4
	22.34 ± 0.04	F2[i]	2	
3-OCH_3	22.07 ± 0.05	FH[g]	3	22.1
	22.11	MFH[h]	1	
4-Cl	20.79 ± 0.02	F2[i]	2	20.8
	20.76	2NPANH[j]	1	
3-Cl	19.94 ± 0.00	CNAH[k]	2	19.9
3-CN	18.95	2NANH[j]	1	19.1
	19.07 ± 0.03	CNAH[k]	2	
3,4-Cl_2	18.64 ± 0.06	PFH[l]	2	18.6_5
	18.66 ± 0.06	CNAH[k]	3	
4-CF_3	18.15 ± 0.04	PFH[l]	2	18.1_5
4-CN	15.88 ± 0.03	MCLPFH[m]	2	15.9
	15.85	PFH[l]		

[a] Measured by the method described in previous papers from this Laboratory. [b] Indicator acid (see footnotes below, pK_a's are given in parentheses). [c] 1,1,3-Triphenylpropene (25.6). [d] Dibenzo-[*b*,*d*]-1-azacyclohept-4-ene (26.1). [e] 1,1,3-Triphenyl-2-aza-1-propene (24.3). [f] 9-(*tert*-Butyl)fluorene (24.3_5). [g] Fluorene (22.6). [h] 9-Methylfluorene (22.34). [i] 9-Benzylfluorene (21.37). [j] 2-Naphthylacetonitrile (20.66). [k] 4-Chloro-2-nitroaniline (18.9). [l] 9-Phenylfluorene (17.9). [m] 9-(*m*-Chlorophenyl)fluorene (16.8). [n] Runs were usually three-point titrations. [o] The assigned pK_a is the average of all the runs performed.

to be subject to severe steric effects, and it was of interest to see how our estimated ΔBDEs (or RSEs) would be affected by these structural changes. We realize that ΔBDEs for bonds A–B and A–C, where B and C are atoms of different kinds, cannot be equated with RSEs because the ΔBDEs depend on differences in A–B and A–C ground-state energies, as well as on the stabilities of the A•, B•, and C• radicals being formed. In *families* of H–A molecules, however, differences in ground-state energies are expected to be relatively small compared to differences in the energies of the A• radicals being formed. Furthermore, steric effects caused by phenyl substituents should be taken care of by the pK_{HA} term in eq 1 because phenyl delocalization effects on carbanions and carbon-centered radicals should be subject to similar constraints. For this reason we believe that our previous analysis[8] in terms of ΔBDE = RSE can be extended to the substrates studied herein.

Results and Discussion

Equilibrium Acidities. The equilibrium acidities in Me_2SO for a number of 3- and 4-substituted α-*N*-morpholinyl-, α-*N*-piperidinyl-, and α-cyclohexylarylacetonitriles are summarized in Tables I–III.

Examination of Tables I–III shows that α-*N*-morpholinyl-, α-*N*-piperidinyl-, and α-cyclohexylphenylacetonitriles have pK_a's of 22.4, 23.1, and 24.2, respectively. For comparison, phenylacetonitrile has a pK_{HA} = 21.9. The 2 unit pK_{HA} decrease in acidity (statistically corrected) for replacement of an α-hydrogen atom in the latter by cyclohexyl is believed to be caused by steric inhibition of solvation. Similar steric effects presumably also result by replacement of the α-hydrogen atom by *N*-morpholinyl or

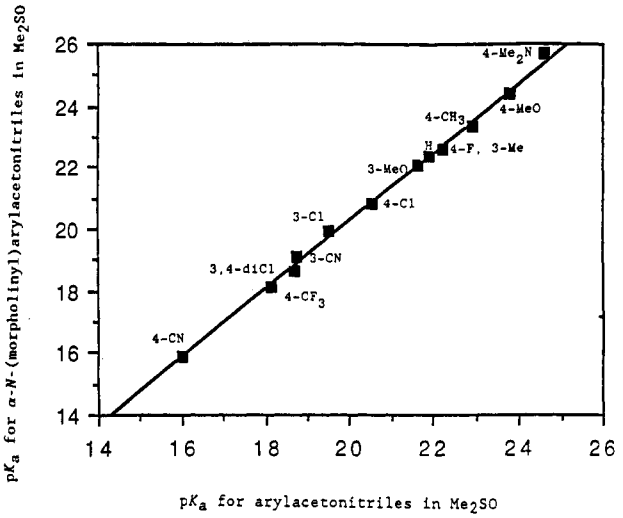


Figure 1. Plot of pK_{HA} values for α-*N*-morpholinylarylacetonitriles versus pK_{HA} values for arylacetonitriles.

Table II. Equilibrium Acidities of Ring-Substituted α-*N*-Piperidinylarylacetonitriles in Me_2SO at 25 °C

substituent	pK_a[a]	HIn[b]	runs[k]	assigned pK_a[l]
4-$N(CH_3)_2$	26.26 ± 0.04	HBl[c]	2	26.3_5
	26.54	MCLPXH[d]	1	
4-OCH_3	25.14 ± 0.04	HBl[c]	2	25.1
4-CH_3	24.15 ± 0.02	T-BUFH[e]	2	24.2
	24.20	FH[f]	1	
H	23.08 ± 0.01	MFH[g]	2	23.1
	23.09 ± 0.01	FH[f]	2	
4-Cl	21.59 ± 0.04	FH[f]	2	21.5
	21.46 ± 0.03	MFH[g]	2	
	21.45 ± 0.01	CNAH[h]	2	
3-Cl	20.36 ± 0.01	2NPANH[i]	2	20.3_5
	20.33	CNAH[h]	1	
3,4-Cl_2	19.24 ± 0.05	2NPANH[i]	2	19.2
	19.19	PFH[j]	1	
	19.14	CNAH[h]	1	

[a] Measured by the method described in previous papers from this laboratory. [b] Indicator acid (see footnotes below, pK_a's are given in parentheses). [c] Dibenzo[*b*,*d*]-1-azacyclohept-4-ene (26.1). [d] 9-(*m*-Chlorophenyl)xanthene (26.6). [e] 9-(*tert*-Butyl)fluorene (24.3_5). [f] Fluorene (22.6). [g] 9-Methylfluorene (22.34). [h] 4-Chloro-2-nitroaniline (18.9). [i] 2-Naphthylacetonitrile (20.66). [j] 9-Phenylfluorene (17.9). [k] Runs were usually three-point titrations. [l] The assigned pK_a is the average of all the runs performed.

Table III. Equilibrium Acidities of Ring-Substituted α-Cyclohexylarylacetonitriles in Me_2SO at 25 °C

substituent	pK_a[a]	substituent	pK_a[a]
4-Me	25.20	3-Cl	21.7[b]
3-Me	24.6[b]	3-CF_3	21.2[b]
H	24.2	3,4-Cl_2	20.5[b]
4-Cl	22.7		

[a] Measured in Me_2SO by the method described in earlier papers from this laboratory unless otherwise noted. [b] Estimated from a three-point Hammett correlation ($\rho \simeq 6.2$). A Brønsted plot for rates of reactions of α-cyclohexylarylacetonitrile ions bearing 4-Me, H, 4-Cl, 3-Cl, and 3-CF_3 substituents reacting with *n*-BuCl in Me_2SO is linear (R^2 = 0.998) and has a slope comparable to the Brønsted plot for α-*N*-piperidinylarylacetonitriles reacting with *n*-BuCl (T. A. Cripe, unpublished results).

N-piperidinyl groups, but their effects on pK_{HA}'s are moderated somewhat by field/inductive effects due to the greater electronegativity of nitrogen. A plot of pK_{HA} values for α-*N*-morpholinylarylacetonitriles versus pK_{HA} values for arylacetonitriles for 12 substituents is linear (R^2 = 0.998) with a slope of 1.1 (Figure 1). The precise linearity of this plot constructed from pK_{HA} values measured by two

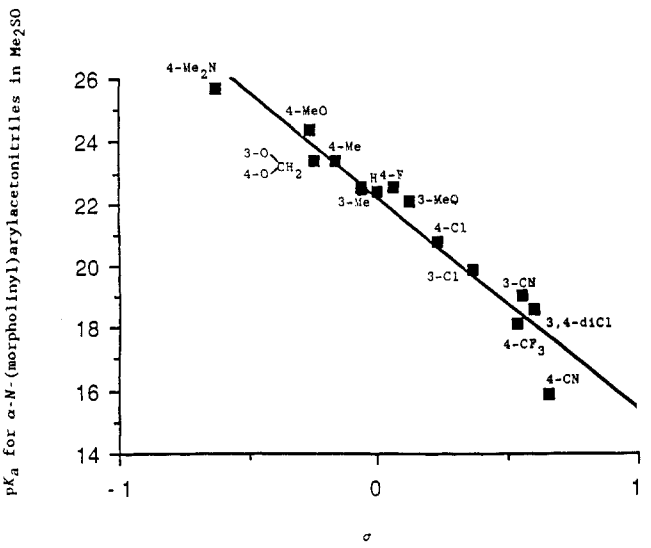
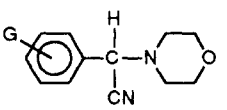


Figure 2. Hammett plot of pK_{HA} of α-*N*-morpholinylarylacetonitriles vs σ.

Table IV. Oxidation Potentials of α-*N*-Morpholinylarylacetonitride Ions



G	$E_{ox}(A^-)^a$	G	$E_{ox}(A^-)^a$
H	−0.433	4-F	0.403
4-Me_2N	−0.663	3-Cl	0.280
4-MeO	−0.557	4-Cl	0.343
3-MeO	−0.403	3,4-Cl_2	0.217
4-Me	−0.487	4-CF_3	0.179
3-Me	−0.444	4-CN	0.177
3,4-(−OCH_2O−)	−0.507	3-CN	0.211

[a] Measured in Me_2SO by cyclic voltammetry with a Ag/AgI reference electrode under the conditions previously described,[12] and referenced to the standard hydrogen electrode by adding −0.125 V algebraically.

different investigators testifies to the accuracy of the method.

The points for a Hammett plot for the pK_{HA}'s of α-*N*-morpholinylarylacetonitriles versus σ fall reasonably close to the line (ρ = 6.5) except that for 4-CN (Figure 2). The σ constant of 0.02 for 3-MeO, which was derived from acidity measurements of acetophenones in Me_2SO,[10] gives a better fit than the classical Hammett σ of 0.12. The apparent σ constant for the methylenedioxy function derived from the plot if −0.2, and the apparent σ^- constants for 4-CN is 1.0. The Hammett ρ values for the α-*N*-piperidinyl- and α-cyclohexylarylacetonitriles are also in the 6–7 range. These high ρ values point to a substantial buildup of negative charge on the benzylic carbon atom in the anion.

Oxidation Potentials and Equilibrium Acidities. In Tables IV and V we summarize the results of measurements of oxidation potentials of the conjugate bases of the compounds listed in Tables I–III.

A plot of $E_{ox}(A^-)$ of α-*N*-morpholinylarylacetonitriles versus pK_{HA} (both axes in kilocalories/mole), using the data in Tables I and IV, is nicely linear with a slope near unity (Figure 3); the slope is nearly identical with that for a comparable plot with arylacetonitriles.[11] There are

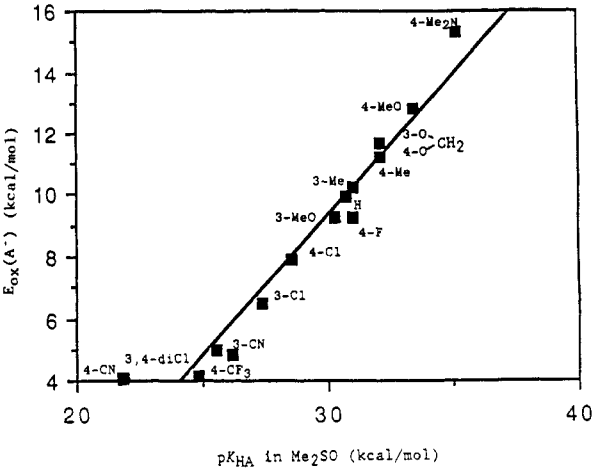
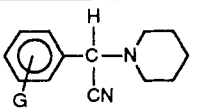
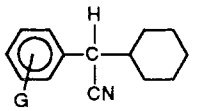


Figure 3. Plot of $E_{ox}(A^-)$ vs pK_{HA} values for α-*N*-morpholinylarylacetonitriles in Me_2SO.

Table V. Oxidation Potentials of α-*N*-Piperidinyl- and α-Cyclohexylarylacetonitride Ions





G	$E_{ox}(A^-)^a$	G	$E_{ox}(A^-)^a$
H	−0.510	H	−0.340
4-Me_2N	−0.712		
4-MeO	−0.631	3-Me	−0.352
4-Me	−0.555	4-Me	−0.416
4-Cl	−0.408	4-Cl	−0.248
3-Cl	−0.342	3-Cl	−0.176
3,4-Cl_2	−0.273	3,4-Cl_2	−0.148

[a] Measured in Me_2SO by cyclic voltammetry with a Ag/AgI reference electrode under the conditions previously described[12] and referenced to the standard hydrogen electrode by adding −0.125 V algebraically.

significant differences in the points that deviate from the line in the two plots, however. In the plot for arylacetonitriles the point for 4-CN does not deviate appreciably from the line,[11] but the 4-Me_2N group makes the anion about 4 kcal/mol easier to oxidize than predicted by the line. In the plot for α-*N*-morpholinylarylacetonitriles the point for the 4-Me_2N group deviates from the line by only about 1.5 kcal/mol, but the point for 4-CN deviates by about 3.5 kcal/mol. These trends are understandable in terms of the strong donor properties of the morpholinyl group, which brings out the radical acceptor properties of the 4-CN group but dampens the radical donor properties of the 4-Me_2N group (synergistic and cross-conjugative effects).

Plots of oxidation potentials of anions in Me_2SO versus pK_{HA}'s with slopes near unity have been observed in a number of other systems including: (a) 2- and 2,7-substituted fluorenide ions,[11] (b) 3-aryl-1,1,5,5-tetraphenyl-1,4-pentadienes,[13a] and (c) hydrocarbons giving highly delocalized carbanions.[13b] These correlations show that the ion oxidation potentials are directly related to their basicities, i.e., most remote substituents in these systems

(10) Bordwell, F. G.; Cornforth, F. D. *J. Org. Chem.* **1978**, *43*, 1763–1768.

(11) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1979–1985. The 4-CN point was not plotted on the original arylacetonitrile graph, but can be added from the data in ref 12.

(12) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209–223.

(13) (a) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. *J. Am. Chem. Soc.* **1988**, *110*, 2872–2877. (b) Bordwell, F. G.; Harrelson, J. A., Jr.; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101–3105.

(14) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231.

Table VI. Effects of Phenyl, Piperidinyl, and Morpholinyl Groups on Acidities and Radical Stabilization Energies

HA	pK_{HA}	$E_{ox}(A^-)^b$	RSE[c]	RSE[c]
$PhCOCH_3$	24.7	0.143	(0.0)	
$PhCOCH_2Ph$	17.7	0.123	10.3	(0.0)
$PhCOCHPh_2$	18.7	0.052	11.0	0.68
c-$C_5H_{10}NCH_2COPh$	23.5	−0.687	21.1	
c-$C_5H_{10}NCH(Ph)COPh$	21.5	−0.382	17.1	6.9
$PhCH_2CN$	21.9	−0.159	(0.0)	
Ph_2CHCN	17.5	−0.102	5.2	
c-$C_6H_{11}CH(Ph)CN$	24.2	−0.340	1.5	
c-$C_5H_{10}NCH(Ph)CN$	23.1	−0.510	6.9	
c-$OC_4H_8NCH(Ph)CN$	22.4	−0.433	6.1	
CH_4	(56)[a]		(0.0)[d]	
$PhCH_3$	(43)[a]		17	
Ph_2CH_2	32.2	−0.790	23[e]	
Ph_3CH	30.6	−0.36	24[e]	

[a] Extrapolated. [b] Measured by cyclic voltammetry under the conditions previously described[12] and referenced to the standard hydrogen electrode by adding −0.125 V. [c] Calculated from eq 1 unless otherwise noted. [d] ΔBDEs. [e] BDE calculated from: BDE = $1.37pK_{HA} + 23.1E_{ox}(A^-) + 55.9$.[14]

exert neither stabilizing nor destabilizing effects on the radicals being formed. Similar plots of $E_{ox}(A^-)$ vs pK_{HA} were obtained for the α-*N*-piperidinylarylacetonitriles and α-cyclohexylarylacetonitriles using the data in Tables II–V.

The effects of phenyl, cyclohexyl, piperidinyl, and morpholinyl groups on radical stabilization energies (RSEs) have been evaluated by eq 1 from acidity and oxidation potential data given in Table VI.

Examination of Table VI shows that substitution of an α-Ph group into acetophenone causes a 9.9 kcal/mol increase in acidity (statistically corrected for the number of acidic hydrogen atoms) and a shift of about 0.5 kcal/mol to a more negative oxidation potential. In other words, the resulting 10 kcal/mol increase in RSE in the $PhCO\dot{C}HPh$ radical, relative to that of the $PhCOCH_2^\bullet$ radical, is almost entirely a consequence of the lower ground-state energy of the $PhCO\bar{C}HPh$ ion. The RSE for Ph here is small, however, compared to the 17 kcal/mol ΔBDE observed for introduction of Ph into CH_4 (Table VI). The size of the synergistic effect, if any, between the Ph donor and PhCO acceptor in the $Ph\dot{C}HCOPh$ radical can be estimated by the method previously used to estimate the synergistic effect of MeO in the $MeO\dot{C}HCOPh$ radical.[8] The RSE of the $PhCOCH_2^\bullet$ radical is estimated from eq 1 to be 12 kcal/mol.[8] To this we add the observed 10.3 kcal stabilizing effect for the Ph group when it replaces one of the α-hydrogen atoms in the $PhCOCH_2^\bullet$ radical (Table VI) and add 25% of this value to account for the saturation effect. From this sum we subtract the sum of the RSEs for the $PhCOCH_2^\bullet$ and $PhCH_2^\bullet$ radicals, relative to the $CH_3^\bullet$ radical, taken from ΔBDE data[9] (eq 2).

$$\text{syn} = [12 + 10.3 + (0.25 \times 10.3)] - (12 + 17) = -4 \quad (2)$$

Steric effects and a larger than estimated saturation effect presumably account for the negative value. In any event, it is clear that this method fails to provide evidence of a synergistic effect.

Introduction of a second α-Ph group into acetophenone causes the ground-state energy of the resulting $PhCO\bar{C}Ph_2$ ion, as judged by ΔpK_{HA}, to increase by about 1 kcal/mol, apparently due to destabilization of the anion as a result of steric inhibition of resonance, but the RSE of the corresponding radical appears to increase slightly, nonetheless, evidently because delocalization is more effective in stabilizing the radical than the anion. Substitution of an α-piperidinyl group into acetophenone has been shown to cause only a 2 kcal/mol lowering of the ground-state energy of the carbanion (ΔpK_{HA}), but the RSE decreases by 21 kcal/mol because of the powerful radical-stabilizing ability of the α-piperidinyl group.[8] This effect is equal to that of the Me_2N group in the $Me_2NCH_2^\bullet$ radical. It does not represent "extra stabilization" (a captodative effect),[6] but, as was brought out earlier, the apparent absence of a saturation effect does indicate the presence of at least a 5 kcal/mol synergistic effect between the donor and acceptor groups.[8] Introducing the α-Ph group into the c-$C_5H_{10}N\bar{C}HCOPh$ ion increases the RSE of the corresponding radical by about 3 kcal/mol as a consequence of reducing the anion ground-state energy (ΔpK_{HA}) but makes the $E_{ox}(A^-)$ of the anion about 7 kcal/mol more positive. The net effect is to lower the RSE by 4 kcal/mol, which can be considered to be the combined result of steric inhibition of radical delocalization, cross conjugation between the two donor groups, and saturation effects. The presence of steric effects in the radical is made evident by the change from irreversibility for the oxidation potential of the c-$C_5H_{10}N\bar{C}HCOPh$ ion to reversibility for that of the c-$C_5H_{10}N\bar{C}(Ph)COPh$ ion. When one considers all the factors tending to decrease the RSE in this trisubstituted radical, the 17 kcal/mol value seems remarkably large and suggests that some synergism between the donor and acceptor groups might remain. On the other hand, when one looks at the effect of substituting an α-piperidinyl group into $PhCOCH_2Ph$, we see that the RSE is only increased by 6.9 kcal/mol (column 5 in Table VI) compared to 21 kcal/mol for substitution into $PhCOCH_3$. From this point of view it is clear that the presence of the Ph group in the substrate has a large perturbing effect on conjugation between the c-$C_5H_{10}N$ and COPh functions.

The effect of substitution of a Ph group for a hydrogen atom in CH_3CN decreases the pK_{HA} by 9.6 units (Table VI) This ΔpK_{HA} is 2.4 units larger than that between CH_3COPh and $PhCH_2COPh$. The substitution of a second Ph group into $PhCH_2CN$ produces a much larger increase in RSE than for the $PhCOCH_2Ph$ to $PhCOCHPh_2$ substitution (5 vs 1 kcal/mol), which is consistent with the much smaller steric demands of the CN group. Substitution of an α-cyclohexyl group for a hydrogen atom in $PhCH_2CN$ causes a 4.2 kcal/mol increase in pK_{HA} and 5.7 kcal/mol shift in the oxidation potential, giving a net 1.5 kcal/mol increase in RSE. Substitution of an α-piperidinyl group for a hydrogen atom in $PhCH_2CN$ causes a smaller increase in pK_{HA} (2.1 kcal/mol) and a larger shift in $E_{ox}(A^-)$ (8.1 kcal/mol). The net 6.9 kcal/mol increase in RSE is identical with that resulting from a substitution of an α-piperidinyl group into $PhCOCH_2Ph$ (Table VI).

Summary and Conclusions

A plot of $E_{ox}(A^-)$ vs pK_{HA} for α-*N*-morpholinylarylacetonitriles for 12 meta and para substituents was found to be linear with a slope near unity, indicating that most remote substituents have RSEs near zero. The anions bearing *p*-Me_2N and *p*-CN were more readily oxidized than predicted by the line, however, indicating small stabilizing effects on the radicals being formed. Substitution of an α-Ph group into $PhCOCH_3$ increases the RSE of the corresponding radical by about 10 kcal/mol, an effect caused primarily by lowering the ground-state energy of the carbanion and radical. Substitution of a second α-Ph group increases the RSE of the corresponding radical by only 1 kcal/mol; the smaller effect is attributed to saturation and steric effects. Substitution of an α-*N*-piperidinyl group into $PhCOCH_2Ph$ increases the RSE of the corresponding radical by 6.9 kcal/mol, but this effect is small compared to the 21 kcal/mol effect on the $PhCOCH_2^\bullet$ radical brought about by introducing an α-*N*-piperidinyl group. (The latter large effect is believed to

be a consequence of synergism between the donor and acceptor groups in the c-$C_5H_{10}N\dot{C}HCOPh$ radical.[8]) We conclude that not only are captodative (extra stabilization) effects absent in these trisubstituted radicals, but the presence of steric and cross conjugative effects strongly disrupts the synergism present in analogous, less hindered, disubstituted radicals.

Experimental Section

General. Nuclear magnetic resonance (NMR) spectra were obtained on either a Varian EM-360 or a Varian EM-390 spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard. Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. High-performance liquid chromatography (LC) analyses were obtained on a Waters 6000 instrument using a 254-nm detector and a Whatman Partisil 10 PAC MA column. Gas chromatography (GC) was performed on a Varian 3700 instrument using a flame ionization detector and an Alltech column (no. 8011/2; liquid phase, 5% SE30; support, W-HP; length, 6 ft; inner diameter, 0.085 in.). Mass spectra were run by Dr. H. L. Hung on an HP 5984 GC/MS system. Elemental analyses were performed by Micro-Tech Laboratories of Skokie, IL. The purification of Me_2SO and the preparation of $CH_3COCH_2^-K^+$ have been described elsewhere.[15] Equilibrium acidities were determined by the overlapping indicator method described previously using either a Perkin-Elmer 442A or a Carey 14 UV/VIS spectrometer.[15] Oxidation potentials of the conjugate bases were measured in Me_2SO with 0.1 M tetraethylammonium tetrafluoroborate electrolyte by cyclic voltammetry.[12] The working and auxiliary electrodes were Pt and the reference electrode was Ag/AgI. The sweep rate was 100 mV/s with a reversible ferrocene–ferrocenium redox couple at $E_{1/2}$ = 0.875 V as a standard.

Materials. Phenylacetonitrile, deoxybenzoin, diphenylmethane, triphenylmethane, and diphenylacetonitrile were commercially available and purified prior to use. α,α-Diphenylacetophenone was prepared from the reaction of desyl bromide with benzene in the presence of $AlCl_3$ according to the procedure described by Zook.[16] α-*N*-Piperidinylphenylacetophenone[17] and α-*N*-piperidinylacetophenone[18] were prepared from the reactions of piperidine with desyl bromide and phenacyl bromide, respectively.

α-Cyclohexylarylacetonitriles (G-CAAN). Both 4-CH_3 and 4-H CAANs were prepared by method A, which is modified from the procedure described by Hancock and Cope.[19] 4-ClCAAN was prepared according to the unmodified procedure described by Hancock and Cope.[19] The remaining five G-CAANs were prepared by method B derived from that of Hancock and Cope.[19]

Method A. The appropriate phenylacetonitrile (10 mmol) was dissolved in Me_2SO (20 mL) under nitrogen and titrated with $CH_3SOCH_2^-K^+$ solution using diphenyldiphenylmethane (DDH) as an indicator. This anion solution was added via syringe under N_2 to a stirred solution of bromocyclohexane (1.63 g, 10 mmol) in Me_2SO (30 mL). After being stirred for 2 h at room temperature, the reaction solution was poured into H_2O (100 mL) and extracted with a total of 200 mL of 50:50 pentane/ether mixture. The organic extracts were washed with saturated NaCl aqueous solution (2 × 25 mL) and evaporated at 35 °C (20 mmHg). The crude product was recrystallized from a mixture of EtOH and H_2O in a ratio of 4 to 1, respectively.

Method B. The appropriate phenylacetonitrile (35 mmol) was dissolved in Me_2SO (10 mL), and this solution was added dropwise to a stirred solution of *t*-BuO^-K^+ (3.90 g, 35 mmol) in Me_2SO (20 mL) under N_2. After 15 min bromocyclohexane (6.05 g, 37 mmol) was added in one portion. The mixture was stirred for 50 min and allowed to sit overnight. The deep orange anion solution turned first to emerald green and eventually to deep azure blue. The mixture was treated with water (60 mL) and extracted with hexane (4 × 50 mL). The hexane solutions were combined, washed with saturated NaCl aqueous solution, dried over anhydrous $MgSO_2$, and evaporated. The product was prepurified by distillation with a Kugelrohr (135 °C (0.03 mmHg)) and purified by GLC (injector temperature, 240 °C; column temperature, 210 °C; detector temperature, 240 °C, on AW/DCMS Chromosorb W with 10% SE30 stationary phase; He carrier at 60 mL/min).

4-Me-CAAN: mp 56.5–57.5 °C (lit.[20] bp 150 °C (0.05 mm)); ^{1}H NMR ($CDCl_3$) δ 1.1–1.3 (m, 5 H), 1.6–1.9 (m, 6 H), 2.4 (s, 3 H), 3.6 (d, 1 H), 7.25 (s, 4 H).

3-Me-CAAN: liquid; ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 11 H), 2.4 (s, 3 H), 3.6 (d, 1 H), 7.1–7.2 (m, 4 H).

CAAN: mp 54–55 °C (lit.[21] mp 55–56 °C, lit.[19] mp 56–57 °C); ^{1}H NMR ($CDCl_3$) δ 1.1–1.3 (m, 5 H), 1.6–2.0 (m, 6 H), 3.6 (d, 1 H), 7.3 (s, 5 H).

4-Cl-CAAN: mp 70–72 °C (lit.[22] 71–73 °C); ^{1}H NMR ($CDCl_3$) δ 1.1–1.4 (m, 5 H), 1.6–2.0 (m, 6 H), 3.64 (d, 1 H), 7.2–7.5 (m, 4 H).

3-Cl-CAAN: liquid; ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 11 H), 3.55 (d, 1 H), 7.2–7.3 (m, 4 H).

3-CF_3-CAAN: liquid; ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 11 H), 3.7 (d, 1 H), 7.4–7.6 (m, 4 H).

α-*N*-Piperidinylarylacetonitriles (G-PAAN) and α-*N*-Morpholinylarylacetonitriles (G-MOAAN). Seven G-PPAs and 14 G-MOPAs were made by the following procedure, which was adapted from the literature.[23] Perchloric acid (70%, 9 mL, 11 mmol) was added dropwise to morpholine or piperidine (2 mL). The appropriate aryl aldehyde (10 mmol) was dissolved in morpholine or piperidine (9 mL) and added to the reaction flask. The solution was then stirred at 60 °C for 1 h. Sodium cyanide (0.54 g, 11 mmol) was dissolved in a minimum amount of water and added dropwise to the reaction mixture during a 15-min period. The solution was then stirred at 90 °C for 1 h. Ice-cold water (100 mL) was then added to the reaction solution. The resulting precipitate was isolated via filtration and recrystallized 2 to 3 times from a mixture of ethanol and water. The physical and spectral data of these compounds are listed below.

4-(Me_2N)-PAAN: mp 77.5–78.5 °C (lit.[24] mp 78–80 °C); ^{1}H NMR ($CDCl_3$) δ 1.35–1.70 (m, 6 H), 2.3–2.6 (m, 4 H), 2.9 (s, 6 H), 4.68 (s, 1 H), 6.6–7.4 (q, 4 H).

4-CH_3O-PAAN: mp 75.0–75 °C (lit.[24] mp 76–78 °C); ^{1}H NMR ($CDCl_3$) δ 1.4–1.7 (m, 6 H), 2.4–2.55 (m, 4 H), 3.88 (s, 3 H), 4.7 (s, 1 H), 6.9 (d, 2 H), 7.4 (d, 2 H).

4-CH_3-PAAN: mp 61.0–61.5 °C (lit.[24] bp 108–110 °C (0.2 Torr); lit.[25] bp 121–122 (4.0 Torr)); ^{1}H NMR ($CDCl_3$) δ 1.35–1.70 (m, 6 H), 2.3 (s, 3 H), 2.3–2.6 (m, 4 H), 4.7 (s, 1 H), 7.0–7.5 (q, 4 H).

PAAN: mp 63–64 °C (lit.[24] mp 62–64 °C); ^{1}H NMR ($CDCl_3$) δ 1.35–1.70 (m, 6 H), 2.4–2.6 (m, 4 H), 4.75 (s, 1 H), 7.2–7.6 (m, 5 H).

4-Cl-PAAN: mp 79.0–79.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.3–1.7 (m, 6 H), 2.4–2.6 (m, 4 H), 4.75 (s, 1 H), 7.2–7.55 (m, 4 H).

3-Cl-PAAN: mp 49–50 °C (lit.[25] bp 117–118 °C (3 Torr)); ^{1}H NMR ($CDCl_3$) δ 1.4–1.7 (m, 6 H), 2.4–2.6 (m, 4 H), 4.75 (s, 1 H), 7.2–7.6 (m, 4 H).

3,4-Cl_2-PAAN: mp 91.0–92.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.3–1.7 (m, 6 H), 2.3–2.7 (m, 4 H), 4.75 (s, 1 H), 7.4–7.7 (m, 3 H).

4-(Me_2N)-MOAAN: mp 137.5–138.5 °C (lit.[26] mp 137–139 °C); ^{1}H NMR ($CDCl_3$) δ 2.5–2.7 (m, 4 H), 2.98 (s, 6 H), 3.6–3.8 (m, 4

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H), 4.7 (s, 1 H), 6.6-7.5 (q, 4 H).

4-Me-MOAAN: mp 89-90.5 °C (lit.[25] bp 120-122 °C (4 Torr)); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.5-2.6 (m, 4 H), 3.6-3.8 (m, 4 H), 4.73 (s, 1 H), 7.15-7.5 (m, 4 H).

3-Me-MOAAN: mp 59.5-61 °C (lit.[27] mp 59-60 °C); ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.5 (m, 4 H), 3.6 (m, 4 H), 4.7 (s, 1 H), 7.1-7.3 (m, 4 H).

4-F-MOAAN: mp 64.5-66.0 °C (lit.[27] mp 60-63 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.75 (s, 1 H), 6.9-7.7 (m, 4 H).

3,4-(methylenedioxy)-MOAAN: mp 117.0-117.5 °C (lit.[28] mp 118-120 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.3-3.5 (m, 4 H), 4.68 (s, 1 H), 5.98 (s, 2 H), 6.7-7.3 (m, 3 H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.31; H, 5.61.

MOAAN: mp 67-69 °C (lit.[22] mp 68-70 °C); ^{1}H NMR ($CDCl_3$) δ 2.5-2.7 (m, 4 H), 3.65-3.8 (m, 4 H), 4.8 (s, 1 H), 7.4-7.7 (m, 5 H).

3-MeO-MOAAN: mp 44.5-45.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.4-3.9 (m, 4 H), 3.8 (s, 3 H), 4.7 (s, 1 H), 6.8-7.5 (m, 4 H). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.02; H, 6.87.

4-Cl-MOAAN: mp 75-76 °C (lit.[27] mp 70-71 °C).

3-Cl-MOAAN: mp 71.5-72.5 °C (lit.[25] mp 72-73 °C).

3-CN-MOAAN: mp 101.0-101.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.8 (s, 1 H), 7.3-7.9 (m, 4 H). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77. Found: C, 68.19; H, 5.57.

3,4-Cl_2-MOAAN: mp 74.3-74.9 °C (lit.[27] mp 62-64 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.55-3.75 (m, 4 H), 4.7 (s, 1 H), 7.1-7.6 (m, 3 H). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 53.16; H, 4.46. Found: C, 53.52; H, 4.41.

4-CF_3-MOAAN: mp 89-90 °C (lit.[27] mp 89-90 °C); ^{1}H NMR ($CDCl_3$) δ 2.4-2.7 (m, 4 H), 3.6-3.8 (m, 4 H), 4.75 (s, 1 H), 7.65 (s, 4 H).

4-CN-MOAAN: mp 117-118 °C (lit.[26] mp 128-128.5 °C).

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Registry No. 4-(Me_2N)-MOAAN, 17766-45-9; 4-(Me_2N)-MOAAN (anion), 123567-65-7; 4-MeO-MOAAN, 15190-13-3; 4-MeO-MOAAN (anion), 123567-66-8; 4-Me-MOAAN, 42419-53-4; 4-Me-MOAAN (anion), 123567-68-0; 3,4-(-OCH_2O-)-MOAAN, 37673-10-2; 3,4-(-OCH_2O-)-MOAAN (anion), 123567-70-4; 3-Me-MOAAN, 66549-30-2; 3-Me-MOAAN (anion), 123567-69-1; 4-F-MOAAN, 68415-10-1; 4-F-MOAAN (anion), 123567-86-2; MOAAN, 15190-10-0; MOAAN (anion), 123567-64-6; 3-MeO-MOAAN, 123567-57-7; 3-MeO-MOAAN (anion), 123567-67-9; 4-Cl-MOAAN, 33599-26-7; 4-Cl-MOAAN (anion), 123567-88-4; 3-Cl-MOAAN, 66548-90-1; 3-Cl-MOAAN (anion), 123567-87-3; 3-CN-MOAAN, 123567-58-8; 3-CN-MOAAN (anion), 123567-92-0; 3,4-Cl_2-MOAAN, 66549-47-1; 3,4-Cl_2-MOAAN (anion), 123567-89-5; 4-CF_3-MOAAN, 66573-60-2; 4-CF_3-MOAAN (anion), 123567-90-8; 4-CN-MOAAN, 28951-73-7; 4-CN-MOAAN (anion), 123567-91-9; 4-(Me_2N)-PAAN, 123567-59-9; 4-(Me_2N)-PAAN (anion), 123567-72-6; 4-MeO-PAAN, 15190-14-4; 4-MeO-PAAN (anion), 123567-73-7; 4-Me-PAAN, 42419-52-3; 4-Me-PAAN (anion), 123567-74-8; PAAN, 5766-79-0; PAAN (anion), 123567-71-5; 4-Cl-PAAN, 64661-38-7; 4-Cl-PAAN (anion), 123567-75-9; 3-Cl-PAAN, 42419-54-5; 3-Cl-PAAN (anion), 123567-76-0; 3,4-Cl_2-PAAN, 123567-60-2; 3,4-Cl_2-PAAN (anion), 123567-77-1; 4-Me-CAAN, 81311-83-3; 4-Me-CAAN (anion), 123567-80-6; 3-Me-CAAN, 123567-61-3; 3-Me-CAAN (anion), 123567-79-3; CAAN, 3893-23-0; CAAN (anion), 123567-78-2; 4-Cl-CAAN, 76618-95-6; 4-Cl-CAAN (anion), 123567-81-7; 3-Cl-CAAN, 85522-98-1; 3-Cl-CAAN (anion), 123567-82-8; 3-CF_3-CAAN, 123567-62-4; 3,4-Cl_2-CAAN, 123567-63-5; 3,4-Cl_2-CAAN (anion), 123567-83-9; PhCOMe, 98-86-2; PhCOMe (anion), 34438-71-6; $PhCOCH_2Ph$, 451-40-1; $PhCOCH_2Ph$ (anion), 54282-53-0; c-$C_5H_{10}NCH_2COPh$, 779-52-2; c-$C_5H_{10}NCH_2COPh$ (anion), 123567-84-0; c-$C_5H_{10}NCH(Ph)COPh$, 794-05-8; c-$C_5H_{10}NCH(Ph)COPh$ (anion), 123567-85-1; $PhCOCHPh_2$, 1733-63-7; $PhCOCHPh_2$ (anion), 111286-46-5; $PhCH_2CN$, 140-29-4; $PhCH_2CN$ (anion), 18802-89-6; Ph_2CHCN, 86-29-3; Ph_2CHCN (anion), 18802-83-0; CH_4, 74-82-8; PhMe, 108-88-3; Ph_2CH_2, 101-81-5; Ph_3CH, 519-73-3; Ph_2CH_2 (anion), 18802-87-4; Ph_3CH (anion), 40006-86-8; p-$MeC_6H_4CH_2CN$, 2947-61-7; m-$MeC_6H_4CH_2CN$, 2947-60-6; m-$ClC_6H_4CH_2CN$, 1529-41-5; m-$CF_3C_6H_4CH_2CN$, 2338-76-3; p-$Me_2NC_6H_4CHO$, 100-10-7; p-MeC_6H_4CHO, 104-87-0; 3,4-(-OCH_2O-)C_6H_3CHO, 120-57-0; m-MeC_6H_4CHO, 620-23-5; p-FC_6H_4CHO, 459-57-4; PhCHO, 100-52-7; m-$MeOC_6H_4CHO$, 591-31-1; p-ClC_6H_4CHO, 104-88-1; m-ClC_6H_4CHO, 587-04-2; m-CNC_6H_4CHO, 24964-64-5; 3,4-$Cl_2C_6H_3CHO$, 6287-38-3; p-$CF_3C_6H_4CHO$, 455-19-6; p-CNC_6H_4CHO, 105-07-7; p-$MeOC_6H_4CHO$, 123-11-5; c-$C_6H_{11}Br$, 108-85-0; c-$C_5H_{10}N$, 110-89-4; morpholine, 110-91-8.

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Palladium-Catalyzed Alkenylation and Alkynylation of Polyhaloarenes

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Alkenylation of several polyhaloarenes proceeded in low to moderate yields. Iodo groups could be reacted selectively in the presence of bromo groups; however, no more than two alkenyl groups could be introduced on contiguous, aromatic carbons. Alkynylation was more successful. Even hexa- and pentaalkynylarenes were obtainable in reasonable yields. Again, iodo groups could be reacted selectively in the presence of bromo groups. Convenient syntheses of a variety of 1,2,4,5-, 1,3,4,5-, and 1,2,4,6-tetrasubstituted aromatic compounds are possible by use of these reactions.

Several years ago we reported the palladium-catalyzed dialkenylation of *o*- and *p*-diiodobenzene[1] and later the selective monoalkenylation of *o*- and *p*-bromoiodobenzenes.[2] In the last examples it was noted that only the iodo group reacted when palladium acetate was the catalyst while both iodo and bromo groups reacted if a triarylphosphine was present in addition to the palladium acetate.[2] Chloro substituents were unreactive with either catalyst system.[3] Little additional work has been reported

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