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Diminished Reactivity of Ortho-Substituted Phenacyl Bromides toward Nucleophilic Displacement

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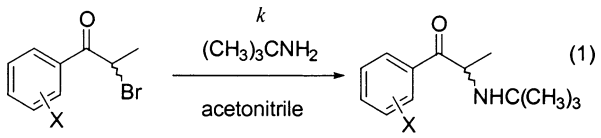
Abstract: A systematic increase of substitution rates by *tert*-butylamine on α-bromopropiophenones is observed with meta or para substituents with increasing electron-withdrawing ability ($k \times 10^3$ L M^{-1} min^{-1} = 12.7 (*p*-CH_3), 15.7 (*o*-F), 20.5 (H), 20.0 (*p*-Cl), 23.6 (*m*-Cl), 27.3 (*p*-CF_3)). Within an ortho-substituted series, the reactivities decrease ($k \times 10^3$ L M^{-1} min^{-1} = 7.64 (*o*-OCH_3), 5.31 (*o*-CH_3), 2.85 (*o*-Cl), 2.40 (*o*-CF_3)). Ortho-substitution results occur from rotational barrier effects and an Aδ_{o^+} Bδ_{o^+} repulsion. The major bonding contribution between reaction and α-substituent centers (A−B) is only the σ bond. When π bonding is allowed between A and B (meta/para-substitution), delocalization and stabilization of the reacting center occurs.

Nucleophilic substitution of α-bromoketones is synthetically useful and a topic of earlier mechanistic studies.[1] The synthesis of bupropion hydrochloride, **1**, first prepared in these laboratories,[2] relies on this chemistry and is commercially important as the active drug substance for the antidepressant Wellbutrin and the smoking cessation therapy Zyban. In the course of systematic modifications on the basic bupropion skeleton, it was noted that analogues with ortho substituents required significantly longer reaction times (eq 1).[3] This



(1)

1, X = *m*-Cl

offers a process advantage in the preparation of bupropion, because low-level *o*-chloropropiophenone impurities do not readily convert to bupropion analogues or give impurities, which are difficult to remove. In this report, we examine the effect ortho, meta, and para substituents impose upon S_N2 reaction rates for phenacyl bromides with *tert*-butylamine.

Dewar's delocalized transition state model has significant appeal to explain accelerated displacement rates of α-halo ketones.[4] A composite of propiophenones with meta/para substituents compared to ortho substituents for eq 1 presents a notable set of contrasting behaviors, which clarify the nature of delocalization in the reactive chemical intermediate.

Previous reports show a positive ρ value Hammett-correlated stabilization trend for displacement intermediates in meta/para-substituted phenacyl halides.[5] Likewise, we have shown (Table 1) a systematic increase in the rate of *tert*-butylamine substitution on α-bromopropiophenones with meta or para substituents, which have increasing electron-withdrawing ability. However this pattern reverses with groups in the ortho position. The compounds studied provide comparable electron donating/withdrawing properites and analogues with ortho-steric bulk. Ortho substituents present a rotational barrier in the transition state, which forces the phenyl ring away from π-orbital collinearity with the reacting "enolate type" transition state. This can be seen by AM1 minimization of the ground-state α-bromoketones (Table 1), which show greater phenyl-ring/carbonyl torsional angles for the ortho-substituted compounds. In addition to calculations, ^{13}C NMR measurements by Dhami and Stothers have demonstrated this type of twist for *o*-phenacyl compounds, and ^{17}O NMR studies on ortho-substituted acetophenones by Oakley and Boykin showed a deshielding pattern that was explained by steric inhibition of resonance.[6] From these studies, "in-plane" and "out-of-plane" substitution for the substrates examined in this study are grouped based on the measured ^{13}C chemical shift of the carbonyl carbon of the α-bromoketones. Note, the *o*-fluoro compound may be less bulky, and by physical measurement (both ^{13}C NMR and reaction rate) that material is more appropriately included with the "in-plane" substrates.

Meta and para electron-withdrawing groups cause a rate increase, but ortho substitution {with accompanying ortho-steric bulk} decreases this property. Trends within the "in-plane" vs "out-of-plane" series warrant discussion.

The p-orbitals in the reactive region of the transition state have a net negative charge, and meta/para-substitution allows alignment with the benzene ring (Figure 1). Hence, electron-withdrawing substituents enable greater conjugative charge delocalization.

The steric effect of ortho substituents hinders such extended π orbital alignment (Figure 2). Consequently, geometry restricts conjugative delocalization of negative charge.

Further, electron-withdrawing groups place ever-increasing partial positive charge directly adjacent to the electropositive carbonyl carbon of the reactive system. This, in turn, leads to a repulsion between positive charges that is most readily corrected by reduced polar-

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(6) (a) Dhami, K. S.; Stothers, J. B. *Can. J. Chem.* **1965**, *43*, 479. (b) Dhami, K. S.; Stothers, J. B. *Tetrahedron Lett.* **1964**, 631. (c) Oakley, M. G.; Boykin, D. W. *J. Chem. Soc., Chem. Commun.* **1986**, 439.

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TABLE 1. Bimolecular Rate Constants[a] for Eq 1 at 60 °C[b,c]

"In-Plane" Substitution					
p-CH_3	*o*-F[d]	H	*p*-Cl	*m*-Cl	*p*-CF_3
12.7 ± 0.3 {23.3°} (193.4 ppm)	**15.7 ± 0.9** {43.1°} (192.7 ppm)	**20.5 ± 0.5** {10.7°} (193.7 ppm)	**20.0 ± 0.5** {11.2°}	**23.6 ± 0.7** {26.1°} (192.4 ppm)	**27.3 ± 1.5** {27.9°} (192.6 ppm)

"Out-of-Plane" Substitution			
o-OCH_3	*o*-CH_3	*o*-Cl	*o*-CF_3
7.64 ± 0.19 {58.4°} (196.7 ppm)	**5.31 ± 0.27** {57.3°} (197.1 ppm)	**2.85 ± 0.14** {66.4°} (197.1 ppm)	**2.40 ± 0.25** {50.9°} (197.9 ppm)

[a] Rate constants are reported as k x 10^3 L mol^{-1} min^{-1}. [b] Dihedral angles between the phenyl ring and carbonyl oxygen of the α-bromoketones are in braces. [c] Carbonyl carbon ^{13}C NMR chemical shifts for the α-bromoketone are in parentheses. [d] The *o*-fluoro compound fits the meta/para trend rather than ortho in terms of both ^{13}C NMR and rate data.

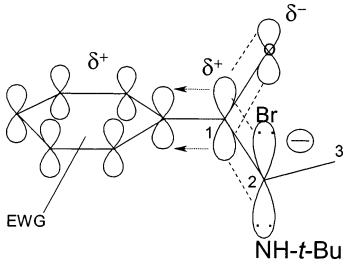

FIGURE 1. "In-plane" p-orbital transition state orientation.

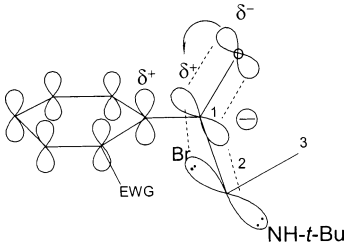

FIGURE 2. "Out-of-plane" p-orbital transition state orientation.

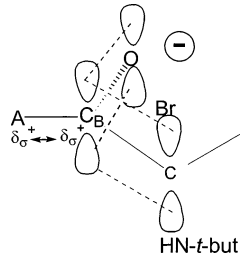

FIGURE 3.

ization of the carbonyl group. The carbonyl in this instance would be less able to delocalize the negative charge of the Dewar transition state.

We characterize this destabilizing interaction as $A\delta_{\sigma^+}$ $B\delta_{\sigma^+}$ since the major bonding contribution between centers A and B is only the σ bond (Figure 3). When π bonding is allowed between A and B, delocalization overcomes the $A\delta_{\sigma^+}$ $B\delta_{\sigma^+}$ repulsion and transition state stabilization of the reacting center occurs.

The $\alpha - \delta_{\sigma^+}$ effect occurs when electropositive α-carbons [7] cannot interact with electron-rich p-orbital systems, and they induce a δ^+ "like-charge" repulsion with the δ^+ nature of the transition state carbonyl carbon through the σ bond.

In summary, carbonyls and especially those with α-phenyl groups offer an extended stabilizing transition state π orbital system to S_N2 displacements. Steric hindrance, induced by a single *o*-phenacyl substituent, poses a rotational barrier to π orbital extension and results in a repulsion, $\alpha - \delta_{\sigma^+}$, which translates to transition state destabilization (augmented by electron-withdrawing groups). Magnification of this property observed in the 2,6-dichloro system[8] (>13-fold rate diminution vs 2-chloro) is consistent with a significant shutdown of the π orbital extension effect offered by the phenyl ring. Other observations for S_N2 reaction centers influenced by α-groups are explained by this $\alpha - \delta_{\sigma^+}$ effect. For example, Bordwell and Brannen reasoned that α-phenacyl groups offer a rate-enhancing conjugative effect. However, in the absence of conjugation, α-C_6H_5-SO_2- and α-CF_3 groups showed 1.6×10^6 and 2.0×10^8 rate diminutions ($\alpha - \delta_{\sigma^+}$), respectively, vs the α-phenacyl group.[1b]

Experimental Section

General. Reagents were commercially available and used directly without further purification. Propiophenones not readily available were prepared by a Grignard addition/Jones oxidation sequence. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were measured in $CDCl_3$ with $SiMe_4$ (δ 0 ppm) as an internal standard. HPLC data were collected with use of a short path C_{18} 3-μm column and UV detection at 220 nm.

Representative synthesis of propiophenones:

1-(2-Methylphenyl)-1-propanol. To an ether (200 mL) solution of *o*-methylbenzaldehyde (12 g, 0.1 mol) was added ethylmagnesium chloride (50 mL, 2.0 M in ether). The reaction mixture was quenched with HCl (110 mL, 1.4 M). The organic layer was washed with water (2 × 50 mL) and concentrated to an oil, 13.9 g (92%).

***o*-Methylpropiophenone.** To an acetone (160 mL) solution of 1-(2-methylphenyl)-1-propanol (13 g, 0.086 mol) chilled to 10 °C was added a 20% CrO_3/water/sulfuric acid solution (60 mL, 0.1 mol) and the temperature was held for ~2 h. The reaction mixture was added to water (150 mL) and extracted with methylene chloride (2 × 100 mL), and the organic layers were washed with water (2 × 50 mL) and concentrated. The resulting oil was distilled at 62−64 °C and 1 Torr, 8.8 g (69%).

(7) Described as rate retarding σ-acceptors: McLennan, D. J.; Pross, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, *981*.

(8) The substitution rate constant for α-bromo-2,6-dichloropropiophenone (eq 1) is k(60 °C) × 10^3 = 0.21 ± 0.016 L mol^{-1} min^{-1}.

Preparation of α-Bromopropiophenones. To a methylene chloride (5 mL) solution of the propiophenone (10 mmol) was added one drop of hydrobromic acid (48% aqueous solution) and one drop of bromine. The mixture was stirred and heated (∼35 °C). When the bromine color was discharged, bromine (10 mmol, total including the original 1 drop) was added dropwise with stirring. The reaction mixture was concentrated to remove the solvent and HBr, the reaction completion was confirmed by ^{1}H NMR and HPLC, and the concentrate was used directly in the *tert*-butylamine reaction without purification.

Kinetics for α-*tert*-Butylaminopropiophenones. Reactions were carried out in a heated 25-mL flask, internally thermostated at the desired temperature ± 0.2 °C by a J-Kem Model 250 temperature controller. Initial concentrations were adjusted to 1 M for the α-bromopropiophenone and 2.05 M for *tert*-butylamine in acetonitrile. Samples (0.1 mL) were taken at appropriate intervals and quenched in $CDCl_3$ for analysis by both ^{1}H NMR and HPLC. Equation 1 stoichiometry is A + 2B → C + D for (A) α-bromopropiophenone, (B) *tert*-butylamine, (C) *tert*-butylaminopropiophenone, and (D) *tert*-butylamine hydrobromide. The integrated rate expression for this reaction is:

$$k_t = 1/([B_o] - 2[A_o])\ \ln\{1 + [C_t]/[A_t](1 - 2[A_o]/[B_o])\} \quad (2)$$

This algebraic form for a bimolecular reaction is particularly useful because eq 2 employs the concentration ratio, [C]/[A], which is readily obtained by either NMR or HPLC [the ratio of integration areas does not require component concentration measurements]. The product:starting material ratio was determined by integration of the well-separated carbinyl proton peaks in the NMR, and by measurements of the area under the curve in the HPLC for each time point. Second-order rate constants (k = slope) for each reaction were determined by linear regression, using Microsoft Excel 97 SR-2.

Supporting Information Available: ^{1}H NMR spectra for the *o*-propiophenones, selected α-bromo compounds, and mass spectral product characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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