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LARGE RATE ACCELERATIONS IN ALDOL REACTION OF *ORTHO*-SUBSTITUTED BENZALDEHYDES

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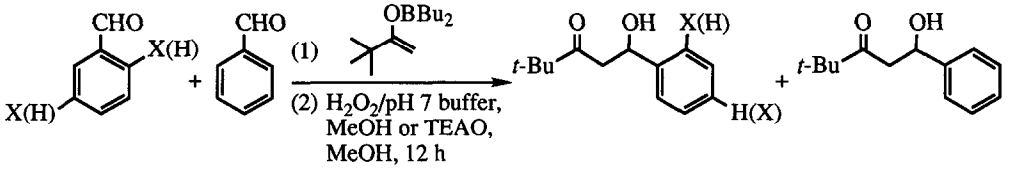
Abstract: *The relative reactivities of ortho- and para-substituted benzaldehydes with the dibutylboron enolate of pinacolone have very different substituent dependences ortho substituents give large rate enhancements with electron-releasing substituents, while para substituents give extremely small rate effects Since chelation is inaccessible to the boron enolate (which must also complex to the aldehyde), the origin of the large ortho effects was investigated by multiple regression analysis, which shows that the rates are insensitive to steric effects, but are dominated by resonance interactions, The polarizability and, to a small extent, the field effect of the substituents also affect the reactivity. The most consistent mechanistic explanation involves a variable transition structure with the relative degrees of aldehyde C—O bond-breaking and enolate–aldehyde C C bond-making changing with substituents*

The increased reactivity of *o*-anisaldehyde vs. benzaldehyde ($k_{o\text{-MeO}}/k_H$ = 6.5) in methyl addition from $MeTi(OCHMe_2)_3$ was suggested to result from chelation involving the *ortho*-methoxy group, which is in a potentially chelating orientation.[1,2] In view of our recent discovery that chelation is not operative in the very large rate enhancements we found in aldol reactions of α-alkoxy ketones with lithium pinacolone enolate,[3] we were led to ask whether chelation would be obtained in *aldol* reactions of *o*-anisaldehyde. An acceleration, $k_{o\text{-MeO}}/k_H$ = 1.75, is seen with lithium pinacolone enolate. We examined the question of chelation using the corresponding dibutylboron enolate—after complexation to the aldehyde carbonyl oxygen, boron would be incapable of further chelation. The result is striking: $k_{o\text{-MeO}}/k_H$ now = 66.7 (whereas $k_{p\text{-MeO}}/k_H$ = 0.69)! Clearly, there is a source of *ortho* rate enhancement other than chelation.



Because the large rate effect observed with the boron enolate is both unexpected and potentially useful in designing selective reactions of aromatic aldehydes (and possibly of related aldehydes as well), it would be very desirable to know its origin. We have therefore measured relative reactivities for a series of substituted benzaldehydes and carried out multiple-regression analyses to determine the nature of the *ortho* substituent effects. The results show that the large rate acceleration has little steric, or chelation, or field effect component, whereas we found that the reactivity of α-substituted aliphatic ketones is almost entirely determined by a very strong field effect.[3] Instead, the source is revealed to be *mainly a resonance effect.*

The rate-enhancing influence of ortho substituents, particularly an *o*-MeO group, in other nucleophilic additions to benzaldehydes has been documented.[4,5] Although the effects of *p*-substituents on the reactivity of benzaldehydes in nucleophilic additions and the aldol reaction have been reported,[6] there has been no systematic study on the effect *o*-substituents in aldol reactions.

We have discovered that all *ortho*-substituted benzaldehydes, particularly π-donors, accelerate the boron-mediated aldol reaction. Our results show that resonance, polarizability, and (to a very minor extent) inductive effects of the *o*-substituent determine relative reactivity. Within the substituent range studied, electronegativity and steric effects are found to be unimportant.

We determined relative reactivities of *o*- and *p*-substituted benzaldehydes[7] with the dibutylboron enolate of pinacolone in diethyl ether at −78 °C (Table I).[8] Relative reactivities were calculated from 500-MHz ^{1}H NMR product ratios using previously derived equations.[3,9] Unlike the *o*-substituted benzaldehydes, *p*-substituted benzaldehydes showed only modest variation in reactivity[6] on changing the substituent. We determined the relative reactivities with *o*-anisaldehyde for the corresponding Li-, $Ti(OCHMe_2)_3$-, and $TiCl_3$-enolates as well as in the Mukaiyama reaction ($TiCl_4$ + the corresponding trimethylsilyl enol ether). Chelation could be invoked to explain the accelerations for *o*-anisaldehyde, especially for the $TiCl_3$-enolate and the Mukaiyama reaction,[1a] but *the boron enolate showed the largest rate enhancement!*[10]

Table I. Relative Reactivities of XC_6H_4CHO in Aldol Reactions with Pinacolone at −78 °C

Aldehydes *o*-X–PhCHO/PhCHO	$k_{rel}(k_X/k_H)$	Aldehydes *p*-X–PhCHO/PhCHO	$k_{rel}(k_X/k_H)$
o-MeO–	66.7[a]; 46[b]; 7[c]; 2.4[d]; 1.75[e]	*p*-MeO–	0.69[a,f]
o-MeS–	29.6[a,g]	*p*-Me_2N–	[a,h]
o-Cl–	29.5[a]	*p*-Cl–	1.09[a,f]
o-Br–	28.6[a]	*p*-F–	0.66[a,f]
o-F–	8.4[a]	*p*-O_2N–	1.82[a,f]
o-Me–	5.5[a]		
o-F_3C–	2.56[a]; 1.77[e]		
o-O_2N–	3.37[a]		
o-Me_2N–	3.48[a]		
o-NC–	6.86[a,g,i,j]		

[a]Competitive reactions were performed with dibutylboron enolate in diethyl ether using a large excess of both aldehydes;[3] average (standard) deviations for two (or more) runs were usually a few %, always ≤ 10%. [b]Mukaiyama reaction conditions, in dichloromethane. [c]Reaction with preformed trichlorotitanium enolate. [d]Reaction with triisopropoxytitanium enolate in diethyl ether. [e]Reaction with lithium enolate, in diethyl ether [f]Relative reactivities obtained indirectly by multiplication of independently measured ratios using $(k_X/k_H) = (k_X/k_{o\text{-Me}}) \times (k_{o\text{-Me}}/k_H)$. [g]Workup performed using excess trimethylamine oxide in methanol at 25°C, 20 h. [h]Attempted determination was unsuccessful under a variety of conditions: this aldehyde was insufficiently soluble to permit competitive rate determination. [i]Estimated by extrapolation from the relative reactivities at −35°C and −15°C. [j]In this case the initial aldol adduct reacted intramolecularly to form the lactam.

Because boron cannot coordinate to both the carbonyl and the OMe, the acceleration by *ortho* substituents must result from other effects. The results for *ortho*-substituted benzaldehydes show a substantial variation in reactivity, making it possible to carry out a multiple-regression analysis of the origin of the substituent effects. However, the very small rate effects with *para* substituents preclude any such analysis. Considerable success has been obtained in modeling the *ortho* effect in terms of linear combination of the resonance, field and steric effects.[11,12] The close similarity of *o*-O_2N and *o*-Me_2N reactivities (Table I) shows that both substituents are noncoplanar and essentially not conjugated with the ring, as was found previously for *o*-O_2N.[13,14] Moreover, we have carried out extensive computations which show that statistically significant results are only obtained with substituent constants characteristic of perpendicular conformations of these groups ($\sigma_R = 0$). Therefore, perpendicularity is assumed in all correlations presented below. We also found that the resonance parameter σ_R^+ gave considerably better correlations than σ_R^0 or σ_R^-. A forward stepwise regression analysis[15] using σ_R^+, σ_F, σ_α (polarizability), σ_χ (electronegativity), and ϕ_v (Charton steric parameter) gave eq 1.[16,17] where n

$$\log (k_X/k_H) = \rho_R^+\sigma_R^+ + \rho_\alpha\sigma_\alpha + \rho_F\sigma_F + h \quad (1)$$

$\rho_R^+ = -3.40 \pm 0.34$; $\rho_\alpha = -0.98 \pm 0.20$; $\rho_F = 0.50 \pm 0.22$; $h. = 0.04$; $n = 11$, $R = 0.974$, $F = 42.46$, $s = 0.15$

is the number of substituents, R is the multiple correlation coefficient, and F is the F-statistic. In the course of this analysis, the terms containing both σ_χ and ϕ_v were shown to be totally insignificant (partial F values < 1), demonstrating that there are no significant steric or electronegativity effects controlling the rates. A backward-elimination stepwise regression analysis gave exactly the same results.

The *o*-MeS substituent gave, by far, the largest discrepancy between predicted and observed reactivities. In fact, other workers have found that it is not possible to define a consistent σ_R^+ value for MeS.[18,19] Moreover, there is evidence of special sulfur–carbonyl oxygen interactions in *o*-MeS-benzaldehyde.[20,21] If this far-outlying substituent is removed from the multiple correlation, eq 2 results. The overall result is not changed in

$$\log (k_X/k_H) = \rho_R^+\sigma_R^+ + \rho_\alpha\sigma_\alpha + \rho_F\sigma_F + h \qquad (2)$$

$\rho_R^+ = -3.77 \pm 0.16$; $\rho_\alpha = -1.31 \pm 0.11$; $\rho_F = 0.39 \pm 0.10$; $h. = -0.04$; $n = 10$, $R = 0.995$, $F = 207.75$, $s = 0.07$

any fundamental way, but the fit is significantly improved ($F = 208$)! We believe that these results (eq 2) reflect the best estimate of the true origin of the effects of *ortho* substituents on rates in this aldol reaction. The variables σ_R^+, σ_F, and σ_α are not significantly colinear in this system, as shown by $|r| \leq 0.12$.[15] A plot of the experimentally observed values of log (k_X/k_H) vs. those calculated from eq 2 is shown in Figure 1.

It is of considerable interest that highly significant correlations involving *ortho* substituents were possible in these reactions. The demonstrated unimportance of steric interactions is especially noteworthy. We have also carried out many other multiple regressions using other sets of substituent constants. In all cases, the basic conclusions are unaffected: in particular, the rate effects are found to be dominated by resonance interactions, and the values of ρ_R^+ did not differ by more than 10%. Hence, resonance control with a very significant negative ρ_R^+ seems established.

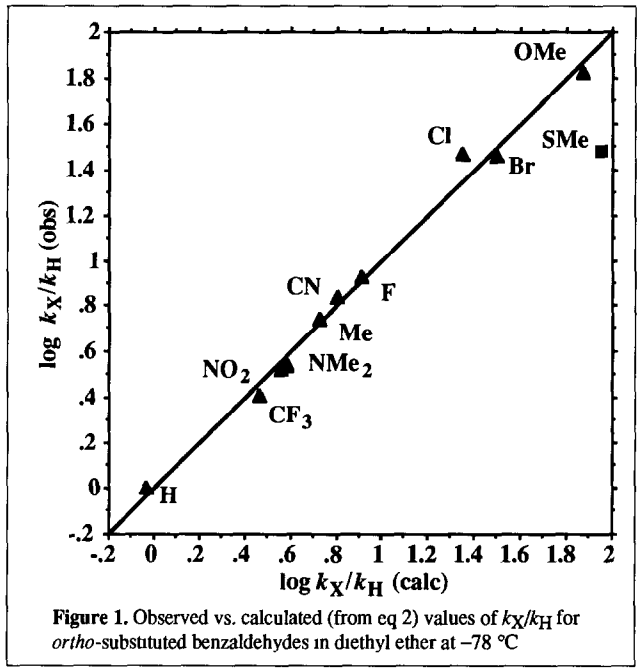


Figure 1. Observed vs. calculated (from eq 2) values of k_X/k_H for *ortho*-substituted benzaldehydes in diethyl ether at –78 °C

Our reactivity data were measured and computed to give ratios which necessarily reflect the rates of reaction of the *aldehydes* and not aldehyde–enolate complexes, even if the complexes are populated to a large extent in the first step of a two-step aldol process. The large, negative value of ρ_R^+ shows that the carbonyl carbon in the transition structure is highly electron-deficient relative to the reactant aldehyde. This result is most consistent with a transition state in which boron–oxygen bond formation is more advanced than C–C bond formation. A stepwise process involving coordination of boron to the carbonyl oxygen followed by rate-determining attack of the enolate on the highly electron-deficient carbonyl carbon in an early transition structure seems likely.

Significant polarizability interactions, as indicated by correlation, are quite consistent with the above type of transition structure, given the proximity of the *ortho* substituents and the extra electron deficiency present in the transition structure relative to the reactant aldehydes. The virtual absence of field effects is surprising but is consistent with a transition structure in which *ortho* substituents may be oriented with their dipoles not far from perpendicular to the dipolar structure of the pericyclic aldol reaction site.

The insensitivity of the reaction to *para* substituents remains to be considered. In principle, the difference could result from different mechanisms, a change of rate-determining step within the same mechanism, or a variable transition structure within basically the same rate-determining step.[22] It cannot be ruled out that the *para* substrates might react by a concerted pathway, which would involve incomplete B···O bond formation in the transition structure and thus probably a lower δ+. Different mechanisms are difficult to accept based on the demonstrated unimportance of *ortho* steric effects and the fact that the *ortho* aldehydes react faster; there is

no known reason why the whole range of *para* substituents would proceed by a different mechanism. A change of rate-determining step requires that the set of rates exhibiting low sensitivity to substituents must be higher than those of the substituent-sensitive set.[22] Here, the substituent-insensitive *para*-substituted aldehydes react *more slowly* than *ortho*, which is inconsistent with a change of rate-determining step. This conclusion is not perfectly rigorous because of the structural difference between *ortho* and *para* sites, but the demonstrated insensitivity of the *ortho* rates to steric effects strongly suggests that the ortho and *para* sites are comparable, and thus that a change of rate-determining step is improbable.

A variable transition structure, with the relative degrees of aldehyde C⋯O bond-breaking and enolate–aldehyde C⋯C bond-making changing with substituents, is entirely consistent with the data.[23,24] Curved substituent-effect plots are common with substituted benzylic systems, because substituents simultaneously affect both bond-breaking and bond-breaking at the benzylic carbon. For example, a curved plot giving a range of rates comparable to those observed here has been shown for the SN_2 reactions of *p*-substituted benzyl chlorides with aniline.[25] The present aldol reaction is closely analogous, and our results appear to show similar behavior when *ortho* and *para* substituents are taken together. The electron-releasing *o*-MeO group is expected to loosen the transition structure[23,24] to give a relatively high δ+ on the "benzylic" carbonyl carbon, and other substituents would give tighter transition structures, eventually giving a leveling off or even a minimum in rates. Since *p*-substituents are really "vinylogous *ortho*" substituents, their effects would be attenuated relative to *ortho*, with the result that the *para* rates might be near the expected leveling off point or minimum *relative to ortho*, just as in Table I. This variable transition structure hypothesis provides the most reasonable mechanistic explanation for the differences between our *ortho* and *para* substituent effects.

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