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A PREDICATIVE MODEL FOR CERTAIN DIRECTED METALATIONS, II; APPLICATION TO THE BEHAVIOR OF p-FLUOROANISOLE

D. W. Slocum and D. S. Coffey, Department of Chemistry,
Western Kentucky University, Bowling Green, KY, 42101

A. Siegel and P. Grimes, Department of Chemistry,
Indiana State University, Terre Haute, IN, 47809

Abstract: A theoretical model has been developed which predicts that the p-fluoro substituent should significantly accelerate the rate of directed metalation of anisole. This electronic effect has been demonstrated; it can be generalized.

Having achieved some insight into factors that influence/control the rate and extent of ortho-lithiation of anisole,[1] our interest turned to comparison of these results with those for para-substituted anisoles. In particular, the results of study of the metalation of p-fluoroanisole (p-FA) is intriguing. More than 50 years ago Gilman and coworkers[2] reported a "violently exothermic reaction" when an ether solution of p-FA was treated with n-BuLi. After 20h at 34°C, the solution was poured over dry ice and a yield of 13% of the carbonation product ortho to the methoxy group was isolated. Similarly, Eaborn and Walton[3] metalated p-FA at room temperature with PhLi followed after 30 min by treatment with trimethylsilylchloride (TMS-Cl) to produce a 13% yield of the ortho-to-the-methoxy TMS product. A better yield (33%) of the carbonation product was produced after 5 hr when p-FA in THF was treated with n-BuLi at room temperature.[4] The initial observation of an exotherm by Gilman[2] can be attributed to the formation of the methoxy benzyne intermediate initiated by metalation ortho to the fluoro substituent.[5]

Subsequent reports describe results for metalation at -78°C. These reports are puzzling since, as part of the study described in our companion paper,[1] we had treated anisole with n-BuLi at temperatures of 0°C and lower. Anisole undergoes metalation very slowly at 0°C and virtually not at all at temperatures below this.[6] On the other hand fluorobenzene can only be metalated at -50°C (or below) and does so fairly readily.[7] At temperatures above -50°C the benzyne intermediate is formed.

Thus it was doubly intriguing to us when reports began to be published of the behavior of p-FA when it was treated with alkyllithium reagents at these low temperatures. In one study, use of sec-BuLi in THF provided, after 15 min, a 3:1 mixture of two products, one ortho to the methoxy, the other ortho to the fluoro, with the ortho-to-methoxy product predominating.[8] In other studies metalation and derivatization ortho to the fluoro substituent, i.e., a reversal of orientation, in high yield was achieved by 1) complexation of p-FA by the $-Cr(CO)_3$ moiety[9] and 2) by metalation with "superbase" (n-BuLi/KOtBu).[10] These latter two results were achieved by metalation for one and two hours, respectively, at -78°C. Seemingly, these low temperature runs were proceeding faster than those at 25°C.

To our view, these observations were mutually contradictory unless a heretofore unidentified factor were operating. This factor would serve to provide an acceleration of the rate of metalation ortho to either substituent; in particular this factor would operate at -78°C as well as 25°C. In other words, an electronic effect on the course of metalation in this system must exist.

The presence of this effect is readily revealed in the plot in Figure I. In particular, use of 2 eq. of n-BuLi affords a gc yield (uncorrected) of greater than 55% of the ortho-to-the-methoxy TMS product[11] in just one hour. This is four times the extent of metalation of anisole under identical conditions. If the reaction is allowed to proceed for longer periods, less of this product is achieved, presumably because of metalation/transmetalation taking place ortho to the fluorine with subsequent benzyne formation. A number of the anticipated benzyne products for this reaction were detected by gc-mass spec.[12]

We propose that the ground state resonance structures that raise the ground state energy and reduce π-donation at the ortho and para positions to both substituents[13] (Fig. II) render the methoxy group a better coordinative director in this system than it is in anisole. The unshared electron pairs on the methoxy group are less involved with overlap with the ring and consequently more available to coordinate with the organolithium oligomer. In addition the ring protons are rendered more acidic than those in anisole both by a cumulated electron-withdrawal effect of the two electronegative ring substituents as well as by a decrease at each ring position in localized π-donated negative charges. Thus metalation ortho to the methoxy group in p-fluoroanisole should proceed at a much faster rate than metalation of anisole.

These observations allow an interpretation of the data obtained by previous investigators. For the three early papers, in one the metalation was run too long, too weak a base was used in the second as well as an insufficient amount of alkyllithium reagent in all three. For metalation to be achieved at all at -78°C, the accelerating effect of the p-substituent must be operating. For metalation to take place ortho to the fluoro substituent exclusively, no coordinative directed metalation can occur, rather the overriding base effect must be operative.[1] This is conveniently achieved by the "superbase" system or by rendering the ring protons significantly more acidic by complexation with the $Cr(CO)_3$ moiety so that n-BuLi in effect functions by the overriding base mechanism.

This interpretation leads to the prediction that similar π-donating substuents, -Cl, -Br, -I, $-NMe_2$, -OMe and possibly alkyl groups located in the p-position of anisole should provide the same acceleration. Preliminary data supports this contention.

FIGURE I

Rate and Extent of DM of Anisole and p-Fluoroanisole (p-FA)

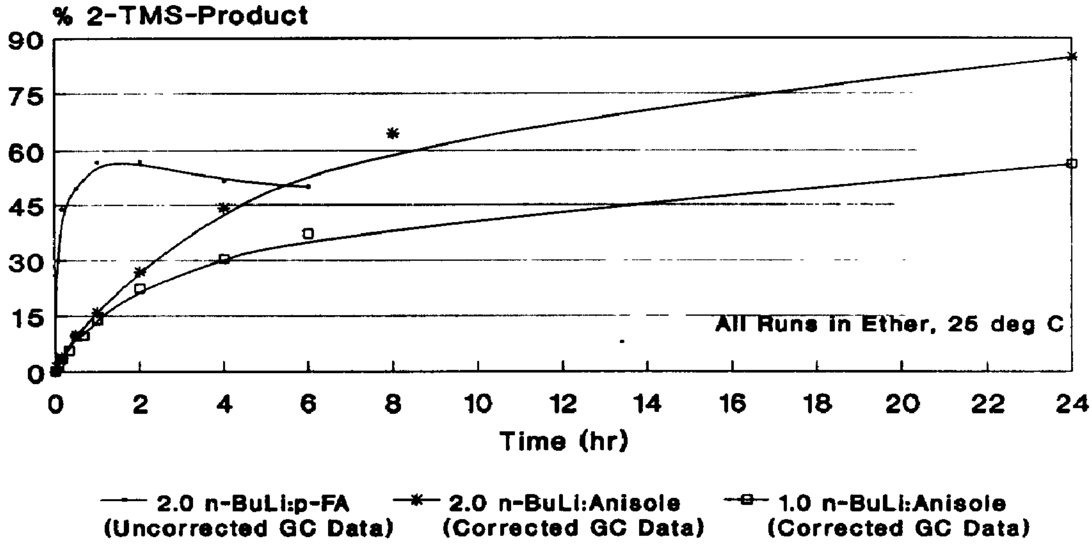
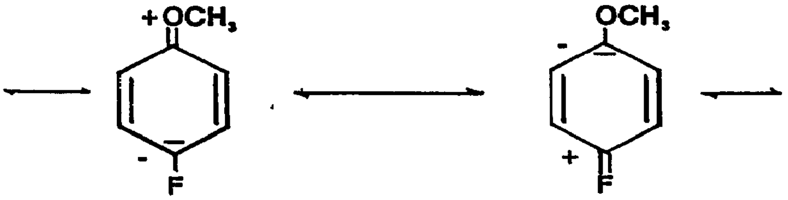


FIGURE II

Ground State Resonance Structures in p-Fluoroanisole (p-FA)



- Opposing g.s. resonance structures raise g.s. energy: reduces π - donation at ortho and para positions.

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11. Concentrations, methods and procedure are described in our companion paper.[1] It proved too difficult a task to effectively correct the GC spectra of the mixture of products from this reaction; corrected 2-TMS-4-fluoroanisole percentage would not dramatically change our qualitative results.

12. HP 5890A Gas Chromatograph coupled with an HP 5970 series mass selection detector; detected were masses corresponding to two butylanisoles and two TMS butylanisoles.

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