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A PREDICATIVE MODEL FOR CERTAIN DIRECTED METALATIONS, I; APPLICATIONS TO THE BEHAVIOR OF ANISOLE

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Abstract: A model whereby the relative ability of the methoxy group to direct metalations in aromatic systems is described. Evidence is presented for a dramatic acceleration of the rate of metalation of anisole provided by the presence of TMEDA resulting in the largest yield of ortho-metalation (>95%) heretofore reported. Lastly, significant acceleration of the rate of metalation of anisole has been found using a catalytic amount of TMEDA.

Nothing seems to have defeated the probes of mechanistic comprehension longer than the reaction sequence known as directed metalation. From its period of discovery[1,2] through numerous examinations, little insight has been gained into the details as to how the reaction progresses.[3] By making certain assumptions regarding the relative importance of various steps in the reaction sequence, we have discovered a model whereby two important features of the system can be predicted, namely, the relative reactivity of a directing group when placed in various competitive environments as well as the position of attack when more than one acidic site is present in the same molecule.

Aromatic substitution via metalated intermediates generated by organolithium reagents (AS_M) is made regiospecific by virtue of the presence of an ortho-directing metalation group (DMG). Often, but not always, this DMG possesses a heteroatom containing an unshared pair of electrons which serves to coordinate with the organolithium oligomer as·a prelude to the ultimate hydrogen-metal exchange. For such directing groups the availability of this unshared electron pair is the key to predicting the rate and extent of metalation provided by a particular DMG in a particular environment.

When the heteroatom is bonded to an aromatic system, ground state resonance decreases the availability of this electron pair. This idea is illustrated for anisole in Figure I. Ground state resonance depletes the electron density on oxygen rendering it a less effective coordinating DMG. Moreover, ground state resonance serves to decrease the inductively-induced acidity of the ortho protons. Complexation of this oxygen atom must take place to remove the restrictions placed on the molecule. Such a complex and the envisioned

FIGURE I
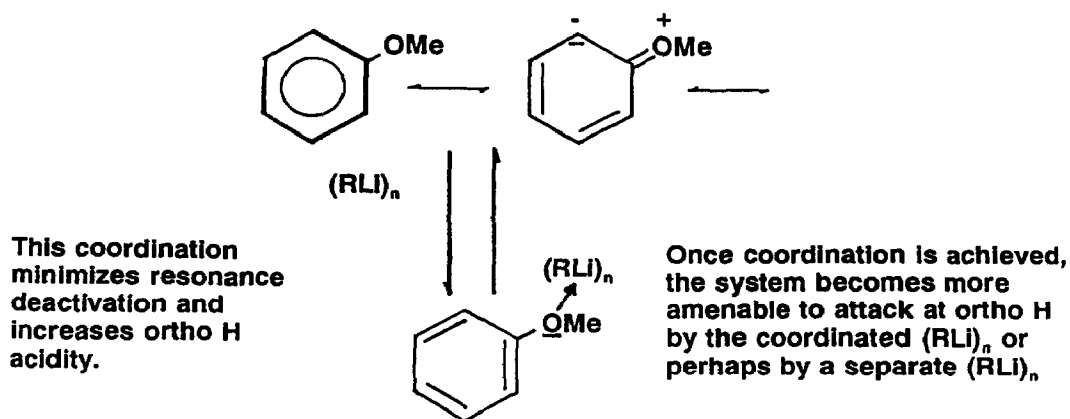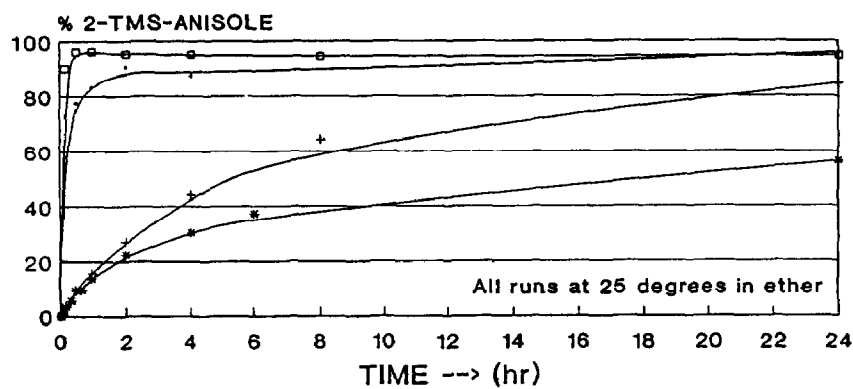
Directed Metalation of Anisole

(RLI)$_n$

This coordination minimizes resonance deactivation and increases ortho H acidity.

Once coordination is achieved, the system becomes more amenable to attack at ortho H by the coordinated (RLi)$_n$ or perhaps by a separate (RLi)$_n$

FIGURE II

Rate and Extent of DM of Anisole Using n-BuLi and TMEDA

% 2-TMS-ANISOLE

All runs at 25 degrees in ether

TIME --> (hr)

Ratios relative to 1.0 anisole

— 2.0 n-BuLi/0.2 TMEDA   —+— 2.0 n-BuLi

—*— 1.0 n-BuLi   —•— 2.0 n-BuLi/2.0 TMEDA

intermediate necessary to form it are also depicted. Similar complexes for directed metalation have been suggested previously,[3] but the overall implications of their formation have not been exploited.

The mechanism envisioned for the ortho-metalation when directed by a coordinating electron pair on a DMG is a simple one, a relatively slow initial coordination by the organolithium oligomer followed by fast metal-hydrogen exchange, either within the same oligomer structure or by reaction with a second oligomer. This mechanism has served to correlate the relative reactivities of several systems presently under examination. Thus, to provide prediction of relative reactivity in the DM reaction, estimation of the contribution of ground state resonance involving the DMG provides the initial insight. Consideration of the effectiveness of the heteroatom(s) in the DMG to coordinate lithium (N>O>hal) and to withdraw inductively electron density from the ortho positions (F>O>N) must also be made. Using anisole as an example we can state the following: oxygen is intermediate in its coordinating ability and inductive withdrawal but is relatively strong in its π-donating ability to the benzene ring. Formation of the coordinated intermediate would be predicted to be relatively slow; hence the initial rate of the reaction will be slow and the overall progression of the metalation modest.

The validity of this analysis is illustrated in Figure II. A 1.0 eq n-butyllithium: 1.0 eq anisole reaction at 25°C in ether at modest concentration proceeds to only a little better than 50% completion in 24 hrs [as measured by trapping with trimethylsilylchloride (TMS-Cl) and subsequent gc analysis (corrected)].[4] A 2:1 ratio of reactants affords a moderately faster rate and a greater extent of metalation. It should be mentioned that only by inspection of plots of the analytical results from samples taken during the course of the reaction (four samples during the first hour and four subsequent samples) can we make these comparative observations.

A remarkable change in the course of the reaction upon addition of TMEDA (tetramethyl-ethylenediamine) is revealed in Figure II. Within 1/2 hour an extent of metalation >95% is achieved for the system 2.0 eq. n-BuLi:2.0 eq. TMEDA:1.0 eq. anisole. Acceleration of the rate of metalation of anisole by TMEDA was first reported more than 20 years ago[5] Extent of metalation was investigated more recently, but a maximum yield of only 73% metalation was achieved using a 3:3:1 ratio of reactants.[6]

The progress of metalation profile revealed in Figure II dictates that metalation with TMEDA present is not proceeding via the coordinative mechanism proposed above. We project that this ortho metalation takes place via a simple "overriding base" metal-hydrogen exchange which has the ability to react rapidly with the relatively acidic ortho protons. Coordination is not involved and thus the slow step in the sequence is avoided.

One last feature of the insight that these deliberations have provided is the revelation that TMEDA is effective in less-than-stoichiometric amounts. Figure II shows a reaction profile for the system 2.0 eq. n-butyllithium: 0.2 eq. TMEDA: 1.0 eq. anisole. This plot illustrates that this system is about 90% as effective as when the full 2 eq. of TMEDA is used. In other words, TMEDA is functioning catalytically! We have noted this effect in several related systems presently under investigation.

Insight into experimental observations can be made from these deliberations. We previously had observed that p-methoxydimethylbenzylamine can be effectively metalated with n-BuLi ortho to the amine group but that metalation occurred ortho to the methoxy group when the n-BuLi/TMEDA complex was utilized.[5,7] This phenomenon can now be attributed to the dramatic acceleration of the rate of metalation ortho to the methoxy group provided by the presence of TMEDA. An assumption implicit in this argument is that such dramatic acceleration of the rate of metalation by TMEDA will not be imparted to DMG's lacking an electronegative atom bonded to the ring. Preliminary examination of the metalation of dimethylbenzylamine in the presence of TMEDA suggest that this is indeed the case.

Application of the theory to a number of related systems, p-chloro and p-methylanisole, 1,4-dimethoxybenzene, 1- and 2-methoxynaphthalene as well as certain more complicated substituted systems has allowed us to predict their sites(s) of metalation and relative reactivities. Results from these studies will be published in due course. The provocative insights and results for p-fluoroanisole, a direct result of application of our theory, are described in the following paper.

Acknowledgements:

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4. HP 5890 with an OV-17 packed glass column. The rate and extent of metalation of anisole is concentration dependent. The data recorded in Figure II was attained using the following quantities: .04 mole anisole, 60 mL dry ether, .04(.08) mole n-BuLi (2.5 M) in n-hexane, .008 (.08) mole TMEDA.

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