COMPETITIVE METALATION OF SOME NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

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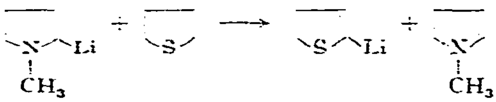
It has been apparent for some years[1] that the most important factor which influences the position of the entering metal atom in the metalation of aromatic and heterocyclic systems with alkylalkali compounds is the inductive effects of ring substituents or ring heteroatoms. Strong electronegative substituents polarize the ring C–H bonds rendering them more susceptible to a "protophilic" attack[2] which removes the proton. Such an attack seems to be particularly rapid when there exists opportunity for prior coordination of the metalating agent with a substituent, followed by removal of H^+ via a quasi-ring transition state[1]. In correlation of the available data on orientation of the entering metal atoms and relative rates of reaction in a variety of systems, there seems to emerge a significant amount of evidence against the "normal" patterns of electrophilic and nucleophilic aromatic substitutions which involve discrete intermediates with both attacking and leaving groups bound to the ring. The metalation reaction probably involves quite temporary and relatively minor distortions of the aromatic π-electron cloud compared with the other substitution reactions. These ideas have gradually evolved from the accumulating data of various workers over the past fifteen years, but perhaps the single most significant statement on the matter was made by Bryce-Smith[2].

An apparent exception to the idea of the predominant importance of the inductive effect of substituents and heteroatoms in the control of metalation orientation is found in the earlier literature of the metalation reaction. Gilman and co-workers studied the relative tendencies of oxygen, nitrogen and sulfur as heteroatoms to activate adjacent ring positions toward attack by metalating agents. It was demonstrated[3] that the order of degree of activating influence was oxygen > sulfur > nitrogen. This order was established by intermolecular competitive metalation processes with dibenzofuran, dibenzothiophene and N-ethylcarbazole and also by the observation that dibenzothiophene was metalated by 1-lithio-N-ethylcarbazole but N-ethylcarbazole was not metalated by 4-lithiodibenzothiophene. Also supporting the above order are results of metalation of phenoxathiin which indicated orientation of the entering lithium atom adjacent to the oxygen rather than the sulfur atom[4] and the metalation of N-ethylphenothiazine adjacent to sulfur rather than nitrogen[5].

The apparent predominance of the inductive effect in control of the orientation of the entering metal atom should indicate the order of activation of adjacent positions as oxygen > nitrogen > sulfur, which is the order of decreasing electronegativities of the atoms in the Pauling scale. This order exchanges the positions of nitrogen and sulfur compared with the series derived above from the metalation results. These comparisons are complicated by the use of *N*-ethyl derivatives of the heterocycles in placing nitrogen in the series, since steric factors may be involved in the relatively slow metalation at positions adjacent to *N*-ethyl groups. At the same time it is not valid to use the heterocycles containing >N–H groups for the nitrogen comparison since these are rapidly converted to >N–Li types by the metalating agent.

It is the purpose of this work to look further at the relative influence of heterocyclic nitrogen and sulfur atoms toward the metalation process. This involves an examination of some additional systems not included in the earlier work and the use of *N*-methyl groups in the nitrogen-containing heterocycles.

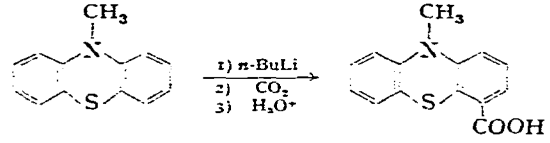
Both thiophene[6] and *N*-methylpyrrole[7] metalate readily with *n*-butyllithium in the 2-position. A mixture of four equivalents each of thiophene and *N*-methylpyrrole was allowed to compete for one equivalent of *n*-butyllithium after which the organolithium compounds present were converted to carboxylic acid salt with carbon dioxide. The acid products were isolated with minimum possible disturbance of product composition. The product was essentially pure thiophene-2-carboxylic acid indicating much faster metalation of the sulfur-containing ring. It was also observed that 2-lithio-*N*-methylpyrrole metalated thiophene but 2-lithiothiophene was without effect on *N*-methylpyrrole.



The above results were substantiated by experiments in which the metalations of thiophene and *N*-methylpyrrole were carried out separately by an insufficient amount of *n*-butyllithium and the time required for the disappearance of *n*-butyllithium (as measured by the Gilman Test II[8]) was noted. Only three minutes were required in the thiophene case as compared with five hours for the *N*-methylpyrrole.

The competitive metalation of thianaphthene and *N*-methylindole was conducted as indicated above with the result that only thianaphthene-2-carboxylic was isolated. Also 2-lithio-*N*-methylindole was found to metalate thianaphthene, but 2-lithiothianaphthene failed to metalate *N*-methylindole. The individual heterocycles had been metalated previously[9] in good yield.

N-Methylphenothiazine has not previously been metalated and contains both the ring-bound sulfur and *N*-methyl groups. Metalation with slightly more than one equivalent of *n*-butyllithium occurred at the 4-position (adjacent to sulfur) as indicated by carbonation of the metalation product.



All of the experimental results reported above are consistent with each other and with the earlier results[3] to the effect that metalation is faster at positions adjacent to ring-bound sulfur than at positions adjacent to *N*-methyl groups, in spite of the probable greater inductive effect of electron attraction of the latter group. These results may be rationalized by use of the idea originally put forth by Roberts and

Curtin[1] that metalation occurs via an initially formed complex between the alkyllithium (acceptor) and the heteroatom of the substrate (donor). Such complexes are likely formed rapidly and reversibly and the rate of the subsequent slow protophilic step would depend on the concentration of the complexed species. It appears not unreasonable that a combination of polarizability and steric factors leads to a greater equilibrium concentration of $RLi \rightarrow S\!<$ than of $RLi \rightarrow N(CH_3)\!<$ species and consequently to faster metalation of the sulfur-containing heterocycles.

EXPERIMENTAL

Competitive metalation of thiophene and N-methylpyrrole

A solution of 16.8 g (0.20 mole) of thiophene and 16.2 g (0.20 mole) of N-methylpyrrole in 100 ml of dry ether was treated (2 min) with a solution of 0.05 mole of *n*-butyllithium in 35 ml of ether. Gilman Test II[8] was negative within one minute after completion of the addition. The mixture was stirred at room temperature for one hour and treated with excess powdered solid carbon dioxide followed by excess water. The ethereal and aqueous layers were separated and the aqueous layer extracted with additional ether. The remaining aqueous layer was acidified with hydrochloric acid and the precipitated carboxylic acids were collected and reprecipitated from aqueous sodium hydroxide solution. The product (2.6 g) melted at 126–127° and a mixture with authentic thiophene-2-carboxylic acid (m.p. 127–128°) melted at 126–128°. The infrared spectrum (KBr disc with a Perkin-Elmer Model 21 instrument) of the product acid was identical with the spectrum of thiophene-2-carboxylic acid. The infrared spectrum of N-methylpyrrole-2-carboxylic acid has a strong band at 8.9 microns which does not appear in the spectrum of thiophene-2-carboxylic acid. A synthetic mixture of 95% of thiophene-2-carboxylic acid and 5% N-methylpyrrole-2-carboxylic acid gave definite evidence of the band at 8.9 microns, which indicates that the metalation product contained more than 95% of thiophene-2-carboxylic acid.

Metalation of thiophene with N-methyl-2-lithiopyrrole

N-Methylpyrrole (0.20 mole) was metalated with 0.05 mole of *n*-butyllithium in 150 ml of ether for 14 h at room temperature. The Gilman Test II[8] for the presence of alkyllithium was negative and 0.20 mole of thiophene in 50 mole of ether was added. After 12 h the mixture was carbonated and worked up as described above. The product (2.1 g) was essentially pure (m.p. 125–127°) thiophene-2-carboxylic acid as indicated by the infrared spectrum (see above).

A similar experiment in which 2-lithiothiophene was treated with N-methylpyrrole gave no evidence for the metalation of N-methylpyrrole.

Competitive metalation of thianaphthene and N-methylindole

This system was studied in the same manner as the thiophene and N-methylpyrrole case described above and the results were essentially similar.

In separate experiments it was demonstrated that N-methyl-2-lithioindole metalates thianaphthene to the exhaustion of the N-methyl-2-lithioindole and that 2-lithiothianaphthene remains unchanged in the presence of N-methylindole.

Metalation of N-methylphenothiazine

A solution of 10.3 g (0.05 mole) of N-methylphenothiazine in 200 ml of ether was treated with 0.06 mole of *n*-butyllithium in 70 ml of ether. The reaction mixture was stirred at reflux temperature for 16 h and then carbonated with excess carbon dioxide and worked up as described above except that the carboxylic acid from base–acid reprecipitation was recrystallized twice from toluene and once from a 3:1 mixture of benzene and methanol. There was obtained 5.2 g (43% based on N-methylphenothiazine) of an N-methylphenothiazinemonocarboxylic acid, m.p. 243–245° (dec. in a sealed capillary). From the ethereal layer was obtained 3.9 g or 38% of unchanged N-methylphenothiazine. The metalation product was indicated to be a monocarboxylic acid by neutralization equivalent values and elemental analyses. (Found: C, 65.31, 65.50; H, 4.63, 4.30; N, 5.68, 5.67; neutr. equiv., 252, 255. $C_{14}H_{11}NO_2S$ calcd.: C, 65.33; H, 4.31; N, 5.44%; neutr. equiv., 258.)

The methyl ester of the above acid was prepared by the action of ethereal diazomethane. The ester melted at 77–77.5° after crystallization from petroleum ether (b.p. 30–60°) and aqueous methanol. (Found: C, 66.46, 66.06; H, 5.00, 5.16; N, 5.42, 5.23. $C_{15}H_{13}NO_2S$ calcd.: C, 66.39; H, 4.79; N, 5.16%.)

Degradation of N-methylphenothiazinecarboxylic acid with hydriodic acid

A mixture of 2.0 g (7.8 mmoles) of N-methylphenothiazinecarboxylic acid and 23 ml of 47% aqueous hydrogen iodide was heated under reflux until hydrogen sulfide was no longer evolved (46 h). The carboxylic acid slowly went into solution during the reflux period yielding a yellow solution. The solution was concentrated to a volume of about 10 ml and 15 ml of water were added. The mixture was cooled and the precipitated solid was reprecipitated from dilute aqueous ammonia with hydrochloric acid. The resulting product was crystallized twice from benzene–petroleum ether (b.p. 65–75°) to yield 0.8 g (49%) of white crystalline product, m.p. 140–141°. The product was indicated to be 3-carboxydiphenylamine by identity of melting point with that reported in the literature[5a] and proper values for the neutralization equivalent and elemental analyses. (Found: C, 73.23, 73.15; H, 5.21, 5.29,(N, 6.32, 6.34; neutr. equiv., 210, 212. $C_{13}H_{11}NO_2$ calcd.: C, 73.22; H, 5.20; N, 6.57%; neutr. equiv., 213.)

The formation of 3-carboxydiphenylamine from the N-methylphenothiazinecarboxylic acid obtained via the metalation indicates metalation occurred at either the 2-position or the 4-position. The 4-position as the site of metalation is indicated by the earlier results from the study of the metalation of N-ethylphenothiazine[5].

All elemental analyses were performed by Weiler and Strauss, Oxford, England.

SUMMARY

It has been shown in three separate systems that metalation by *n*-butyllithium of sulfur-containing heterocycles occurs faster than similar heterocycles containing the N-methyl group. The systems selected for study were thiophene–N-methylpyrrole, thianaphthene–N-methylindole and N-methylphenothiazine. These data are in harmony with earlier studies of the dibenzothiophene–N-ethylcarbazole system and N-ethylphenothiazine, but not in line with predominant control of the metalation

orientation by inductive effects predicted from relative electronegativities of sulfur and nitrogen. The results are rationalized in terms of equilibrium concentrations of the respective heterocycle–*n*-butyllithium complexes, rapid and reversible formation of which precedes rate-controlling removal of adjacent ring hydrogen.

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