

On the Mechanism of Ring Metallation of Aromatic Compounds. Metallation of Thiophen by Lithium and by Lithium Dihydroarylides

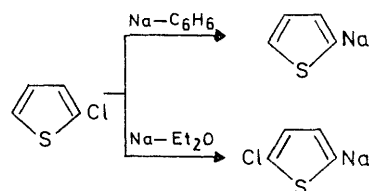
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Thiophen is metallated by lithium metal or lithium dihydroarylides in the 2-position. Product yields and magnetic titration results indicate that the transformation is a two electron process. The process becomes one-electron when the reaction is carried out in the presence of 1,1-diphenylethylene or α -methylstyrene. Paramagnetic decay in solutions of various lithium dihydroarylides and thiophen is of the first order. The $\log k_1$ values correlate with the π -energy change of the reaction $\text{ArH}^{\cdot-} \rightarrow \text{ArH} + e^-$. A mechanism for the metallation of thiophen by lithium dihydroarylides involving an unstable thiophen radical-anion intermediate is suggested. It is also suggested that metallation by conventional lithiating agents takes place through the intermediacy of a radical-anion.

BUTYL-LITHIUM in cyclohexane has been reported¹ to exhibit a strong absorption band with a maximum at 207 nm. The origin of this absorption was attributed to charge transfer transitions.² A new band appears to arise at 277 nm and it is thought of as a result of charge-transfer-to-solvent when adding Lewis bases, such as 7-oxabicyclo[2.2.1]heptane.² In some instances it is possible that organolithium reagents can eject an electron into a broad continuum of states where the electron is no longer bonded to its source.³ This can be achieved either by irradiation, hence the ready photolysis^{2,4} of organolithium compounds, or through the addition of substances of great electron affinity (thermal electron transfer). There is ample experimental evidence that organolithium compounds can function as single electron donors. Two important pieces of such evidence are (a) the generation of radical anions by the action of lithium alkyls on aromatic substrates⁵ and (b) the conversion of stable radicals into carbanions in a Lewis base catalysed reaction.⁶ In a number⁷ of instances alkali metals have been reported to metallate various organic compounds under conditions normally employed for the generation of radical anions⁸ (direct metallation). A question thus arises: are radical anions intermediates in conventional and/or direct metallation reactions? In order to answer this question it was decided to study the direct lithiation of thiophen as well as its metallation by lithium dihydroarylides. Thiophen was chosen as a model compound because it does not exhibit any pronounced carbon acidity although it undergoes ready metallation by butyl-lithium.

Two related studies should be noted: Schick and Hartough found⁹ that 2-chlorothiophen is directly metallated by sodium in ether, but in benzene solution halogen-metal exchange took place. Eisch and Kaska reported¹⁰ that in the metallation of fluorene by lithium

in tetrahydrofuran (THF) the hydrogen replaced by the metal reacted with the aromatic hydrocarbon to produce partially reduced fluorenes.



RESULTS AND DISCUSSION

Thiophen was metallated in the 2-position with lithium metal in THF; 2-thenoic acid (12%) was obtained after carbonation. Addition of naphthalene in the reaction mixture resulted to an increase in rate as well as in yield (41%). These results were markedly improved by treating preformed lithium dihydroarylides with thiophen. Aliquot portions of lithium dihydronaphthylide or -biphenylide (analysed for active lithium) were treated with an excess of thiophen. The yield of thienyl-lithium was determined by carbonation and isolation of 2-thenoic acid. Table I summarises the results. In no case did the yield of 2-thenoic acid significantly exceed 50%. The amount of thiophen that is required in order to bring about complete discharge of paramagnetism in a given amount of lithium dihydronaphthylide was determined by magnetic titration (Figure 1). A well-defined discontinuity occurs at a $[\text{C}_4\text{H}_4\text{S}] : [\text{Li}^+\text{C}_{10}\text{H}_7^{\cdot-}]$ ratio of ca. 0.5. These results indicate that the reaction is a two-electron process. The stoichiometry changes drastically when the reaction is carried out in the presence of 1,1-diphenylethylene or α -methylstyrene. In these cases the yield of 2-thenoic

⁵ G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, 1962, **84**, 4163; G. A. Russell, E. G. Janzen, and E. T. Strom, *ibid.*, 1964, **86**, 1807; H. W. Brown and R. C. Jones, *J. Chem. Phys.*, 1962, **37**, 1571.

⁶ C. G. Screttas, *Chem. Comm.*, 1971, 406.

⁷ L. Hackspill, *Ann. chim. Phys.*, 1913, **28**, 653; A. Schönberg, E. Petersen, and H. Kaltschmitt, *Ber.*, 1933, **66**, 232; H. Gilman and F. Breuer, *J. Amer. Chem. Soc.*, 1934, **56**, 1123; F. Bergmann and E. Bergmann, *ibid.*, 1940, **62**, 1699; O. Neuhoeffer and H. Woggon, *Annalen*, 1956, **600**, 34; H. Normant and B. Angelo, *Bull. Soc. chim. France*, 1960, 354; L. Horner and H. Gtisten, *Annalen*, 1962, **652**, 99.

⁸ G. E. Coates, 'Organometallic Compounds,' Methuen, London, 1960, 2nd edn., p. 32.

⁹ J. W. Schick and H. D. Hartough, *J. Amer. Chem. Soc.*, 1948, 286.

¹⁰ J. J. Eisch and W. C. Kaska, *J. Org. Chem.*, 1962, **27**, 3745.

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¹ F. A. Settle, jun., Ph.D. Thesis, University of Tennessee, 1964; J. B. Smart, R. Hogan, P. A. Scherr, L. Ferrier, and J. P. Oliver, *J. Amer. Chem. Soc.*, 1972, **94**, 8371.

² C. G. Screttas, Ph.D. Thesis, University of Tennessee, 1966.

³ For reviews of charge transfer phenomena see W. Kauzmann, 'Quantum Chemistry,' Academic Press, New York, 1957, p. 687; E. Rabinowitch, *Rev. Modern Phys.*, 1942, **14**, 112; E. Orgel, *Quart. Rev.*, 1954, **8**, 422.

⁴ E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *J. Amer. Chem. Soc.*, 1965, **87**, 4964; 1971, **91**, 641; W. H. Glaze and T. L. Brower, *ibid.*, 1969, **91**, 4490; W. H. Glaze and A. C. Ranade, *J. Org. Chem.*, 1971, **36**, 3331.

acid was in the range *ca.* 80–100% (Table 2). This result, which might be of mechanistic significance, suggests

TABLE 1

(a) Metallation of thiophen by lithium dihydronaphthylide* at *ca.* 20–26°

[C ₄ H ₄ S]/mM	t/h	Yield of acid (%)
60	0.5	48
60	1.0	46.5
60	5.0	48.5
60	2.0	53
60	0.25	56
60	3.0	54
120 ^b	0.5	52

(b) Metallation of thiophen by lithium dihydrobiphenylide* at *ca.* 20–30°

[C ₄ H ₄ S]/mM	t/h	Yield of acid (%)
60	3	54
60	3	45
60	3	52.5
60	0.03	34
5	3	28.5 ^c
60	3	47.5 ^d

* Concentration 10mM except where stated. ^b Concentration of Li⁺C₁₀H₈²⁻ 20mM. ^c A 28% yield of phenylcyclohexadienecarboxylic acid was also obtained. ^d Temperature -20 to +18°.

TABLE 2

Metallation of thiophen by lithium dihydronaphthylide in the presence of 1,1-diphenylethylene or α -methylstyrene at *ca.* 20–38°

[Li ⁺ C ₁₀ H ₈ ²⁻]/mM	[C ₄ H ₄ S]/mM	[Ph ₂ C=CH ₂]/mM	[PhCMe=CH ₂]/mM	t/h	Yield of acid (%)
10	50		25	0.25	77
10	50		25	3	78
10	50	20		3	75
20	60	30		2	93
20	60		38	2	95
8*	50		25	0.25	99

* Lithium dihydrobiphenylide.

that the reaction becomes a one-electron process in the presence of a substance that can dimerise or polymerise

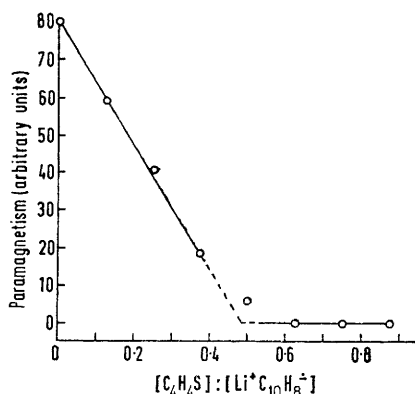


FIGURE 1 Magnetic titration of lithium dihydronaphthylide against thiophen

under the reaction conditions. The n.m.r. spectrum of the neutral fraction after carbonation of a metallation carried out in the absence of additives shows that

¹¹ (a) D. F. Evans, *Proc. Chem. Soc.*, 1958, 115; *J. Chem. Soc.*, 1959, 2003; (b) C. G. Screttas, *J.C.S. Chem. Comm.*, 1972, 869.

naphthalene remains unchanged but some minor components exhibit resonances in the olefinic and aromatic regions. The neutral fraction from runs with diphenylethylene and methylstyrene were shown to contain (Ph₂CHCH₂)₂ and polymethylstyrene, respectively. G.l.c. analysis indicated the presence of butan-1-ol in the reaction mixture of lithium dihydronaphthylide and thiophen.

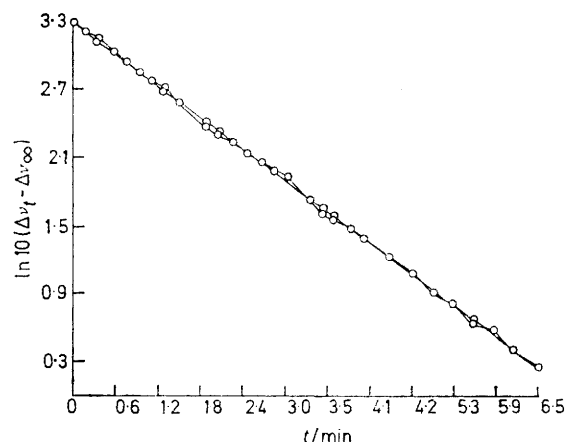


FIGURE 2 A typical first-order plot for the disappearance of paramagnetism in lithium dihydroarylide-thiophen mixtures

Evans' method¹¹ for measuring paramagnetic susceptibility was adapted to our kinetic study. In mixtures of various lithium dihydroarylides and thiophen in THF paramagnetism decays according to the first-order rate law. Thus linear plots of $\ln(\Delta v_t - \Delta v_{\infty})$ versus time were obtained (Figure 2). Table 3 summarises the

TABLE 3

Apparent first-order rate constants of the reaction Li⁺ArH²⁻ + thiophen at 40 ± 0.5°. [Li⁺ArH²⁻]₀ = 0.50M; [C₄H₄S]₀ = 1.25M

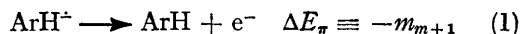
ArH	k ₁ /min ⁻¹	-m _{m+1}
Biphenyl	2.06 ± 0.21 ^a	0.705
Naphthalene	0.556 ± 0.006	0.618
Naphthalene	0.474 ± 0.003	
Phenanthrene	0.088 ± 0.005	0.605
Phenanthrene	0.062 ± 0.001	
Stilbene	0.125 ± 0.005	0.504
Stilbene	0.123 ± 0.005	
Anthracene	0.018 ± 0.001	0.414

^a Estimated from a $\log k$ vs. $\log [C_4H_4S]_0$ plot at [Li⁺ArH²⁻]₀ = 0.50M, by linear extrapolation: k₁ = 1.20 ± 0.006 min⁻¹, [C₄H₄S]₀ = 0.46M; k₁ = 1.80 ± 0.03 min⁻¹, [C₄H₄S]₀ = 0.63M.
^b Initial rate.

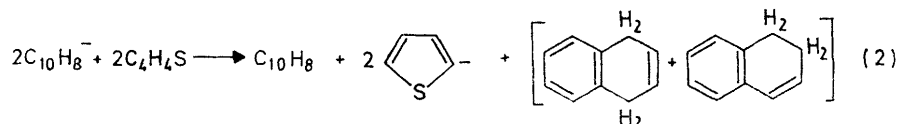
kinetic results. Obviously the specific rate constants depend very strongly on the type of arene. The reactivities of the lithium dihydroarylides toward thiophen decrease as the electron affinities of the parent hydrocarbons increase. Phenanthrene seems to be an exception. In Figure 3 $\log k_1$ values are plotted against m_{m+1} (in units of β) where m_{m+1} is the Hückel value of the coefficient of the MO resonance integral in the expression for the energy of the lowest unoccupied orbital, and β is the resonance integral.¹² With the

¹² m_{m+1} Values were taken from A. Streitwieser, jun., 'Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961, p. 178.

exception of phenanthrene the rest of the data can be correlated. The deviation of phenanthrene is not understood; it can only be noted that lithium dihydronaphthylide in the analogous case of its reaction with anisole exhibits the same deviation from other arenes.^{11b} Similar correlations have been found to hold in the case of the reaction of arylalkali-metal and various alkyl halides.¹³ It should be stressed that $-m_{m+1}$ represents the π -energy change for process (1).



If we attempt to explain the observations on the basis of the most generally accepted reaction scheme for metallation, namely proton abstraction by a carbanion¹⁴



we are led to the overall reaction (2). This process predicts that one half of the naphthalene is converted into dihydronaphthalene and every molecule of lithium dihydronaphthylide produces one molecule of 2-thienyllithium. Both these conclusions contrast with the experimental evidence. The same scheme also fails to

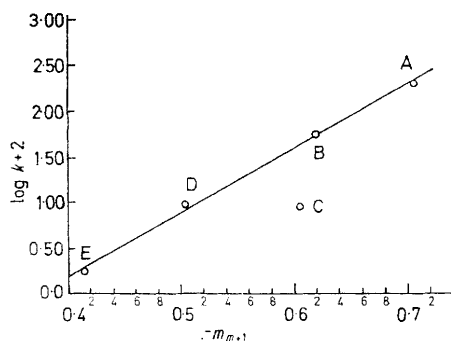
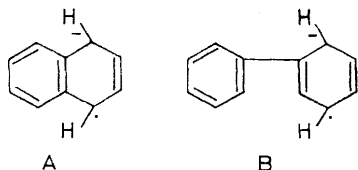


FIGURE 3 Plot of the logarithms of the apparent first-order rate constants against m_{m+1} values for the reaction $\text{Li}^+\text{ArH}^- + \text{thiophen}$: A, biphenyl; B, naphthalene; C, phenanthrene; D, stilbene; E, anthracene

explain the pronounced kinetic dependence on the type of the arene. The structural differences *e.g.* between species A and B do not seem to be so marked as to



warrant such a difference between their reactivities. Similar conclusions are reached on consideration of a reaction scheme in which the anion-radical reacts *via* a hydrogen atom abstraction.

¹³ B. J. McClelland, *Chem. Rev.*, 1964, **64**, 301.

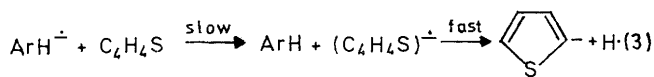
¹⁴ J. M. Mallan and R. L. Bebb, *Chem. Rev.*, 1969, **69**, 693.

¹⁵ T. L. Staples, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, 1969, **91**, 3721.

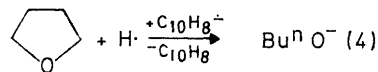
The experimental results are best explained as an initial electron transfer from the arene to thiophen in the rate-limiting step, followed by a relatively fast fission or dissociation of thiophen radical-anion [reaction (3)]. The step in which the second electron enters the reaction sequence is not clear. However, the necessity of a second electron can be understood because of the fact that in most cases a stable chemical system has neutral charge and paired spins. For instance an unstable species produced by the attack of $\text{H}\cdot$ on a solvent molecule would require one electron in order to be converted into a butoxide ion [reaction (4)].

The different results obtained with 1,1-diphenylethylene could possibly arise from reactions (5)–(7).

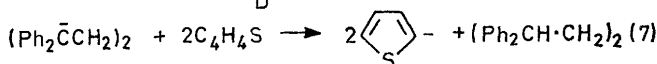
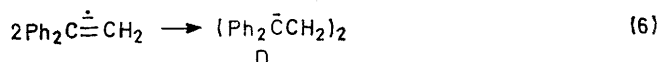
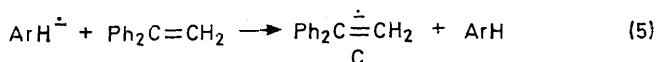
Dimerisation¹⁵ of C leads to the formation of a diamagnetic dianion D which acts as a conventional



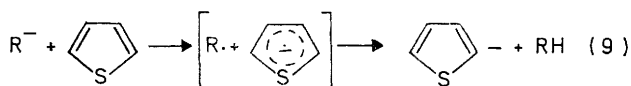
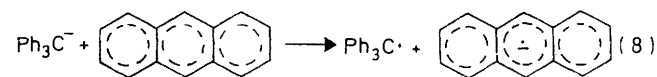
lithiating agent, *i.e.* it metallates thiophen with 1:1 stoichiometry. Of particular relevance to the present



problem is the report¹⁶ of Jagur-Grodzinski and Szwarc on the one-electron oxidation of carbanions by



transfer to aromatic substrates [reaction (8)]. There is no obvious reason that an analogous thiophen radical-anion could not form in a reaction between thiophen



and a carbanion [reaction (9)]. We propose this scheme, in which the intermediate radical-anion dissociates to a carbanion, as an alternative to the mechanism of aromatic ring metallation which involves shifts of electrons in pairs.¹⁴ In the case of lithiation by alkyl-lithiums a solvated oligomer plays the role of a carbanion.

¹⁶ J. Jagur-Grodzinski and M. Szwarc, *J. Amer. Chem. Soc.*, 1969, **91**, 7594.

EXPERIMENTAL

Lithium metal was from Riedel-De Haan AG, thiophen was Fluka puriss and used after drying over molecular sieve 4A. Tetrahydrofuran and 1,2-dimethoxybutane (Fluka purum) were refluxed with lithium aluminum hydride and distilled directly into the storage bottle. Argon (99.99%) was passed through two wash-bottles containing 10% butyl-lithium in decalin and two cold traps containing silica gel and cooled with dry ice-acetone.

Naphthalene (Riedel sublimed), biphenyl, phenanthrene, stilbene, and anthracene (Fluka puriss) were used without further purification. G.l.c. analyses were performed with a Varian Aerograph model 90-P.

Kinetic and Magnetic Titration Methods.—Concentrations of paramagnetic species were measured with a Varian A60 n.m.r. spectrometer according to the method of Evans.¹¹ In the kinetic runs cyclohexane was used as a double reference. The external standard, 10% (v/v) cyclohexane in CCl₄, was sealed in a thin-walled, Pyrex capillary with an internal diameter of ca. 2 mm. The height of the liquid in the capillary was 35–40 mm. The internal reference was 10% (v/v) cyclohexane in THF. The n.m.r. tube was stoppered and the air replaced by oxygen-free argon. Measured volumes of standard, argon-saturated solutions were introduced and the spectra recorded. Reactions with $t_{\frac{1}{2}} \geq 0.5$ min could be studied by this technique. Dilution experiments gave linear plots of chemical shift change against concentration. In the case of magnetic titrations the internal standard was the high field band of THF. Signal separations were recorded 14 h after mixing and were plotted without a correction for volume change.

Preparation of Lithium Dihydroaryllides.—These were prepared in the normal way using aromatic hydrocarbon (0.025 mol) and lithium metal (0.03 g-atom) in THF (25 ml). Analysis by double titration using ethylene bromide showed that $\leq 5\%$ inactive lithium remained.

Metallation of Thiophen with Lithium Metal.—Thiophen (50 ml), THF (100 ml), and a 30% lithium (with 2% sodium)

dispersion in mineral oil (5 g) were stirred under nitrogen for 168 h. The mixture was then poured over ether-crushed dry ice. Work-up gave 2-thenoic acid (3.3 g, 12%), m.p. 115–122°, n.m.r. spectrum identical with that of authentic material.

Metallation of Thiophen with Lithium and Naphthalene.—Lithium (1 g in small pieces) was added to 1,2-dimethoxyethane (DME) (40 ml). The metal was activated by adding t-butyl alcohol (0.3 ml) and naphthalene (12.8 g, 0.1 mol) dissolved in DME (40 ml) was added at once. After a short induction period, the solution turned dark green, and thiophen (25 ml) was added. The resulting mixture was stirred at room temperature overnight, turning red-brown. Carbonation and work-up gave 2-thenoic acid (7.5 g, 41%).

Metallation of Thiophen with Preformed Lithium Dihydronaphthylide.—A 1.0M solution of lithium dihydronaphthylide (20 ml) in THF was mixed with thiophen (10 ml). After ca. 0.5 h carbonation and work-up afforded 2-thenoic acid (52%).

Metallation of Thiophen with Lithium Dihydronaphthylide in the Presence of 1,1-Diphenylethylene.—To 1.0M-lithium dihydronaphthylide (20 ml) was added 1,1-diphenylethylene (4.0 ml) and thiophen (5.0 ml). An exothermic reaction took place and the mixture turned red-brown instantly. After 2 h at room temperature the mixture was carbonated. 2-Thenoic acid was formed in 92% yield. The neutral fraction was freed from naphthalene by sublimation. The semicrystalline residue was recrystallised from boiling ethanol, m.p. 120°, and shown by n.m.r. to be 1,1,4,4-tetraphenylbutane.

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