On the mechanism of the naphthalene-catalysed lithiation: the role of the naphthalene dianion

Miguel Yus,* Raquel P. Herrera and Albert Guijarro

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain

Received 23 March 2001; accepted 26 March 2001

Abstract—Kinetic and distribution product studies on naphthalene-catalysed lithiation reactions of chlorinated precursors have shown the probable participation of a naphthalene dianion (dilithium naphthalene) as the very active electron carrier agent in the chlorine–lithium exchange process. © 2001 Elsevier Science Ltd. All rights reserved.

The use of lithium and a catalytic amount of an arene as the electron carrier has become a useful procedure for the preparation of organolithium compounds under very mild reaction conditions.[1] This lithiation methodology, compared to the use of a stoichiometric amount of an arene,[2] has the advantage of being a very clean process with a simple work-up (not necessary to remove a large amount of the arene) but, above all, the catalytic version is far more reactive, so it is possible to perform new lithiation reactions, which do not work when a lithium–arene is used as lithiation agent.[3] Thus, it appears to be evident that different species take active part in both lithiation processes. In the stoichiometric version, it has been postulated and accepted that a radical anion is the electron transfer (ET) agent, naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB) being the arenes most commonly used. This type of paramagnetic compounds ($LiC_{10}H_8$ or LiDTBB) have been successfully employed for chlorine–lithium[4] and sulphur–lithium[5] exchange as well as for the reductive opening of cyclic ethers.[6] Over-reduction of the radical anion species can be achieved by condensation of potassium and naphthalene vapours,[7] and apparently by prolonged exposure of naphthalene to an excess of lithium metal in THF.[8] On the other hand, double deprotonation of 1,4-dihydronaphthalene with *n*-butyllithium and tetramethylethylenediamine (TMEDA) affords $Li_2C_{10}H_8$·2TMEDA as purple crystals.[9] The reactivity of this diamagnetic species, which can be formulated as shows structure **II** compared with the radical anion **I**, is almost unknown: in fact, it could
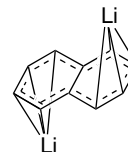
react as a base or as a nucleophile,[10] but also as an ET reagent,[11] in the same way than its radical anion counterpart. The study of this reactivity is interesting from a fundamental point of view in order to clarify the general dichotomy between an ET reaction and a nucleophilic substitution.
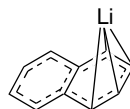
I ($LiC_{10}H_8$) **II** ($Li_2C_{10}H_8$)

In order to study the reactivity of the radical anion and the dianion species, we used organic chlorides and naphthalene as the arene. Employing competitive kinetic techniques[12] it is possible to measure accurately the relative reaction rates by comparing simultaneously the reactivity of the species **I–IV** with two different organic halides (1- and 2-chlorooctane, 2-chloro-2-methylheptane and chlorobenzene). As reactive anionic species, the radical anion **I** [prepared with lithium and naphthalene (1:1.1), green solution], and dianions **II** [prepared with an excess of lithium and naphthalene (5:1), purple solution when freshly prepared], **III** ($Li_2C_{10}H_8$·2TMEDA, from 1,4-dihydronaphthalene an *n*-butyllithium, purple when freshly prepared) and **IV** (as for **II**, but with 2 TMEDA, purple when freshly prepared) were used. In a representative example, to a mixture of 1-chlorooctane, 2-chlorooctane and a carefully weighed amount of dodecane (internal standard; ca. 1:1:0.5, 0.01 M) was added a solution of lithium

---

naphthalene ($LiC_{10}H_8$, **I**) in THF at 0°C in small portions. A sample of this reaction mixture was taken after each addition and hydrolysed (phosphate buffer, 0°C) and submitted to quantitative GLC analysis. After determination of the concentration of both organic chlorides a relative reaction rate[12] of $k_{2\text{-octylCl}}/k_{1\text{-octylCl}} = 0.91$ was obtained. The same procedure was repeated for all pairs of organic chlorides and the species **I–IV** (clear solutions without any lithium metal), the resulting reproducible relative rates being referred to the primary chloride. The obtained results are summarised in Fig. 1, where reactivity profiles for all four reagents are essentially identical. According to these data, *dilithium naphthalene behaves as an ET reagent towards organic chlorides*, being indistinguishable with lithium naphthalene as far as the reactivity profiles are concerned.

Regarding the mechanism of the lithiation, there is no selectivity for the structure of the organic halide in the process as it would be expected from an outer sphere ET in the determining step of the reaction.[12] This is the mechanism of reaction for most radical anions, such as **I**, with organic halides. The resulting flat profiles displayed discard other possible metallation mechanistic pathways for the dianion, such as a back approach to the halide in a S_N2 transition state metallation type [e.g. ferrates,[13] or Co(I) reagents,[14] which would display a *primary>secondary≫tertiary alkyl* or *aryl* chlorides reactivity profile] or the intervention of an 'ate' transition state or an intermediate (e.g. alkyllithiums[15] and presumably dialkylmagnesium reagents[16] would afford a different profile: *aryl≫primary>secondary>tertiary alkyl* chlorides).

The generally accepted mechanism for the reaction of arene radical anions (e.g. $C_{10}H_8^{\cdot-}$) is in principle, applicable to naphthalene dianion (Scheme 1, Eqs. (1)–(3)). It is not likely that the radical anion present in the reaction media can compete with the dianion for organic chlorides when both are present in similar concentrations based on both (a) less favorable reduction potentials,[17] and (b) dissimilar electronic configurations of reactants criteria. Neither is the S_N2 competence versus ET for organic chlorides as it can be inferred from the reactivity profiles (Eq. (1)). In the subsequent step, both reducing agents can in principle participate (Eq. (2)), the coupling of R and the radical anion being most likely the source of coupling by-products (isomeric $RC_{10}H_9$, $R_2C_{10}H_8$ and dimers) (Eq. (3)).
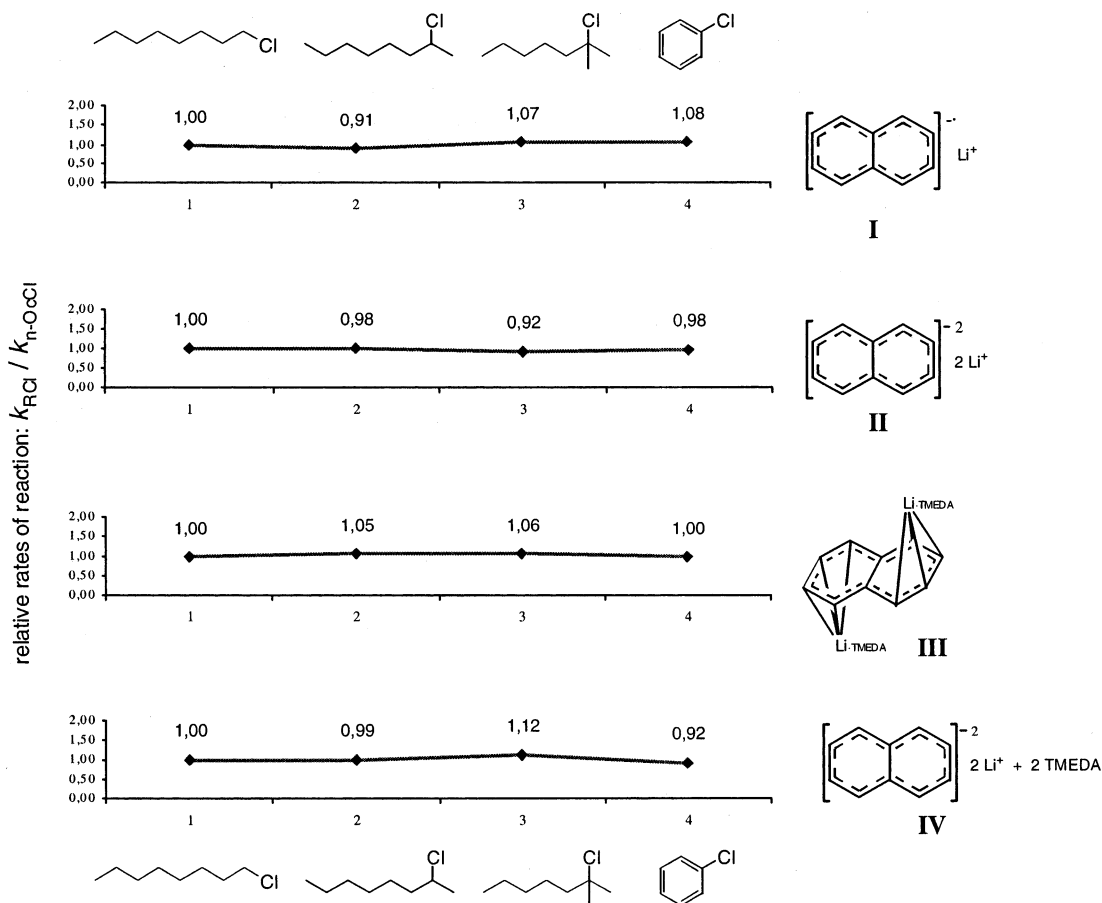

Figure 1. Reactivity profiles of naphthalene radical-anion (**I**) and dianions (**II–IV**) in their reactions with organic chlorides. Each relative rate has been obtained by evaluation of the slope by linear regression analysis of plots representing the decay of the concentration of both chlorides,[12] and are arbitrarily referred to 1-chlorooctane. Each of these plots contained 5–8 points and were linear to greater than 90% consumption of the reacting chlorides (first order reactions with respect to the alkyl chloride), the regression coefficients being >0.995 in all cases.
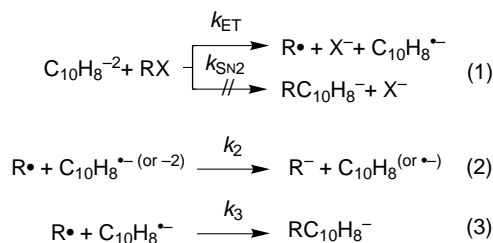
Scheme 1.

The k_2/k_3 ratio is a key parameter of the process when the aim is to maximise the formation of R^-. For radical anions, the ratio k_2/k_3 seems to be dependent on the standard reduction potential of the arene, the most negative ones having the higher k_2/k_3 ratios, resulting in higher yields of carbanionic species.[18] This trend is manifested by the dianion as small but reproducible better yields in the lithiation process using **II** compared to **I**.

At this stage, a study of the distribution of products was undertaken to obtain information about the evolution of the radical species initially formed from the ET step. As expected, further reduction to afford organolithium compounds is the main reaction outcome for dianions as well as for the radical anion. To demonstrate that, the reaction of **I–IV** with 1-chlorooctane was carried out in THF at −60°C (temperature at which crystalline **III** showed adequate solubility) followed by reaction with chlorotrimethylsilane or pivalaldehyde as electrophilic reagents and final hydrolysis, giving trimethyl octyl silane or 2,2-dimethyl-3-undecanol, respectively The first step was carried out with an excess of lithiating reagent (4:1 molar ratio) and was monitored until the concentration of the starting material dropped below detection limits (<0.01%), then an excess of the electrophilic reagent was added, the reaction was allowed to warm up slowly to 0°C and was hydrolysed as before. Quantitative analysis of the reaction products afforded comparable distribution of major products for both **I** and **II** (reactions in the absence of TMEDA), reagent **II** invariably giving slightly better yields that **I** for the aforesaid reasons.[18] Yields were found to be very similar specially for **III** and **IV** (reactions in the presence of TMEDA) (Fig. 2). These last results confirm how close is the nature of the species generated after exposure of naphthalene to an excess of lithium, and pure dilithium naphthalene.

Advantages of arene dianions in lithiation processes versus arene radical anions inevitably comes from the higher reduction potential of the corresponding redox pairs, which broaden the scope of current lithiating agents to functional groups reducible only with difficulty. Studies to implement this hypothesis to a real case are currently underway. Preliminary results show that alkyl fluorides readily react with solutions containing dilithium naphthalene (**II** or **III**). Thus, for instance, the reaction of 1-fluorononane with **II** at 0°C is completed in 10 min. After hydrolysis with water it afforded nonane (7%) and a separable mixture of 1-nonyl-1,4-
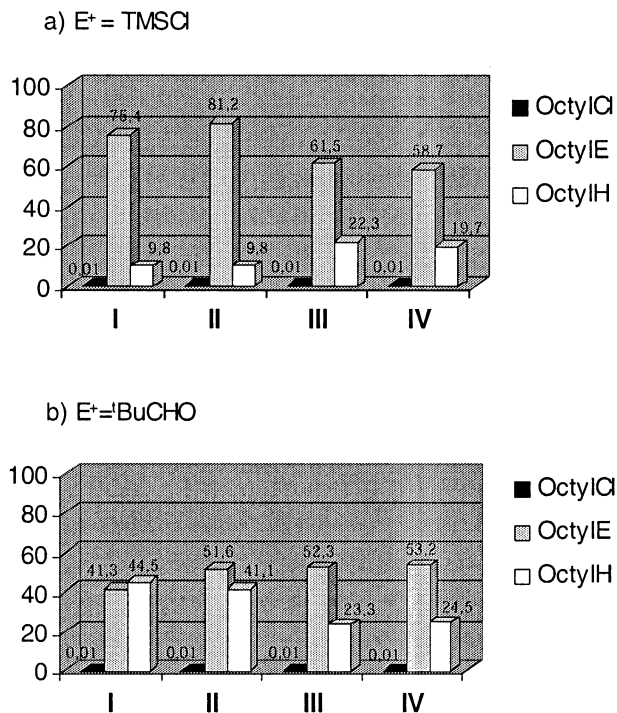

Figure 2. Distribution of products corresponding to the reaction of 1-octylchloride with the lithiating reagents **I–IV** and capture of 1-octyllithium with (a) TMSCl or (b) *t*-BuCHO. Yields of the products were determined by quantitative GLC using pure isolated products in the determination of response factors, and were averaged for 4–5 runs.

dihydronaphtalene (47%) and 1-nonyl-1,2-dihydronaphthalene (36%) as major products.

Some conclusions can be drawn from the present work. The answer to the original question whether dianions are or are not active part in the mechanism of the arene-catalysed lithiation, for which organic chlorides are their natural substrates, has now been addressed. Dilithium naphthalene arises as a formal lithiating agent in its reaction with organic chlorides, and presumably with other functional groups,[19] displaying an outer sphere ET reactivity profile in its interaction with these acceptors, excluding alternative mechanisms of halogen–lithium exchange. Endowed with a higher redox potential than its radical anion counterpart, its reactivity spectrum is broadened and so is the range of substrates suitable for lithiation. Hence, we can state that the trivial mechanism of lithiation involving radical anions is not the only operative in arene catalysed lithiations, a more reduced species, i.e. the dilithium salt of the arene or dianion may be responsible instead for the increased reactivity displayed by the mixture.

References

1. (a) Yus, M. *Chem. Soc. Rev.* **1996**, *96*, 155; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225.
2. Holy, N. L. *Chem. Rev.* **1974**, *74*, 243.
3. See, for instance: Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210.
4. See, for instance: (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924; (b) Ramón, D. J.; Yus, M. *J. Org. Chem.* **1991**, *56*, 3825.
5. (a) For a review, see: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152; (b) For a recent account, see: Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241.
6. (a) For a review, see: Yus, M.; Foubelo, F. *Rev. Heteroat. Chem.* **1997**, *17*, 73; (b) First account: Bartmann, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 653; (c) See, also: Dorigo, A. E.; Houk, K. N.; Cohen, T. *J. Am. Chem. Soc.* **1989**, *111*, 8976; (d) Cohen, T.; Jeong, J.-H.; Mudrik, B.; Bhupathy, B.; Awan, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528; (e) Mudrik, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657; (f) Mudrik, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.
7. Brandes, K. K.; Gerdes, R. J. *J. Phys. Chem.* **1967**, *71*, 508.
8. Smith, J. *J. Am. Chem. Soc.* **1965**, *87*, 656.
9. Brooks, J. J.; Rhine, W.; Stucky, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 7346.
10. (a) Korte, W. D.; Cripe, K.; Cooke, R. *J. Org. Chem.* **1974**, *39*, 1168; (b) Sommer, L. H.; Korte, W. D. *J. Org. Chem.* **1970**, *35*, 22.
11. For a number of studies concerning the competition between ET and S_N2, see: (a) Daasberg, K.; Christensen, T. B. *Acta Chem. Scand.* **1995**, *49*, 128; (b) Huang, Y.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1994**, *116*, 2157.
12. (a) Guijarro, A.; Rieke, R. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 1679; (b) Guijarro, A.; Rosenberg, D. M.; Rieke, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4155.
13. (a) Collmann, J. P.; Hegedus, L. S. In: *Principles and Applications of Organotransition Metal Chemistry;* University Science Books: Mill Valley, CA, 1980; Chapter 4; (b) Collman, J. P.; Finke, R. G.; Cawse, J. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 2515.
14. (a) Zhou, D. L.; Walder, P.; Scheffold, R.; Walder, L. *Helv. Chim. Acta* **1992**, *75*, 995; (b) Schrauzer, G. N.; Deutsch, E. *J. Am. Chem. Soc.* **1969**, *91*, 3341.
15. Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988.
16. Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.
17. This is not invariably a guarantee for faster ET reactions: Marcus, R. A. *Pure Appl. Chem.* **1997**, *69*, 13.
18. Fuhlendorff, R.; Occhialini, D.; Pedersen, S. U.; Lund, H. *Acta Chem. Scand.* **1989**, *43*, 803.
19. For reviews, see: (a) Refs. 1 and 6b; (b) Guijarro, D.; Yus, M. *Recent Res. Devel. Org. Chem.* **1998**, *2*, 713.