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On the dichotomy of the S_N2/ET reaction pathways: an apparent S_N2 reactivity in the reaction of naphthalene dianion with alkyl fluorides

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Abstract—Dilithium naphthalene ($Li_2C_{10}H_8$) displays a S_N2 reactivity profile in its reaction with alkyl fluorides (*n*-, *s*- and *t*-octyl fluoride). S_N2 seems to be the dominant mechanism operating with primary alkyl fluorides, which presumably turns into competition with ET as we move to secondary and tertiary alkyl fluorides. Significantly, lithium naphthalene ($LiC_{10}H_8$) seems to have also an important nucleophilic component when reacting with alkyl fluorides, in contrast to the previously proposed general ET process valid for all alkyl halides. These results explain the observed distribution of products and are reinforced by a complete analysis of the products originated by the reaction with 6-halohexenyl radical probes, whose main alkylation products are described here for the first time. © 2003 Elsevier Science Ltd. All rights reserved.

The comparison of reactivity in a series of compounds bearing related functionality (e.g. the alkyl halides series: RI, RBr, RCl and RF) versus a specific reagent is an established strategy to explore the nature of the mechanistic process. Often the behavior of a member can be predicted and explained by comparison of the periodical physicochemical properties of the atoms that form the series. Alkyl fluorides do not always extrapolate well when they are compared to the remaining alkyl halides. Contrary to other alkyl halides, for which S_N2 is no doubt the most emblematic reaction, alkyl fluorides seldom react in a S_N2 fashion and are rarely used as electrophiles for synthetic purposes. In the reaction with arene radical anions, however, alkyl fluorides have been treated as 'normal' alkyl halides, just as chlorides, bromides and iodides. A widely accepted mechanism of reaction for alkyl halides has been described in identical terms for *all* alkyl halides, including alkyl fluorides.[1] It involves ET from the arene radical anion and dissociation of the halide with generation of the alkyl radical. Thus, the reaction of alkyl halides, R–X, with sodium naphthalene affords similar crude products mainly consisting in mixtures of reduction (R–H) and coupling products ($R–C_{10}H_9$, $R_2C_{10}H_8$), regardless of the nature of X (F, Cl, Br or I). According to the authors, the lack of effect of halogen variation on the distribution of products mitigates the possibility of S_N2 reaction pathway. Taken altogether these reactions seemed to be identical in nature, and 'leave little doubt that there are no significant initial S_N2 steps in any reaction of sodium naphthalene with simple alkyl halides in DME'.[1]

Recently, we have focused our interest on the differential reactivity between the naphthalene radical anion and dianion as lithium salts, concerning their roles in the mechanism of the arene-catalyzed lithiation reactions. These species, $LiC_{10}H_8$ (**I**) and $Li_2C_{10}H_8$ (**II**) react as ET reagents versus organic chlorides, according to the reactivity profile displayed by both reagents.[2] It is possible however to find substrates for which **I** and **II** display differential reactivity. Such is the case of their reactions with non-strained cyclic ethers like THF and THP.[2] It seemed reasonable to us that it could also be the case of alkyl fluorides. To check this point, a comparative study of the reaction of lithium and dilithium naphthalene (**I** and **II**) with a primary, a secondary and a tertiary alkyl fluorides was undertaken. First, a reactivity profile for both kinds of reagents, **I** and **II**, was constructed using alkyl fluorides as substrates. Competitive kinetic techniques,[3] allow accurate measurement of the relative rates of reaction of the radical anion (**I**) or dianion (**II**) reacting simultaneously with two organic fluorides. As substrates we include *n*-, *s*- and *t*-octylfluorides (1- and 2-fluorooctane and 2-fluoro-2-methylheptane).[4] In a representative example, to a mixture of 1-fluorooctane,

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2-fluorooctane and a carefully weighed amount of dodecane as internal standard (ca. 1:1:0.5, 0.01 M in THP at 0°C), a solution of **I** ($LiC_{10}H_8$) in THP at 0°C was added in small fractions. A sample of the reacting mixture was obtained after each addition, these aliquots being immediately hydrolyzed (ice cold 0.1 phosphate buffer/pentane) and submitted to quantitative GLC analysis. The simultaneous determination of the concentration of these two organic fluorides in solution that react with **I**, permits the evaluation of their relative reaction rates,[5] i.e. $k_{2\text{-OctylF}}/k_{1\text{-OctylF}}=0.20$ in this case. The same procedure was repeated for all pairs of organic fluorides submitted to test, the resulting relative rates being arbitrarily referred to *n*-octyl fluoride. Unexpectedly, *n*-octylfluoride turned out to be the fastest reacting alkyl fluoride. Reactivity profiles were constructed in this way for **I** (radical anion, $Li+C_{10}H_8$ 1:1.1, green solution), **II** (Li excess+$C_{10}H_8$, ca. 5:1, purple solution). Only clear solutions of **I** and **II** (in the absence of Li metal) were used, all the determinations being carried out in THP at 0°C. The results are collected and represented in Figure 1. As a comparison, Figure 1 includes the reactivity profiles displayed by alkyl chlorides.[2]

The near flat structure–reactivity profile displayed by alkyl chlorides both for **I** and **II** is typical of an outer sphere ET process (or simply ET).[5] Low degree of selectivity is often displayed by this mechanistic pathway, which is characterized by very weak interaction between donor and acceptor at the transition state.[6] If any, the selectivity displayed by an ET reaction would be tertiary>secondary>primary alkyl, reflecting the ability to stabilize the incipient radical which is being developed on the carbon that bears the halide. This is just the opposite profile displayed by the alkyl fluoride series, where the observed trend is primary>secondary>tertiary alkyl fluoride. From Figure 1, *n*-octyl fluoride reacts 6.9 times faster than *s*-octyl fluoride and 8.8 times faster than *t*-octyl fluoride in their reactions with dilithium naphthalene (**II**), the differences being slightly smaller for the lithium naphthalene (**I**). While all three alkyl chlorides react through a rather pure ET mechanism in the initial step of the reaction (determining step), it is our belief that primary alkyl fluorides display a competition between S_N2 and ET [Eq. (1)].[7]

$$C_{10}H_8^{-2} + RF \begin{cases} \xrightarrow{k_{SN2}} RC_{10}H_8^{-} + F^{-} \\ \xrightarrow{k_{ET}} R\bullet + F^{-} + C_{10}H_8^{\bullet-} \end{cases} \tag{1}$$

Under our reaction conditions (i.e. using a fourfold excess of **I** or **II**) the majority of the starting alkyl fluoride (RF) can be quantified as RH or $RC_{10}H_9$, i.e. reduction and alkylation (or coupling) products after hydrolysis [Eqs. (2) and (3)]. Table 1 represents the distribution of products obtained for the reactions of these alkyl fluorides with **I** or **II** and subsequent hydrolysis with water.

$$R\bullet + C_{10}H_8^{\bullet-\,(\text{or }-2)} \xrightarrow{k_2} R^{-} + C_{10}H_8^{(\text{or }\bullet-)} \tag{2}$$

$$R\bullet + C_{10}H_8^{\bullet-} \xrightarrow{k_3} RC_{10}H_8^{-} \tag{3}$$

A number of points should be discussed after examination of the yields in Table 1. First, there is a significant difference in the distribution of products obtained for **I** or **II**. While the main reaction products are the same,

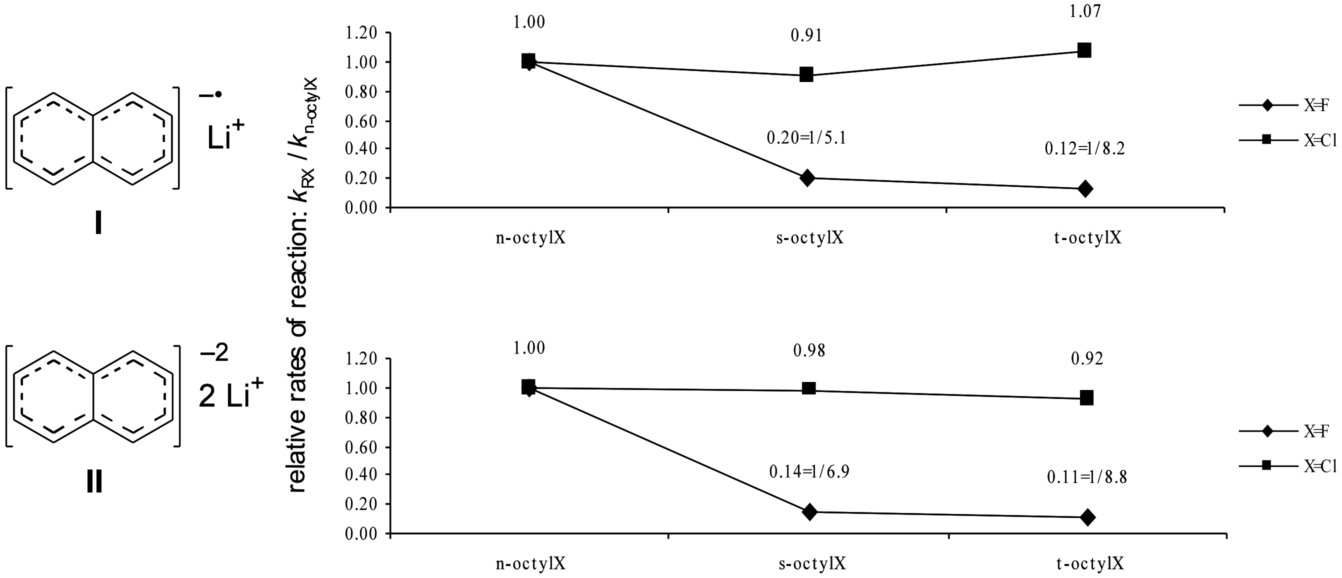
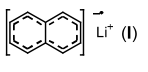
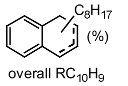
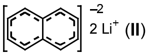


Figure 1. Reactivity profiles of naphthalene radical-anion (**I**) and dianion (**II**) in their reactions with alkyl fluorides and alkyl chlorides. Each relative rate has been obtained by evaluation of the slope by linear regression analysis of plots representing the decay of the concentration of two structurally different halides and are arbitrarily referred to *n*-halooctane. (Each of these plots contained 5–7 points and were linear to greater than 50% consumption of the reacting fluoride (first order reactions with respect to the alkyl fluoride), the regression coefficients being >0.995 in all cases).

Table 1. Reaction of **I** and **II** with structurally different octyl fluorides. Analysis of products

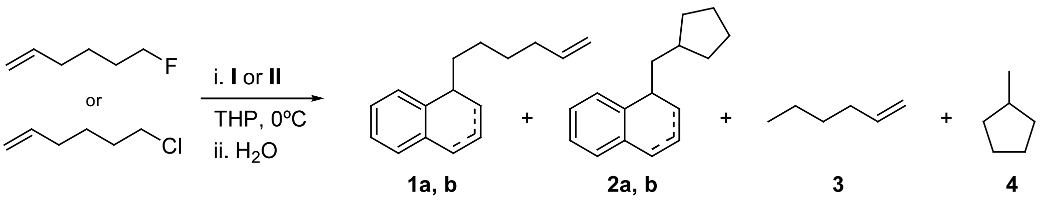
	C_8H_{18} (RH, %)		% quantified
n-$C_8H_{17}F$	49	37	86
s-$C_8H_{17}F$	37	57	94
t-$C_8H_{17}F$	30	64	94
			
n-$C_8H_{17}F$	9	84	93
s-$C_8H_{17}F$	62	36	98
t-$C_8H_{17}F$	51	42	93

a Reactions performed by addition of the alkyl fluoride to a 0.4 M solution of **I** or **II** in THP at 0°C and subsequent hydrolysis with water. Molar ratio: fluoride / **I** or **II** = 1/4. Yields determined by quantitative GLC using pure isolated products for calibration and decane/dodecane as internal standard.

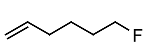
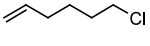
their abundance in the composition of the crude mixture seems to be reversed. This was not observed for alkyl chlorides. Secondary and tertiary octyl fluorides afford higher amounts of coupling products ($RC_{10}H_9$) than reduced products (RH) in their reaction with **I**. The opposite is true for **II**, as expected from its more negative reduction potential. The case of 1-fluorooctane is notorious. It cleanly yields alkylation in its reaction with **II** (dilithium naphthalene) [84%, Table 1)], despite that the corresponding chloride, 1-chlorooctane affords mainly reduction products (RH) in its reaction with **II** (89%).[2] This fact suggests that alkylated products were not originated by radical coupling in the reaction with the fluoride. As the substrates become less prone to undergo S_N2, i.e. secondary and tertiary substrates, the ET pathway becomes dominant. Also, secondary and tertiary radicals are reduced to carbanions with increasing difficulty, so they tend to couple with the naphthalene radical anion (**I**) in greater extension than they are further reduced to afford RH. Thus, both for **I** and **II**, the overall amount of coupling products increases from secondary to tertiary substrates. A rational interpretation for the observed yields can be given considering all the above mentioned factors, and assuming that for primary alkyl fluorides S_N2 reacts competitively with ET.

We reexamined at this point, the rearrangement of radical probes (radical clocks) as an indirect way to detect radicals. The reaction of 6-fluoro-1-hexene with sodium naphthalene in DME at 25°C has been previously studied.[1] In these studies, only low-boiling products were fully identified, with special emphasis given to the 1-hexene (**3**)/methylcyclopentane (**4**) ratios, even though the combined yield **3**+**4** was only 48% (±10%).[1b] These studies are consistent with an ET as the key step in the formation of these light hydrocarbons (C_6). Instead, we have studied the reaction of **I** and **II** with 6-fluoro-1-hexene in THP at 0°C, paying special attention to other major products (Scheme 1). Interestingly, despite their significance, the apparently simple species **1** and **2** are reported here for the first time. Isolation of **1** was only accomplished after chromatographic separation using silica gel doped with 5% of hydroquinone. Otherwise, only complex polymeric/oxidized mixtures are obtained.[2a] We could not detect the reorganized coupling product **2** in the crude mixture when **II** was used as reagent. In order to confirm this finding beyond doubt, **2** was synthesized directly from fluoromethylcyclopentane by reaction with **II** (65%) and was purified as **1**.

The non appearance of **2** in the crude reaction mixture between **II** and a primary alkyl fluoride is also sugges-



I = $LiC_{10}H_8$
II= $Li_2C_{10}H_8$

		1a, b	2a, b	3	4
	**I**	45%	<1%	4%	35%
	II	76%	0%	2%	16%
	**I**	12%	8%	4%	68%
	II	13%	7%	5%	72%

Scheme 1. Comparison of the distribution of products afforded by 6-fluoro and 6-chlorohexenyl probes in their reactions with I or II. Reactions performed by addition of the halide (0.2 mmol in THP) to a 0.2 M solution of I or II in THP at 0°C and immediate hydrolysis. Molar ratio 6-halo-1-hexene/(**I** or **II**) = 1/10. Yields corresponding to the average of 3–5 experiments (σ_{sd} = ±10%), determined by quantitative GLC using pure isolated products and decane as internal standard, contrasted with NMR yields using dimethyl fumarate as internal standard. **a** = 1,4-dihydronaphthalene isomer, **b** = 1,2-dihydronaphthalene isomer; ratio **a**/**b** = ca. 1.2:1.

tive of an S_N2 participation. This can be also extended to the radical anion: **I** also has a nucleophilic character versus alkyl fluorides since very little rearranged product is detected (<1% **2** versus 45% **1**), while the reduction products which are formed in competition are mainly cyclized (35% **4** versus 4% **3**). If coupling products **1** and **2** were mainly formed by radical coupling, a higher amount of reorganized **2** would be expected.[8] These facts, although not conclusive, are highly suggestive of a S_N2 reaction pathway between **I** or **II** and primary alkyl fluorides. An important observation made in the literature is also consistent with our findings. In its Marcus treatment of the ET reaction between arene radical anions and alkyl halides, Eberson observed the failure of alkyl fluorides to conform to the Marcus plot.[9] If the same mechanism of reduction as for alkyl chlorides, bromides and iodides was assumed, no anomalous behavior should have been observed.

Stereochemical experiments are crucial in order to determine the role of the S_N2 pathway in the course of the reaction. Unfortunately, we could not obtain this valuable information with a reasonable degree of confidence yet. While optically pure 2-fluorooctane can be prepared from *R*- or *S*-2-octanol,[10] the reaction with dilithium naphthalene affords complex mixtures of regio and diastereoisomers of alkylated dihydronaphtalenes, which decay easily and could not be appropriately purified and analyzed.[2] Further experiments are being carried out in this direction in order to present further evidence of a competing mechanism alternative to ET. Despite its importance, very little work has been found in the literature for this important test using alkaline salts of naphthalene. In the cases in which stereochemical experiments have been carried out with other systems, such as lithium anthracene ($LiC_{14}H_{10}$), the degree of inversion/racemization was found to be low and leaving group dependent $RCl > RBr \sim RI$,[11] except for alkyl fluorides. Enantiomerically enriched 2-fluorooctane displayed inversion figures (45% inversion) close to that given by a conventional conjugated carbanions (such as 9,10-dihydroanthracenyllithium, $LiC_{14}H_{11}$) reacting in an S_N2 fashion.[12]

In conclusion, the picture that emerges from the reactivity profiles described by the reaction of dilithium naphthalene and lithium naphthalene with alkyl fluorides in THP at 0°C points towards nucleophilic substitution, presumably S_N2, as a competing mechanism to the previously proposed general ET mechanism. This hypothesis is not in conflict with the observed distribution of products and is reinforced by a detailed analysis of the products originated by reaction with 6-halohexenyl radical probes.

Acknowledgements

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