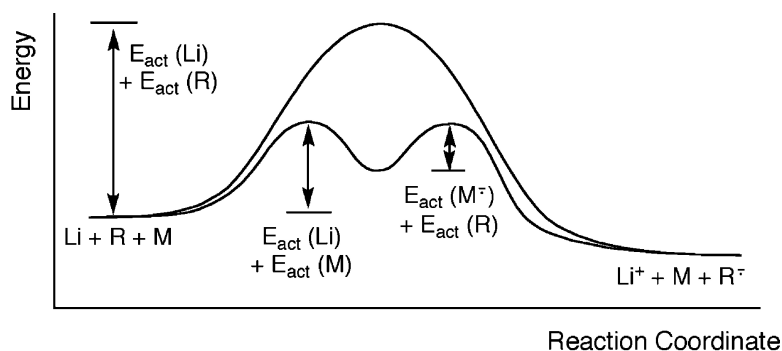


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## Alkali Metal Reductions of Organic Molecules: Why Mediated Electron Transfer from Lithium Is Faster than Direct Reduction

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Lithium has been widely used as a reducing agent in organic synthesis<sup>1</sup> for reactions such as the reductive opening of heterocycles,<sup>2</sup> reductive coupling of carbonyl compounds,<sup>3,4</sup> synthesis/reduction of spiro compounds,<sup>5</sup> and various reactions with benzil<sup>6</sup> and vinylsilanes.<sup>7</sup> There has been recent interest in alkali-metal/arene-based reductions in aprotic media, with the arene acting as a mediator for homogeneous electron transfer via the generation of its radical anion (see scheme 1). Naphthalene and 4,4'-di-*tert*-butyl-1,1'-biphenyl (DBB), in particular, have attracted the most interest as effective mediators in tetrahydrofuran (THF). Many functional groups including thioethers, allylic and benzylic thiols, acetals, disulfides, tertiary alkyl chlorides, and aromatic heterocycles have all been reduced using DBB and naphthalene.<sup>2,8,9</sup> The reductive ring opening of oxygen-containing benzo-fused heterocycles,<sup>10</sup> modification of carbohydrates,<sup>11</sup> and reductive decyanation of nitriles<sup>12</sup> have also been reported.

While the question has been asked why some mediators are more effective than others,<sup>13</sup> the requirement for a mediator has not been explored, and in particular why mediation increases the overall kinetic rate of the electron transfer (ET).<sup>1</sup> A quantitative study of this effect requires data for the ET kinetics of both Li and mediator in an appropriate solvent at a range of temperatures.

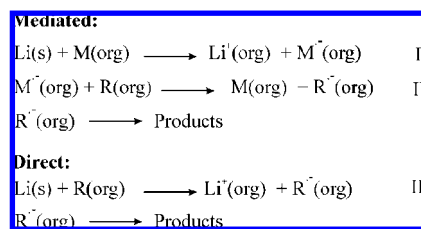
In this communication we present experimental data for the electrode kinetics of the reduction of DBB in THF at a range of temperatures. Using analogous data for the oxidation of Li<sup>14</sup> we provide quantitative estimates of the kinetic advantage in using DBB in Li reductions compared to direct ET from Li to the substrate.

Electrochemical experiments were conducted in a 5.0 mM solution of DBB and 0.1 M tetra-*n*-butylammonium hexafluorophosphate (TBAF) in THF using a 10  $\mu$ m diameter Pt microdisk electrode (see Supporting Information for full details). Cyclic voltammograms were recorded for the one-electron reduction of DBB under thermostatted conditions at solution temperatures 193, 215, 235, 255, 274 and 298 K and analyzed by computer simulation as described previously.<sup>15</sup> The analysis yielded values for the standard electrochemical rate constant ( $k_0$ ), the transfer coefficient ( $\alpha$ ), and formal potential ( $E_f^\circ$ ) measured against a ferrocene/ferrocenium (Fc/Fc<sup>+</sup>PF<sub>6</sub><sup>-</sup>) reference electrode.<sup>13</sup> It was found that  $\alpha = 0.5$  for all temperatures. The value of the diffusion coefficient ( $D$ ) of DBB was found by measurement of the steady-state limiting current ( $I_{lim}$ ) and application of the expression<sup>16,17</sup>

$$D = \frac{I_{lim}}{4Fcr} \quad (1)$$

where  $F$  is the Faraday constant,  $c$  is the bulk concentration, and  $r$  is the electrode radius.

**Scheme 1.** Mediated and Direct Routes for Lithium Reduction of an Organic Reactant, R



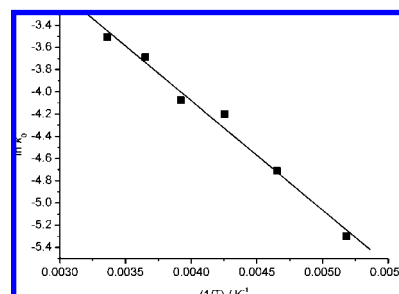
**Table 1.** Experimental Results for the Reduction of DBB

$T/K$	$10^2 k_0 / \text{cm s}^{-1}$	$10^6 D / \text{cm}^2 \text{s}^{-1}$	$E_f^\circ / V$ (vs Fc/Fc <sup>+</sup> PF <sub>6</sub> <sup>-</sup> )
193	0.5	2.7	-3.20
215	0.9	6.0	-3.19
235	1.5	6.0	-3.22
255	1.7	9.2	-3.24
274	2.5	9.9	-3.26
298	3.0	11.5	-3.27

The results (see Table 1) were used to determine the activation energy ( $E_{act}$ ) for the heterogeneous ET by plotting  $\ln k_0$  versus  $1/T$ , yielding  $E_{act} = 8.2 \text{ kJ mol}^{-1}$  (see Figure 1) which is small enough to be consistent with DBB undergoing an outer-sphere ET, where the rate of ET is controlled by solvent dynamics rather than reorganization of the DBB molecule. The temperature dependence of  $D$  and  $E_f^\circ$  were used to extract the activation energy for diffusion ( $6.3 \text{ kJ mol}^{-1}$ ) and entropy change for the reduction ( $-77.5 \text{ J K}^{-1} \text{ mol}^{-1}$ ), respectively (see Supporting Information). The low value for the activation energy for diffusion is also indicative of an outer-sphere process.

In considering the relative reaction rates of mediated and direct (i.e., nonmediated) Li reductions, as in Scheme 1, the general form for the standard rate constant for electron transfer is used<sup>18,19</sup>

$$k_0 = Z \exp\left(-\frac{\Delta G^*}{R_c T}\right) = Z' \exp\left(\frac{\Delta S^*}{R_c}\right) \exp\left(-\frac{E_{act}}{R_c T}\right) \quad (2)$$



**Figure 1.** Arrhenius plot of  $\ln k_0$  vs  $1/T$ , showing a gradient of  $-984.12 \text{ K}$  ( $R^2 = 0.986$ ).

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$$\Delta G^* = \frac{\lambda}{4} \left( 1 + \frac{\Delta G^\circ}{\lambda} \right)^2 \quad (3)$$

where  $\lambda$  is the reorganization energy. An expression for the transfer coefficient can also be derived,<sup>3</sup> namely

$$\alpha = \frac{1}{2} \left( 1 + \frac{\Delta G^\circ}{\lambda} \right) \quad (4)$$

Since  $\alpha = 0.5$  for the reduction of DBB, we can infer that

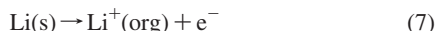
$$\frac{\Delta G^\circ}{\lambda} \approx 0 \quad (5)$$

and so eq 3 can be justifiably simplified (for DBB) to

$$\Delta G^* = \frac{\lambda}{4} \quad (6)$$

If there is no change in the density of energy states in the transition state there is no entropy of activation,<sup>20</sup> and the kinetics are determined by the activation energy  $E_{act}$  (so  $Z = Z'$  in eq 2).

In a previous study,<sup>14</sup> the activation energy for the process



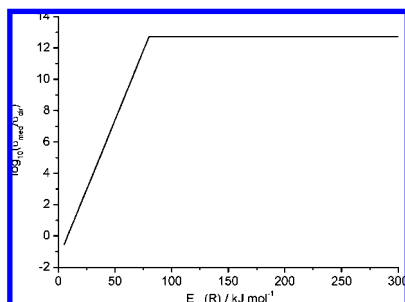
was found to be 80 kJ mol<sup>-1</sup>. Note that the oxidation and dissolution of Li were treated as a single process for simplicity, as the lithium/THF/inert electrolyte system is known to be complex<sup>21</sup> and that this activation energy is approximately 10 times more than that for the reduction of DBB.

With these results and by assuming approximately equal pre-exponential factors ( $Z$ ) for both mediated and direct routes, the ratio of the overall reaction rates for the two competing routes ( $v_{med}$  and  $v_{dir}$ ) were calculated as a function of the unknown activation energy of the reactant R, since

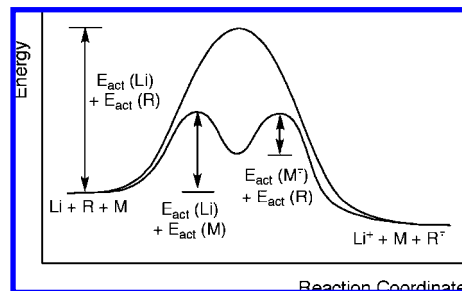
$$v_{dir} = Z \exp \left[ \frac{-\{E_{act}(\text{Li}) + E_{act}(\text{R})\}}{R_c T} \right], v_{med} = Z \exp \left[ \frac{-\{E_{act}(\text{X}) + E_{act}(\text{M})\}}{R_c T} \right]$$

where the activation energy  $E_{act}(\text{X})$  is the lower of  $E_{act}(\text{R})$  and  $E_{act}(\text{Li})$ ,  $R_c$  is the ideal gas constant, and  $T$  is the temperature (in K).

Figure 2 shows the form of this dependence and indicates that there is a rate increase by using a DBB-mediated route provided the activation energy of R,  $E_{act}(\text{R})$ , > 10 kJ mol<sup>-1</sup>, and this increases when  $E_{act}(\text{R}) \geq 75$  kJ mol<sup>-1</sup> to a factor of ca. 10<sup>13</sup> ( $T = 295$  K). Since the usual aim of performing DBB-mediated reductions is synthetic, the activation energy for the reduction of the substrate R would be large due to bond breaking/making. Figure 3 shows a schematic energy profile for the two reaction routes. Note that  $E_{act}(\text{M}) \ll E_{act}(\text{Li})$  or  $E_{act}(\text{R})$  so that the two-step process occurs via reactions with modest activation energies, whereas the single-



**Figure 2.** Relative reaction rates of mediated ( $v_{med}$ ) and direct ( $v_{dir}$ ) reaction paths as a function of activation energy of the target reactant R.



**Figure 3.** Schematic energy diagram for direct and mediated lithium reductions.

step process has an activation energy which is the sum of two large individual contributions;  $E_{act}(\text{Li})$  is 80 kJ mol<sup>-1</sup>,  $E_{act}(\text{M} = \text{DBB}) = 8.2$  kJ mol<sup>-1</sup>, and  $E_{act}(\text{R})$  is likely to be large if the purpose of the reduction is synthetic.

The use of DBB as a mediator in lithium reductions has been shown quantitatively to offer a very large rate increase over a nonmediated route, and this has been rationalized by means of a consideration of electron transfer kinetics. In particular the use of a mediator with a small reorganization energy leads to two steps of modest speed and activation energy of a little over one-half of the direct, slow, nonmediated electron transfer from lithium, where both the substantial reorganization energies for the Li/Li<sup>+</sup> and R/R<sup>-</sup> couples are combined to give one large activation energy.

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**Supporting Information Available:** Experimental details including reagents, instrumentation, and procedures (appendix 1) and additional graphs for the analysis of the experimental data for the DBB reduction (appendix 2). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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