DISSOLVING METAL REDUCTIONS OF KETONES: COMMENTS ON THE DIANION MECHANISM

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ABSTRACT. The reduction of (+)-camphor using Li, Na, and K in THF with sonication is reported. These reductions give the same results as those obtained in NH2. The mechanism of these reactions is discussed.

The detailed mechanism of the reduction of ketones, particularly cycloalkanones, by active metals has attracted considerable attention in the past 35 years. This attention was initially generated by the seeming dilemma created by the observation that under certain conditions metal-ammonia reductions of (+)-camphor and some 12-keto steroids afforded the less stable of a pair of epimeric alcohols.<sup>1</sup> These results were noteworthy in view of the fact that in his pioneering work on conformational analysis Barton had concluded, on empirical grounds, that the dissolving metal reduction of saturated cyclic ketones affords the more stable epimer as the major product.<sup>2</sup> Barton suggested that these reductions occurred via a stepwise two electron reduction of the ketone to a radical anion and then to a dianion (equation 1).3

(1) 
$$\stackrel{R}{\xrightarrow{}} c = 0 \xrightarrow{M^+e^-} \stackrel{R}{\xrightarrow{}} c - \overline{0} M^+ \xrightarrow{M^+e^-} \stackrel{R}{\xrightarrow{}} c - \overline{0} + 2M^+$$

In our early work, we recognized that the metal-ammonia reductions of saturated ketones frequently gave decidedly different product ratios as a function of the presence or absence of an added proton donor and these results were interpreted in terms of the dianion mechanism.<sup>1b,4</sup> However, House subsequently pointed out that the reduction potentials of alkali metals were such that the formation of vicinal dianions from completely aliphatic ketones was unlikely.<sup>5</sup> In our publications variations of the House mechanism were invoked to explain the course of these reductions, both in the presence and absence of added proton donors.<sup>6</sup> In nearly simultaneous work Rautenstrauch found that a nonenolizable ketone, 2,2,6,6-tetramethylcyclohexanone, reacted with one molecular equivalent of lithium in THF to give lithium ketyl aggregates which were stable at low temperature and which <u>were not</u> reduced further with excess lithium. Also, 2,2-dimethylcyclohexanone-6-d, with excess

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alkali metals in liquid ammonia or Li/THF gives 2,2-dimethylcyclohexanone-6-d and 2,2-dimethylcyclohexanol-1-d,6-d<sub>2</sub> in approximately equal amounts.<sup>8</sup> These results, combined with detailed studies on the reduction of (+)-camphor-3-d<sub>2</sub> demonstrated that in the absence of proton donors the reduction of enolizable saturated ketones by dissolving metals proceeds <u>via</u> hydrogen transfer, presumably within a ketyl dimer.<sup>9</sup> Based on these, and a large body of other data, a unified mechanism for the reduction of saturated ketones by dissolving metals, both in the presence and absence of added proton donors was presented.<sup>10</sup> That portion of the mechanism which pertains to reductions in the absence of a proton donor was described above and is summarized in Scheme I.



We were (and are) satisfied that this mechanism is consistent with <u>all</u> of the available data for aliphatic ketones both from our laboratory and presented by others. We are equally satisfied that there are <u>no</u> data which are uniquely consistent with the historically important Barton dianion mechanism and that data exist which are not consistent with this mechanism.

However, in a very recent review S.K. Pradhan exhumed the dianion mechanism for the <sup>11</sup> reduction of saturated ketones by metals in ammonia in the absence of added proton donors. <sup>1</sup> Pradhan presents several arguments which he alleges are consistent with this mechanism among which is the assertion that: "If a proton cannot be added reduction of nonenolizable ketones has to proceed by electron or alkali metal addition to give a dianion...". 2,2,6,6-Tetramethylcyclohexanone reacts with <u>one atom of lithium and only one in both liquid ammonia <sup>12</sup> and THF.</u><sup>7</sup> In addition, products of the reaction of the radical center of this ketyl with THF have been found<sup>7</sup> and we now find that fenchone (0.8 mmol) with excess (3 mmol)Li/THF at 25° gives significant amounts of similar products. These data are consistent with a persistent radical anion <u>which exists in the presence of excess Li</u>. They are not consistent with a dianion intermediate.

Another point raised by Pradhan refers to our assumption that the general mechanism of reduction in THF is the same as that in  $NH_3$ . This assumption is attacked on the grounds that reductions in THF are slower than those in  $NH_3$  and the observation that the seco-steroid 1 gives only cyclized alcohol 2 and recovered ketone on treatment with Li/THF for 70 h.<sup>11</sup> Since the same substrate with Li/NH<sub>3</sub> gives significant amounts of the secondary alcohol, the conclusion is reached that Li/THF affords the radical anion while

Li/NH3 gives the dianion.11



The conclusion that reactions in THF and  $NH_3$  proceed by the same path was based primarily on the observation that reaction of dimethylcyclohexanone with Li/THF and Li/NH<sub>3</sub> gives essentially identical results.<sup>8</sup> We have now carried out reductions of (+)-camphor with metals in THF using sonication and compared the results with those in  $NH_3$ . These data are summarized in Table I and it can be seen that the results are identical (within experimental error) in both systems. Also reduction of (+)-camphor-3-d<sub>2</sub> in THF with sonication<sup>13</sup> gave product ratios and deuterium distributions identical, within experimental error, to those obtained in  $NH_3$ .



<sup>a</sup>All reactions in THF were carried out with the use of ultrasound at ambient temperature for 0.5 to 1.0 h. The product mixtures were analyzed by glc and the results are the average of at least three runs with an estimated error of  $(\pm)4\%$ . In the runs with Li and Na significant amounts of pinacol were obtained.

These results strongly indicate that these reactions follow the same path in  $NH_3$  and THF and the data are entirely consistent with the path we have proposed previously.<sup>10</sup> The failure of 1 to undergo reduction to the alcohol with Li/THF is probably caused by the low solubility of Li in THF. The ketyl monomer is formed relatively slowly and unimolecular cyclization to 2 is concentration independent and very rapid.<sup>14</sup> Reduction occurs within a ketyl aggregate, the rate of formation of which is a function of the concentration of ketyl monomer.

Although Pradhan presents a number of examples to support the dianion mechanism, all can be equally well explained by a ketyl aggregate path or should be the subject of further

investigation. 15 The most compelling argument against the dianion mechanism is, however, that which House invoked some years ago. 5 The reduction potentials of alkali metals in ammonia are approximately  $-2.9V^5$  and that for the addition of one electron to camphor  $-2.75 v^{16}$ . Using the usual relationship between reduction potential and K this leads to K eq = 3.4 x  $10^2$  based on  $\Delta V = 0.15V$ .<sup>17</sup> It has been known for many years that acetone<sup>18</sup> and other aliphatic ketones react with one equivalent of metal in NH2.7,12 Combining these data leads to the conclusion that aliphatic ketones react with one equivalent of metal in an effectively irreversible reaction. The reactions which aliphatic ketones undergo with alkali metals in ammonia are thus the result of one electron reductions to ketyls which are subsequently converted to the observed reaction products without the intervention of dianions.

## References and Notes

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