

Ketone Dianions, Ketone-Ketyl Coupling, and Possible Reaction-during-Mixing
 Effects in Alkali Metal/Ammonia Reductions of Saturated Ketones

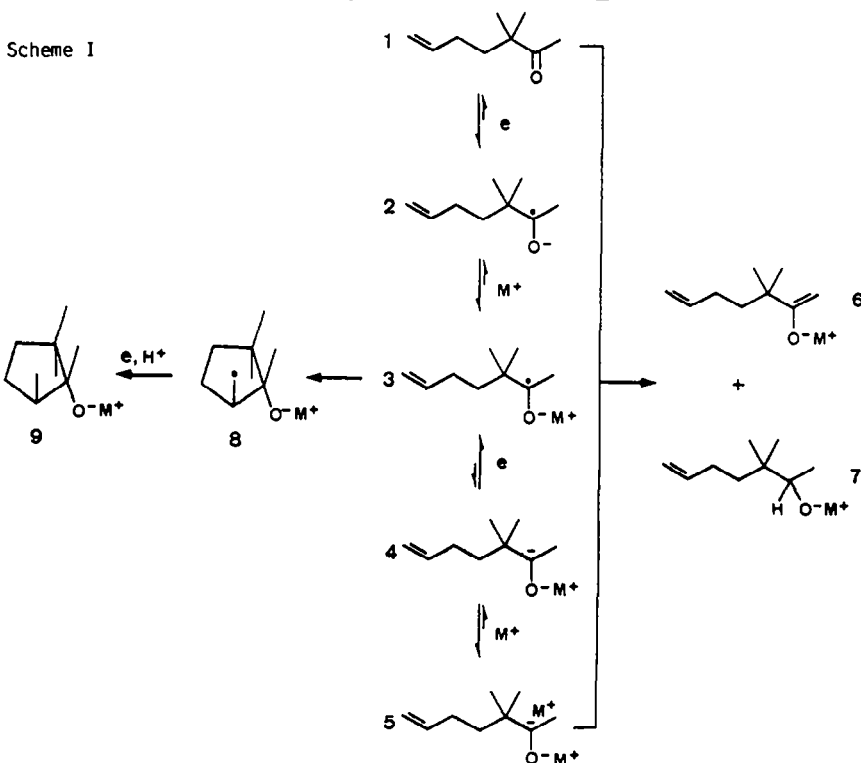
VALENTIN RAUTENSTRAUCH

Firmenich SA, Research Laboratories, Case Postale 239
 CH-1211 Geneva 8

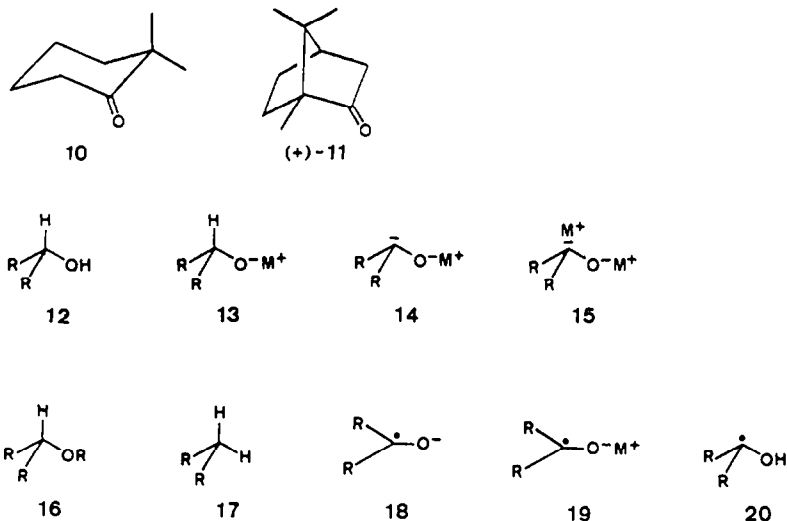
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Abstract: The hypothesis of Pradhan that alkali metal/NH₃ reductions of saturated ketones lead to ketone dianions which then deprotonate unreacted ketone can be excluded because the dianions would have been protonated in experiments in which 50-110 equiv of tert.-BuOH, EtOH, and H₂O were present in the reaction medium: the phenomenon interpreted in terms of the above deprotonation persisted in the presence of these proton sources and is probably instead due to a radical disproportionation of the monoanions (ketyls). Another hypothesis of Pradhan, that pinacol coupling of saturated ketones by Li dissolving in NH₃ involves ketone-ketyl coupling, is implausible because this coupling would be thermodynamically highly unfavorable. Possible alternative interpretations of Pradhan's findings are proposed.

Alkali metal/NH₃ reductions of enolizable ketones R-CH₂-CO-R, R = alkyl or alkenyl with a remote double bond, for example **1** in Scheme I, give 1:1 mixtures of the corresponding enolate **6** and alcoholate **7**¹. We believe¹ that the underlying mechanism is a radical disproportionation² of the M⁺ ketyls **3**, thus of the monoanions of **1**, cf. Scheme II. We think that these disproportionations are likely to have all the characteristics of normal radical disproportionations², for example, near-diffusion-controlled rates. This opinion is to some extent justified by the fact that the self-reactions (disproportionation and combination) of the corresponding ketyl radicals (which would result if the ketyls **2** and **3** were protonated) do have the same characteristics as those of alkyl radicals^{2b,3}. Pradhan has instead hypothesized⁴ that the 1:1 enolate **6** alcoholate **7** mixture is formed through deprotonation of the ketone **1** by its dianions **4** or **5**, cf. Scheme I.



I wish to point out that Pradhan's dianion mechanism can be excluded on the basis of published experiments with the two saturated ketones [6,6-²H₂]dimethylcyclohexanone^{1a} [6,6-²H₂]-10 and (+)-[3,3-²H₂]camphor^{1b} [3,3-²H₂]-11. Here the formation of the 1:1 enolate-alcoholate mixture proceeds by transfer of ²H and this transfer persisted under conditions where the dianions would have been protonated by the reaction medium which was unlabeled.



The second pK_a of a dialkyl carbinol 12, that is, the pK_a of its alcoholate 13, is not known experimentally⁵. It could well be that the substituents $-O^-$ and $-O^-M^+$ actually stabilize the adjacent carbanion in the dianions 14 and 15 (cf. 4, 5, Scheme I) to some extent. I estimate that the pK_a of 13 is similar to that of a secondary ether 16 and smaller than that of an alkane 17. It turns out that the pK_a values of 16 and 17 are close, about 49 for 16^{6,7}, and about 51 for 17⁷. The following argument holds if the pK_a estimate for 13 is in error by as much as 10-15 pK_a units.

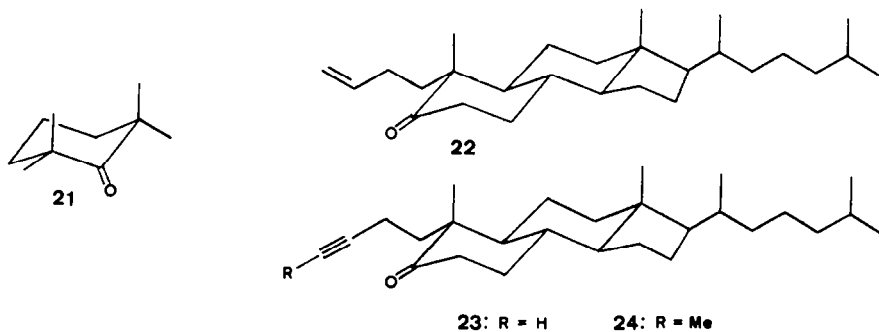
The phenomenon of enolate-alcoholate formation from [6,6-²H₂]-10 and (+)-[3,3-²H₂]-11 by transfer of ²H was not only dominant in NH₃/THF¹ (the pK_a of NH₃ is 38), but largely persisted in NH₃/THF containing 50 equiv (mol/mol of ketone) of tert.-BuOH^{1a} (pK_a 17), or 50 equiv of EtOH^{1a} (pK_a 16), or even 110 equiv of H₂O^{1b} (pK_a 15.7), and was still just detectable in NH₃/THF saturated with NH₄Cl^{1b} (the pK_a of NH₄⁺ is 9.2). Thus there was a huge thermodynamic driving force for the protonation of the hypothetical dianions (cf. 4, 5, 14, 15) of [6,6-²H₂]-10 and (+)-[3,3-²H₂]-11 by all of these proton sources. The kinetics of proton transfers to carbanions and from carbon acids are a knotty problem⁸ but Bunnett^{9a} has made a careful estimate of the rate of the protonation of a primary carbanion by tert.-BuOH in NH₃ and arrived at a half-life of $\leq 1.5 \cdot 10^{-10}$ s for the Na⁺ carbanion pair. In addition, proton transfer from an alcohol or H₂O to the dianions of [6,6-²H₂]-10 and (+)-[3,3-²H₂]-11 is likely to be faster than deuterium transfer from these ketones to their dianions. I conclude that the dianions would have been protonated completely by the tert.-BuOH, EtOH, and H₂O that was present in huge excess, and not deuterated by the ketones (pK_a 19-20) [all the more so since very little of these can have been left unreduced (see below)].

The effects seen in the presence of tert.-BuOH, EtOH, H₂O, and NH₄⁺, are instead entirely consistent with our interpretation^{1,10}, that the free ketyls (cf. 2, 18) and/or the M⁺ ketyls (cf. 3, 19) of [6,6-²H₂]-10 and (+)-[3,3-²H₂]-11 were protonated by these proton sources in line with their pK_a values. The conjugate acids of the ketyls (cf. 18, 19), the ketyl radicals (cf. 20), have pK_a values around 12¹¹, and a strong effect - we think near-complete protonation of the free ketyls - was only seen for NH₄⁺ as the proton source^{1b}.

Pradhan's hypothesis (cf. Scheme I) is also unlikely in that the equilibria between 1, the solvated e⁻, and the M⁺ on the one hand, and the ketyls 2 and then 3 on the other, lie essentially completely on the side of 3. The equilibria can be estimated from the reduction potentials¹². Whether Pradhan's hypothesis is nevertheless kinetically feasible cannot be estimated because the rate of the hypothetical step 3 - 4 is unknown; one can only say that 3 - 4 must be much slower

than $\underline{1} \rightarrow \underline{2} \rightarrow \underline{3}$. The rates of $\underline{1} \rightarrow \underline{2}$ ¹³, $\underline{2} \rightarrow \underline{3}$ (probably diffusion-controlled) and $\underline{3} \rightarrow \underline{2} \rightarrow \underline{1}$ (via the equilibria) could, in principle, be roughly estimated.

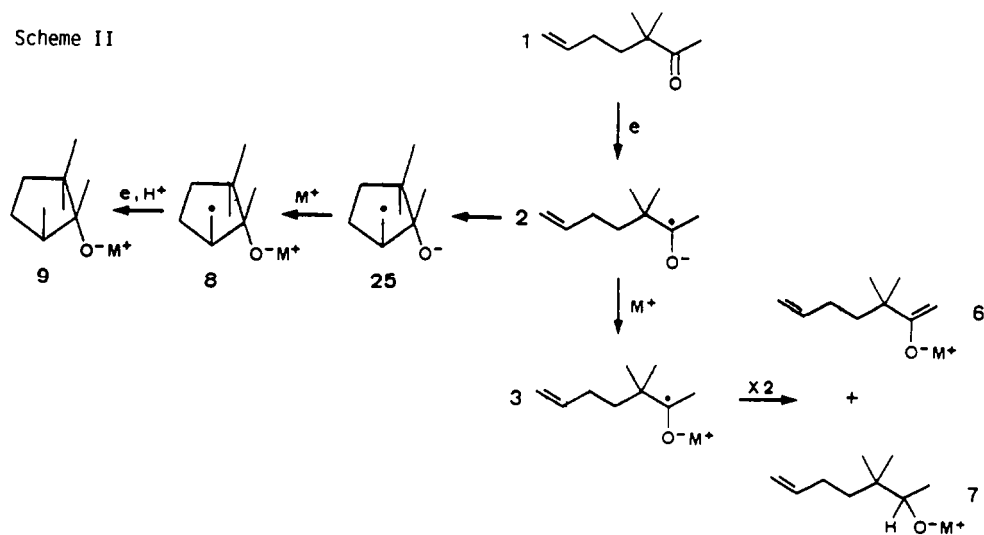
Finally, there is still House's argument^{12a}, that NH_3 -solvated e cannot reduce ketone $\underline{1}$ to dianions $\underline{4}$ or $\underline{5}$, cf. Scheme I. Note in this context that the reaction between 2,2-dimethylcyclohexanone $\underline{10}$ and the stable Li^+ ketyl (cf. $\underline{19}$) of 2,2,6,6-tetramethylcyclohexanone $\underline{21}$ ¹⁴ in NH_3 apparently gives the Li^+ ketyl of $\underline{10}$ which then decays rapidly^{1a}. This means that the Li^+ ketyl of $\underline{21}$ (without excess Li) reduces $\underline{10}$ to the Li^+ ketyl which then decays as it does in the presence of excess Li . Note also that the stable Li^+ ketyl of $\underline{21}$ is not reduced further by excess Li in NH_3 ^{1a}.



The basis of Pradhan's hypothesis⁴ is the following. Addition of the secosteroid ketone $\underline{22}$, which is represented by $\underline{1}$ in Scheme I, in THF solution, to a dilute solution of excess Na in NH_3 gave the corresponding 1:1 enolate $\underline{6}$ - alcoholate $\underline{7}$ mixture and in addition the corresponding cyclic alcoholate $\underline{9}$, cf. Scheme I. The ratio $\underline{7}/\underline{9}$ ($= \underline{6}/\underline{9}$) was found to be independent of the concentration of $\underline{1}$ but dependent on that of Na , as follows: $\underline{7}/\underline{9} = \text{const.} \cdot [\text{Na}]$; thus the more Na was in the solution, the less cyclization occurred. Pradhan concluded that this means that the M^+ ketyl $\underline{3}$ either cyclized or was further reduced. This branching, plus the condition that the branching steps are rate-determining, results in $\underline{7}/\underline{9} = \text{const.} \cdot [\text{Na}]$. Analogous results were obtained with the acetylenic ketones $\underline{23}$ and $\underline{24}$.

However, Na dissolves in NH_3 to give solvated e and Na^+ , and Pradhan's experiments do not distinguish between $[e]$ and $[\text{Na}^+]$. Pradhan assumed that $\underline{7}/\underline{9} = \text{const.} \cdot [e]$, but the interpretation that $\underline{7}/\underline{9} = \text{const.} \cdot [\text{Na}^+]$ is equally valid. It could thus be that the branching occurs between the free ketyl $\underline{2}$ which cyclizes, and ion-pairing which leads to disproportionation, cf. Scheme II, with $\underline{1} \rightarrow \underline{2}$ or $\underline{2} \rightarrow \underline{3}$ and $\underline{2} \rightarrow \underline{25}$ rate-determining. Note again that the rates of $\underline{1} \rightarrow \underline{2}$ (well below diffusion-controlled?¹³) and $\underline{2} \rightarrow \underline{3}$ (probably diffusion-controlled) can be estimated. It is therefore most likely that $\underline{1} \rightarrow \underline{2}$ would be rate-determining.

Scheme II



There are indications in the literature that seem to support this interpretation. Thus the analogous electrochemical reductive cyclizations (2 - 25) that are run in solvents such as DMF in the presence of NR_4^+ salts¹⁵ and analogous reductive cyclizations in which the ketyl is generated by photochemically induced e-transfer from HMPA or from Et_3N in CH_3CN ¹⁶ work much better than Na/NH_3 cyclizations^{15c,16}. In the same vein, it seems that cyclizations with Na are in fact best run in HMPA^{15c,17} or Et_2NCOMe ¹⁸, solvents that are thought to solvate Na^+ exceptionally well¹⁸. Note that in Stork's synthesis of gibberellic acid¹⁹, cyclization was achieved by slowly adding K in NH_3 to a dilute solution of an ynone in NH_3/THF containing excess $(\text{NH}_4)_2\text{SO}_4$; here it was probably the ketyl radical (cf. 20) rather than the ketyl (cf. 2, 3, 18, 19) that cyclized.

For clarity, up to now the assumption has been made that these reductions and cyclizations occur in homogenous solution, and Pradhan has also made this assumption⁴. However, following a suggestion by J. Huffman²⁰, I now suspect that they are so rapid that they in fact "occur during mixing, in local conditions of strong concentration gradients"⁹, with the e moving rapidly into zones that are rich in ketone 1 and leaving behind the Na^+ . Bunnett⁹ has made this proposal for alkali/ NH_3 reductions of 6-halo-1-hexenes and for $\text{S}_{\text{RN}}1$ reactions involving the halobenzenes. We have started experimental work and have found that Na/NH_3 reductions plus cyclizations of simple enones of type 1 by Pradhan's method are indeed over within about the time it takes to mix the system (about 10 sec after adding 1 mmol of substrate in 1 ml of THF to a stirred solution of 6 mmol Na in 100 ml of NH_3/THF at -33°).

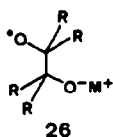
If Bunnett's proposal indeed applies, then the ketone 1 never dissolved in the entire volume of NH_3 in Pradhan's experiments, that is, his "initial concentrations"^{4b} were never reached. $7/9 = \text{const} \cdot [\text{Na}]$ could then be due to [1] in the THF solution that was injected^{4b} not varying significantly. This could simply mean that the M^+ ketyls 3 cyclize (Scheme I) and disproportionate¹ (Scheme II) in parallel, although one might conceivably also see the dependence on $[\text{Na}^+]$ suggested above. Note that the argument concerning the protonation of dianions 4 and 5 would hold^{9a}, but that their formation would be even more unlikely.

Beyond the present argument, note that it is amazing that the phenomenon which we think is ketyl disproportionation, an intermolecular process, competes so efficiently with intramolecular cyclization. In our view¹, this may be due to the fact that these charged radicals associate very rapidly (perhaps more rapidly than uncharged radicals?) and then stay clustered together, unlike uncharged radicals. It should, however, be possible to suppress the self-reaction by further dilution^{9a,19}. Finally, note that Huffman has also criticized the dianion mechanism²¹.

Pradhan has invoked the kinetics of the reactions of Me_2NCHO and EtNCHO with e and Na^+ in NH_3 (in homogenous solution) that have been determined by Dewald²², and that suggest an amide-amide dianion deprotonation mechanism²² in support of his hypothesis, but these kinetics obviously have no bearing on the mechanism of the formation of enolate and alcoholate from ketones. For ketones 1, the equilibrium with e and Na^+ lies far on the side of the ketyls 3 (see above), while it lies far on the side of the unreduced species in the case of the formamides. Indeed, Et_2NCOMe dissolves Na to give blue solutions²³ and has been used as the solvent in the reductive cyclizations of ketones with Na ¹⁸ mentioned above.

Ion-pairing plus reaction-during-mixing effects could also be responsible for an extraordinary stereochemical phenomenon reported by Pradhan²⁴. He has found that Li/NH_3 reduction of (\pm)-camphor (\pm)-11 brings about only homochiral²⁵ pinacol coupling, and furthermore, that its stereochemistry depends on the addition mode: homochiral exo-endo coupling occurs on normal addition (dissolving Li^{1b}) and homochiral endo-endo coupling on inverse addition^{1b} (of (\pm)-11 to a solution of Li). This undoubtedly proceeds via the combination of the Li^+ ketyls^{1b,12a}, combination being the normal counterpart¹ of disproportionation²⁶ in the self-reaction^{2,3}. There is a clear link between the occurrence of this combination in alkali metal/ NH_3 reductions and the size of the M^+ ^{1b,27}. In the case of (+)-camphor (+)-11, Li/NH_3 gives mainly the pinacols, Na/NH_3 traces of pinacols, and K/NH_3 no pinacols^{1b}; this means that the M^+ are directly involved in the coupling.

Pradhan's proposal²⁴ that the exo-endo coupling is a ketone-ketyl (cf. 18,19) coupling is unlikely because this would be thermodynamically highly unfavorable. In other words, the hypothetical coupling product 26 would fragment²⁸



to give ketone and ketyl; Pradhan's proposal requires that it be removed from a hypothetical equilibrium by reduction.

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