Endo-Selectivity and Kinetic Control in Alkali Metal–NH_3–NH_4^+ Reductions of Bicyclo[2.2.1]heptan-2-ones

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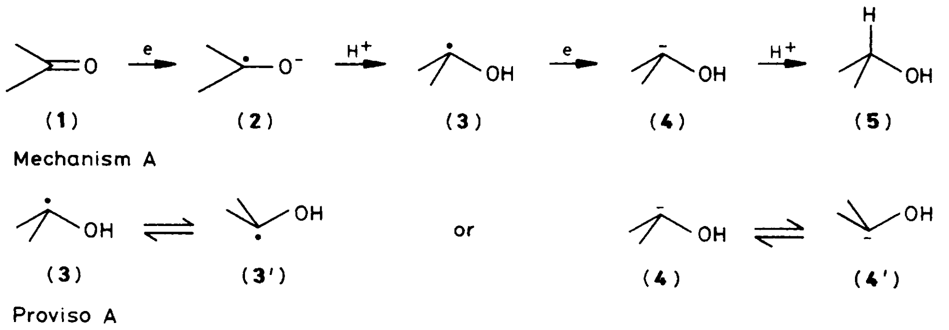
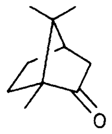
Reduction of five bicyclo[2.2.1]heptan-2-ones (**6**), (**9**), (**12**), (**15**), (**18**) and the parent bicyclo[2.2.1]hept-5-en-2-one (**21**) by alkali metals dissolving in NH_3 and a cosolvent saturated with NH_4Cl affords in every case predominantly (83—>99%) the corresponding *endo*-alcohol (**7**), (**10**), (**13**), (**16**), (**19**), and (**22**), and since two of these *endo*-alcohols are the thermodynamically more stable [(**7**), (**19**)] and two the less stable [(**10**), (**13**)] isomers, these reductions are probably all kinetically controlled; a correlation is made between this *endo*-selectivity and *exo*-hydrogen-exchange in the ketones (**6**), (**9**), (**12**), (**15**), and (**21**).

Dissolving metal reductions of ketones in general and alkali metal–NH_3 reductions of ketones in particular frequently lead to the thermodynamically more stable diastereoisomeric alcohol.[1] A general mechanistic rationale has evolved for these synthetically and theoretically important reactions. This consists of a sequence of reduction and protonation steps: ketone (**1**)$\xrightarrow{e}$ ketyl (**2**)$\xrightarrow{H+}$ ketyl radical (**3**)$\xrightarrow{e}$hydroxycarbanion (**4**)$\xrightarrow{H+}$ alcohol (**5**) (mechanism A, Scheme 1), with the elaborate proviso that the diastereoisomeric, pyramidal species (**3**) and/or (**4**) equilibrate, that these equilibria parallel those between the diastereoisomeric alcohols (**5**), and that (**3**) and/or (**4**) are then reduced and/or protonated indiscriminately (*i.e.* with similar rates) to afford the diastereoisomers (**5**) in close to their equilibrium ratio (proviso A, Scheme 1).[1]



Scheme 1



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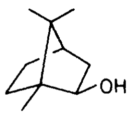

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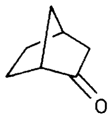

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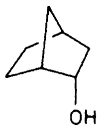

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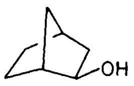

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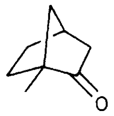

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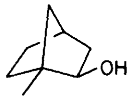

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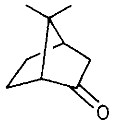

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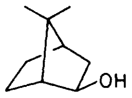

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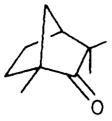

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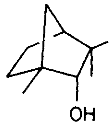

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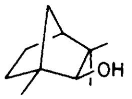

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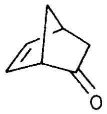

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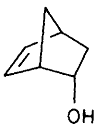

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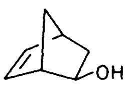

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The equilibration(s) of (**3**) and/or (**4**) would thus, in effect, provide thermodynamic control.

In the 1960s, many exceptions to the above empirical rule were noted. Reduction of various bicyclo[2.2.1]heptanones, steroid ketones, and diterpene ketones by sodium in alcohols or by alkali metals in NH$_3$ alone or in combination with proton sources (usually alcohols, rarely NH$_4$Cl) were found to give predominantly the less stable alcohols.[1c—e] The above rule was accordingly modified to the effect that strained or sterically hindered ketones may give the less stable isomers.[1c]

In 1981—82, we uncovered evidence which suggested that, in fact, alkali metal–NH$_3$ reductions proceed only by mechanism A when NH$_4^+$ is the proton source.[1b] An entirely different, bimolecular mechanism was found to take over in the presence of less acidic proton sources or in NH$_3$ alone.[1b,e,2] The textbook mechanism A is thus only valid for one extreme type of alkali metal–NH$_3$ reduction. Whether or not it also correctly describes other dissolving metal (and electrochemical) reductions, in particular Na–ROH reductions, is not clear.

In this context, we took the fact that alkali metal–NH$_3$–NH$_4^+$ reduction of camphor (**6**) gives mainly borneol (**7**),[1b,3] the more stable *endo*-isomer, as evidence for proviso A.[1b] Huffman, however, pointed out[1e,4] that we had overlooked that norcamphor (**9**) had long been known to give the less stable *endo*-norborneol (**10**) upon alkali metal–NH$_3$–NH$_4^+$ reduction.[3b,4a,5]

This invalidated proviso A, but suggested that bicyclo-[2.2.1]heptanones might in general afford the *endo*-alcohols upon alkali metal–NH$_3$–NH$_4^+$ reduction, regardless of whether they are thermodynamically favoured or not. This has now been checked and found to be so in six cases. Two further cases were already reported[5] and two more examples have been added. Up to now there are no exceptions. Equilibrium ratios for five of the six diastereoisomeric alcohol pairs were also in the literature.[6,7] The data are collected in Table 1. Note that the *endo*/*exo* ratios are virtually the same for dissolving Li, Na, or K, which suggests that free ketyls (**2**) and free carbanions (**4**) are protonated and reduced.[1b,2b] Note also that the same *endo*/*exo* ratio is obtained regardless of whether (+)-camphor [(1*R*)-(**6**)] or its racemate [(1*RS*)-(**6**)] is the substrate, which independently shows that the bimolecular pathway does not interfere.[1b,e,2]

The reductions of (**9**), (**12**), and (**21**) are thus under kinetic control and this suggests that alkali metal–NH$_3$–NH$_4^+$ reductions in general are under kinetic control.† This requires that

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† The following may confuse the reader and evoke a sense of *déjà-vu*. The conclusion *per se* that kinetic control operates in dissolving metal reductions,[9] the assumption *per se* that protonation rates may control their stereochemistry,[10] and even the correlation between the stereochemistry of the reductions and of exchange,[11] were arrived at previously, but in different contexts. The reductions described in ref. 9 proceed by a mechanism different from mechanism A[1b,e,2] (there was also no clear-cut *endo*-preference in ref. 9), the discussion in ref. 10(b) refers to Na–ROH reductions, and the discussion in ref. 10(a) to dissolving metal reductions in general in terms of the early Barton dianion mechanism,[1a] and the correlation in ref. 11 concerns Zn–HOAc reductions of two bicyclo[2.2.1]heptan-2,3-diones. The present conclusions refer specifically to alkali metal–NH$_3$–NH$_4^+$ reductions and to mechanism A–proviso A.

Table 1. Alkali metal–NH_3–NH_4^+ reductions of bicyclo[2.2.1]-heptan-2-ones and -hept-5-en-2-one and equilibrium ratios for the corresponding alcohols.

Ketone[a]	*endo* Alcohol	*exo* Alcohol	Alkali metal	Cosolvent	Temperature /°C	Reduction *endo*/*exo* ratio	Ref.	Equilibrium *endo*/*exo* ratio (equilibrium temperature)	Ref.
(1*R*)-(**6**)	(1*R*)-(**7**)	(1*R*)-(**8**)	Li	Et_2O	−33	92 : 8	3a	89 : 11 (−75)	6
,,	,,	,,	K	,,	,,	90 : 10	,,	84 : 16 (−33)	
(1*RS*)-(**6**)	(1*RS*)-(**7**)	(1*RS*)-(**8**)	Li	,,	−78[a]	90 : 10	3b[a]		
,,	,,	,,	Na	,,	,,	89 : 11	,,		
,,	,,	,,	K	,,	,,	88 : 12	,,		
(1*R*)-(**6**)	(1*R*)-(**7**)	(1*R*)-(**8**)	Li	,,	−33	94 : 6	3c		
,,	,,	,,	Na, K	,,	,,	90 : 10	,,		
,,	,,	,,	Li, Na, K	THF[b]	−75	94 : 6	1b		
(1*RS*)-(**9**)	(1*RS*)-(**10**)	(1*RS*)-(**11**)	Li, Na	Et_2O	−78[a]	89 : 11	3b	5 : 95 (−75)	6
,,	,,	,,	K	,,	,,	90 : 10	,,	8 : 92 (−33)	
,,	,,	,,	Li	,,	−33	89 : 11	5[a]		
,,	,,	,,	,,	,,	,,	85 : 15	4a		
(1*RS*)-**12**)	(1*RS*)-**13**)	(1*RS*)-**14**)	,,	,,	,,	91 : 9	5[a]	ca.40 : 60 (170)	6
(1*R*)-(**15**)	(1*R*)-(**16**)	(1*R*)-(**17**)	,,	,,	,,	83 : 17	5[a]	unknown	
(1*R*)-(**18**)	(1*R*)-(**19**)	(1*R*)-(**20**)	,,	THF	−75	>99 : 1	This work	ca.72 : 28 (170)	6
(1*R*)-(**21**)	(1*RS*)-(**22**)	(1*RS*)-(**23**)	,,	,,	,,	99 : 1	This work	ca.50 : 50 (110)	7

[a] In ref. 3b, the substrate was (1*RS*)-(**6**): see ref. 2b. In ref. 5, the substrates were (1*RS*)-(**9**), (1*RS*)-(**12**), and (1*R*)- or (1*S*)-(**15**): see ref. 8. The reaction temperature in ref. 3b was −78 °C: see note 7 in ref. 4a. [b] THF = tetrahydrofuran. [c] Method of ref. 1b: to a cooled (−75 °C), stirred solution of 2 mmol substrate [(**18**), (**21**)] in 35 ml NH_3 and 10 ml THF containing 30 mmol largely suspended NH_4Cl, 20 mmol Li was added which dissolved/reacted within 55 min [(**18**)] and 5 min [(**21**)]. Work-up gave mixtures of 11% (**18**), 89% (**19**), with (**20**) not detectable (by g.c.), and 20% (**21**), 79% (**22**), 0.9% (**23**).

proviso A be revised. (Mechanism A is not affected.) The simplest and most reasonable revision is that the protonation of the hydroxycarbanion (**4**) determines the stereochemistry.[†,‡] Accordingly, protonations of the hydroxycarbanions derived from bicyclo[2.2.1]-heptan-2-ones and -hept-5-en-2-ones (rapidly equilibrating pyramidal carbanions or planar carbanions?) from the *exo*-side appear to be preferred.[†]

Strikingly, this postulated preference for *exo*-protonation in the reductions [at C(2)] can be correlated with the preference for exchange of the *exo*-H-atom on the adjacent C-atom [C(3)] in the same bicyclo[2.2.1]-heptanones and -heptenones,[†] a phenomenon discovered 20 years ago in these laboratories and still not fully understood.[12] The correlation supports the hypothesis that a protonation step determines the stereochemistry of the reductions and suggests common causes for both phenomena.

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[‡] *Added in proof.* Another possibility is that the *endo–exo* equilibria for the ketyl radicals (**3**) derived from bicyclo[2.2.1]heptan-2-ones favour the radicals with the OH group *endo*, thus do not parallel those for the corresponding alcohols as assumed previously (proviso A).