41. The Stereochemical Outcomes - the Isoborneol/Borneol Ratios - in Lithium, Sodium and Potassium/Ammonia Reductions without a Proton Source of the Enantiomers and the Racemate of Camphor Differ Strongly

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Summary

The stereochemical outcomes [ratios (1*R*,2*R*,4*R*)-isoborneol/(1*R*,2*S*,4*R*)-borneol or (1*S*,2*S*,4*S*)-isoborneol/(1*S*,2*R*,4*S*)-borneol and (1*RS*,2*RS*,4*RS*)-isoborneol/(1*RS*,2*SR*,4*RS*)-borneol] in lithium, sodium and potassium/ammonia reductions without a proton source of the enantiomeric [(1*R*,4*R*) or (1*S*,4*S*)] and racemic (1*RS*,4*RS*) forms of camphor under the same conditions differ strongly. This explains contradictory reports in the literature and, in the case of the reductions with potassium in which pinacol coupling does not compete, proves that the reductions involve bimolecular reactions between two ketyls, or between the ketone and the ketyl or the ketone dianion.

Rassat et al. [1] and *Huffman et al.* [2] reported different stereochemical outcomes in the lithium, sodium and potassium/ammonia reductions without a proton source of camphor (**1**) using at first similar and then, attempting to reproduce each other's results, the same experimental procedures. *Murphy et al.* [3] reported the same stereochemical outcomes as *Rassat et al.* using a somewhat different procedure. The largest discrepancies, isoborneol/borneol ratios (**2**/**3**) of *ca.* 62:38 *vs.* *ca.* 18:82, were noted in the reductions with potassium (see *Table 2*).

I have now resolved the discrepancies. The experimental procedures were the same but the substrates were not! *Rassat et al.* [1]1) and *Murphy et al.* [3] used (1*R*,4*R*)-**1** and determined the ratios (1*R*,2*R*,4*R*)-**2**/(1*R*,2*S*,4*R*)-**3** and *Huffman et al.* [2]2) used (1*RS*,4*RS*)-**1** and determined the ratios (1*RS*,2*RS*,4*RS*)-**2**/(1*RS*,2*SR*,4*RS*)-**3**. For brevity and clarity, I shall specify only one chiral center in the following discussion; thus (1*R*)-**1** represents (1*R*,4*R*)-**1** ((+)-**1**), *etc.*3). That the enantiomeric and racemic forms of **1** are reduced to give the enantiomeric and

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1) Personal communication.

2) *Huffman et al.* did not indicate which camphor they used. Professor *Huffman* has since confirmed that they used (1*RS*,4*RS*)-**1**1).

3) This does not conform to IUPAC rules but does define all other centers in our case. The correct nomenclature is: (1*R*,4*R*)-**1**, (1*S*,4*S*)-**1**, (1*RS*,4*RS*)-**1**, (1*R*,2*R*,4*R*)-**2**, (1*S*,2*S*,4*S*)-**2**, (1*RS*,2*RS*,4*RS*)-**2**, (1*R*,2*S*,4*R*)-**3**, (1*S*,2*R*,4*S*)-**3**, (1*RS*,2*SR*,4*RS*)-**3**. (1*R*)-**1** here = **1** in [4], (1*R*)-**2** here = **2** in [4], (1*R*)-**3** here = **3** in [4].

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racemic forms of **2** and **3** in completely different ratios is due to a bimolecular step intervening in the reductions. This I discuss below. We recently reported independent evidence for precisely such a bimolecular step, using (1*R*)-[3,3-$^2H_2$]-**1** as the substrate [4]. The bimolecular reaction is either a major or the main reaction under the conditions used by *Rassat et al.* and *Huffman et al.* Our experiments suggest that the most likely mechanism is ketyl disproportionation, *i.e.* that a D-atom is transferred from one ketyl to the other. The same mechanism - involving the transfer of a H-atom - must operate with the unlabeled substrate. We suspected that it was responsible for the above stereochemical effects but had assumed that *Huffman et al.* had used (1*R*)-**1**, without carrying out the analysis given below. I belatedly realized that they must have instead used (1*RS*)-**1**[2]).

The mechanisms discussed by *Rassat et al.*, *Huffman et al.* and *Murphy et al.* are all variants of the one given by *House* [5]. These are sequences of electron and proton transfers involving *single* molecules of the ketones, ketyls, *etc.*, and therefore imply that the stereochemical outcomes from substrates (1*R*)- and (1*RS*)-**1** should be the same or similar; that there may be small differences at high concentrations (non-ideal behavior) was recently pointed out by *Wynberg et al.* [6]. Competition by bimolecular processes (see below) can change this picture.

Wynberg et al. [6] have also discussed bimolecular reactions involving enantiomers and racemates in general. Ours is a special, degenerate and, by virtue of the degeneracy, spectacular case. The stereochemical effects prove that a bimolecular step is involved but do not distinguish between three possibilities. These are reactions between the ketyls (the disproportionations), between the ketones and ketyls, and between the ketones and ketone dianions. For clarity, I discuss the phenomenon in terms of the disproportionations only, and formulate below only stoichiometric overall reactions leading from the substrates to the final products.

Disproportionations of the camphor ketyls lead to the camphor enolates and to the alcoholates of the isoborneols (**2**) and borneols (**3**). Subsequent protonations lead to the camphors (**1**) and to **2** and **3**, with **1**/(**2**+**3**) = 1.

$$(1R)\text{-}\mathbf{1} + (1R)\text{-}\mathbf{1} + 2e + 2H^+ \rightarrow x_1(1R)\text{-}\mathbf{2} + y_1(1R)\text{-}\mathbf{3} + (1R)\text{-}\mathbf{1} \quad (1)$$

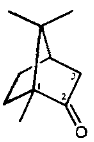
$$(1S)\text{-}\mathbf{1} + (1S)\text{-}\mathbf{1} + 2e + 2H^+ \rightarrow x_1(1S)\text{-}\mathbf{2} + y_1(1S)\text{-}\mathbf{3} + (1S)\text{-}\mathbf{1} \quad (2)$$

$$(1R)\text{-}\mathbf{1} + (1S)\text{-}\mathbf{1} + 2e + 2H^+ \rightarrow x_2(1R)\text{-}\mathbf{2} + y_2(1R)\text{-}\mathbf{3} + (1S)\text{-}\mathbf{1} \quad (3)$$

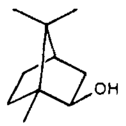
$$(1S)\text{-}\mathbf{1} + (1R)\text{-}\mathbf{1} + 2e + 2H^+ \rightarrow x_2(1S)\text{-}\mathbf{2} + y_2(1S)\text{-}\mathbf{3} + (1R)\text{-}\mathbf{1} \quad (4)$$

$$(x_1 + y_1 = x_2 + y_2 = 1)$$

When (1*R*)-**1** is the substrate, pairs of the derived ketyls can disproportionate in four different ways: H-atoms at positions *exo*- and *endo*-3 of one unit can be transferred to positions *exo*- and *endo*-2 of another. It is not possible to distinguish between the four, but one overall reaction 1, the result of prior reductions (to give the ketyls), the four disproportionations, and subsequent protonations, which leads

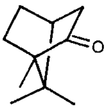


(1*R*)-**1**

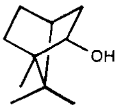


(1*R*)-**2**

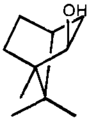
(1*R*)-**3**



(1*S*)-**1**



(1*S*)-**2**



(1*S*)-**3**

to (1*R*)-**2** and (1*R*)-**3** in the ratio x_1/y_1 (and in addition to (1*R*)-**1**) can be defined and x_1/y_1 can be readily determined. When (1*S*)-**1** is the substrate, the enantiomeric [6] overall reaction 2 can be defined (enantiomeric products, same ratio x_1/y_1).

When (1*RS*)-**1** is the substrate, four overall reactions 1 to 4 can be defined. For ideal behavior [6], in dilute solution, every step in the enantiomeric overall reactions 1 and 2 proceeds at the same rate as in the overall reactions 1 and 2 with substrates (1*R*)- and (1*S*)-**1**; reactions 1 and 2 then lead to (1*RS*)-**2** and (1*RS*)-**3** in the ratio x_1/y_1 (and in addition to (1*RS*)-**1**).

Analogous overall reactions 3 and 4 in which the ketyls derived from (1*R*)-**1** and (1*S*)-**1** disproportionate can be defined. Reactions 3 and 4 are again enantiomeric and each is again the result of prior reductions, four indistinguishable disproportionations, and subsequent protonations. Reactions 1 (or 2) and 3 (or 4) are diastereoisomeric [6] and the disproportionations should therefore in principle proceed at different rates. Reactions 3 and 4 should therefore lead to (1*RS*)-**2** and (1*RS*)-**3** in a ratio $x_2/y_2 \neq x_1y_1$ unless $x_2/y_2 = x_1/y_1$ by accident. Kinetic data or a kinetic model are needed to relate x_2/y_2 to the ratio of the (1*RS*)-**2** and (1*RS*)-**3** formed *via* all four overall reactions, x_3/y_3, which can be readily determined, and x_1/y_1. Knowledge of x_2/y_2 is not needed, however, to demonstrate that the diastereoisomeric reactions occur. Showing qualitatively that $x_1/y_1 \neq x_3/y_3$ suffices; this must result unless $x_1/y_1 = x_2/y_2$ by accident or unless the disproportionations in reactions 3 and 4 are much slower than those in reactions 1 and 2.

The disproportionations probably take place between ketyls that are tightly bound to metal cations [4]. This suggests that x_1/y_1, x_2/y_2 and x_3/y_3 are different for each metal.

This proof for a bimolecular step in the reductions is only valid if no other bimolecular reactions take place. Such a reaction is pinacol coupling; it proceeds *via* the dimerization of the ketyls and competes in the reductions with lithium and sodium. Pinacol coupling competing with a suitable reduction mechanism involving single units (see above) can in principle also account for the observed phenomena. In the reductions with potassium in which the strongest effects are observed, pinacols are neither formed from (1*R*)- nor from (1*RS*)-**1**, however, and other bimolecular processes may be excluded or neglected[4]).

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[4]) Our experiments with (1*R*)-[3,3-$^2H_2$]-**1** showed that there is a further, but minor, competing reaction with the medium [4].

I repeated reductions of (1*R*)-**1** and (1*RS*)-**1**[5]) using the procedure used by both *Rassat et al.* and *Huffman et al.* which we had also used in our experiments with (1*R*)-$[3,3\text{-}^{2}\text{H}_{2}]$-**1** but 'titrated', *i.e.* added the substrates to solutions of lithium, sodium and potassium in ammonia until the blue color disappeared, and then added ammonium chloride[6]). These experiments probably involve mainly single cycles of the overall reactions 1 and 1 to 4 (see below) in which the protonations of the enolates regenerate the substrates which can then be isolated. *Table 1* lists[6]) the compositions of the ternary mixtures (1*R*)-**1**, (1*R*)-**2**, (1*R*)-**3** and (1*RS*)-**1**, (1*RS*)-**2**, (1*RS*)-**3** obtained and the corresponding ratios (1*R*)-**2**/(1*R*)-**3** (x_1/y_1) and (1*RS*)-**2**/(1*RS*)-**3** (x_3/y_3).

In our parallel experiments with (1*R*)-$[3,3\text{-}^{2}\text{H}_{2}]$-**1** [4], the substrate rapidly lost its labels through base-catalyzed exchanges with the ammonia. This explains why reductions with excess metal under these conditions proceed until the substrates are completely transformed into the corresponding alcoholates. The enolates formed *via* the disproportionations are protonated by the ammonia (although the equilib-

Table 1. *Reductions of (1*R*)-**1** and (1*RS*)-**1** by 'titration' using the procedure used by* Rassat et al. *and* Huffman et al.; *(1*R*)-**1**, -**2**, and -**3** and (1*RS*)-**1**, -**2**, and -**3** obtained after treatment with ammonium chloride and workup*

*Runs with (1*R*)-**1***	1[a])	2	3	4[b])	5[c])
Metal	K	K	K	Na	Li
(1*R*)-**1**[d])	48	72	73	43	52
(1*R*)-**2**	31 59	17 60	16 60	22 39	11 22
(1*R*)-**3**	21 41	11 40	11 40	35 61	38 78
*Runs with (1*RS*)-**1***	6	7		8	9
Metal	K	K		Na	Li
(1*RS*)-**1**[d])	48	28		50	56
(1*RS*)-**2**	8 15	11 15		7 14	5 12
(1*RS*)-**3**	44 85	61 85		43 86	39 88

[a]) Run 21 in [4]. [b]) Run 25 in [4]. [c]) Run 24 in [4]. [d]) Weight%; ± 1-2%.

Table 2. *Reductions of (1*R*)-**1** by* Rassat et al. *and* Murphy et al. *and of (1*RS*)-**1** by* Huffman et al.; *reported ratios (1*R*)-**2**/(1*R*)-**3** and (1*RS*)-**2**/(1*RS*)-**3***

*With (1*R*)-**1***	Ref.	[1a]	[1b]	[1c]	[3]	[1a]	[1b]	[1c]	[3]	[1a]	[1b]	[1c]	[3]
Metal		K	K	K	K	Na	Na	Na	Na	Li	Li	Li	Li
(1*R*)-**2**		70	60	60	58	40	42	42	50	20	23	23	20
(1*R*)-**3**		30	40	40	42	60	58	58	60	80	77	77	80
*With (1*RS*)-**1***	Ref.	[2b]											
Metal		K	K	K	K	Na				Li	Li		
(1*RS*)-**2**		21	18	18	16	19				15	20		
(1*RS*)-**3**		79	82	82	84	81				85	80		

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[5]) M.p. 165-167°, 95% pure, $[\alpha]_{D}^{20} = 0 \pm 0.05°$ ($c = 10.8$, EtOH)[6]).

[6]) Experimental and analytical procedures correspond to those in [4].

rium lies far on the side of the enolates) and the substrates so regenerated are then either deprotonated again or recycled, *etc. Rassat et al., Huffman et al.* and *Murphy et al.* used excess metal and *Table 2* summarizes their results. *The ratios in* Tables 1 *and* 2 *are nearly identical.*

Wynberg et al. pointed out [6] that for non-ideal behavior, reactions involving single molecules of substrate should differ when the enantiomeric and racemic forms are used because these molecules can nevertheless influence each other. Examples would precisely be the reductions of (1*R*)-**1** or (1*S*)-**1** and (1*RS*)-**1** *via* the type of mechanism given by *House* [5]. The same effects would cause x_1/y_1 in reactions 1 and 2 with substrates (1*R*)-**1** and (1*S*)-**1** to be different from x_1/y_1 in reactions 1 and 2 with substrate (1*RS*)-**1**. Such effects have not been studied systematically but appear to be weak [6] and, weak or not, only come into play at high concentrations. The observed effects at quite low concentrations are so large that they *must* be caused by diastereoisomeric reactions. That they are so large is due to a degeneracy; the *same* products, (1*RS*)-**1**, (1*RS*)-**2**, and (1*RS*)-**3**, are formed from substrate (1*RS*)-**1** by reactions 1 and 2 *and* reactions 3 and 4, reactions 1 (or 2) and 3 (or 4) being diastereoisomeric and reactions 1 and 2, and 3 and 4 being enantiomeric.

A non-degenerate case is exemplified by the pinacol couplings which compete in the reductions with lithium and sodium [4][7]. Here kinetics *and* products differ when ketyls derived from the same ((1*R*)- or (1*S*)-**1**) and different ((1*R*)- and (1*S*)-**1**) enantiomers of the substrate dimerize. Only non-ideal behaviour can lead to different rates of the dimerizations of ketyls derived from the same enantiomers when (1*R*)- or (1*S*)-**1** and (1*RS*)-**1** are the substrates.

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[7] For the pinacol coupling of (1*R*)-**1** see [4]. I did not study that of (1*RS*)-**1** beyond noting that pinacols are formed in the reductions with lithium and sodium and are not in the reductions with potassium. Pinacol coupling of (1*R*)-**1** or (1*S*)-**1** can theoretically lead to three pinacols [1e] [4], two of which were found [4]. That of (1*RS*)-**1** can theoretically lead to the racemates corresponding to the three pinacols derived from (1*R*)- or (1*S*)-**1**, plus a further racemate, plus two *meso*-forms [1e]. We purposely used (1*R*)- rather than (1*RS*)-**1** in [4] in order to halve the number of theoretically possible pinacols. This should have provided the clue to the *Rassat-Huffman* puzzle much earlier. *Rassat et al.* reported that reductions with rubidium and cesium also do not lead to pinacol coupling [1b] [1c].