Nonequilibrium Radical Reductions

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Radical-mediated reduction and addition reactions are important tools for stereoselective synthesis. Anomeric radicals in particular often react stereoselectively,[1] and these intermediates have been used in the synthesis of tetrahydropyrans[1] and β-glycosides.[2,3] Stereoelectronic effects have been invoked to explain the facial preference in these radical addition reactions, with the implicit assumption that the radical is in its most stable conformation.[4] With very few exceptions,[5] radicals are configurationally unstable and epimeric radical precursors generate identical product ratios.[6] One notable exception is the 9-decalyl radical: it can be trapped by oxygen and hypochlorite (but not tin hydride) with partial retention of configuration due to slow *conformational* interconversion.[7] We now report that slow conformational interconversions can be a factor in the reduction of simple 2-tetrahydropyranyl radicals. These nonequilibrium radical reductions provide a new strategy for the control of stereochemistry.

Reductive decyanations are believed to proceed through radical intermediates, with the stability of the radical conformers dictating the stereochemical outcome.[8,9] We became aware of several anomalous systems where the stability of the radical was not a good predictor for the configuration of the product.[10,11] One possible explanation was that reduction of the radical intermediate occurred before it had a chance to reach equilibrium. Pyramidal inversion of radical centers have negligible barriers,[8,12] whereas chair−chair interconversions of tetrahydropyrans have roughly 10 kcal/mol activation energies.[13] Use of this value as a rough estimate of the inversion barrier for a 2-tetrahydropyranyl radical[14] leads to a conformational lifetime of ca. 10^{-2} s at −70 °C, which may be slow enough to allow reduction to compete with conformational equilibration.

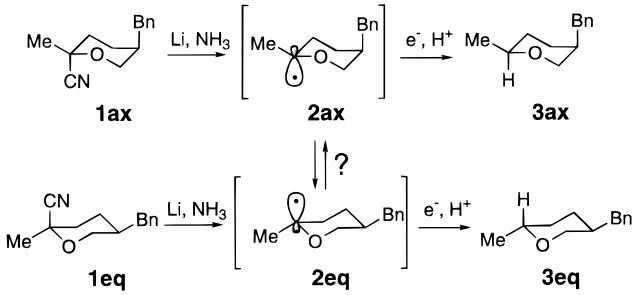

Figure 1. Possible interconversion of the radicals **2ax** and **2eq** during reductive decyanation.

Figure 1 illustrates a study designed to determine if conformational equilibration of radical intermediates influences the stereochemical outcome of reductive decyanation reactions. Both nitriles **1ax** and **1eq** adopt conformations with the nitrile axial and the methyl group equatorial. The relatively small pseudo-*A*-value of a 5-benzyl group, ca. 1.4 kcal/mol,[13,15] is overwhelmed by the conformational bias of the C2 substituents.[16] Reduction with Li/NH_3 gives rise to the radical conformers **2ax** and **2eq**, which could interconvert by radical inversion and chair−chair isomerization. Further reduction introduces an axial hydrogen atom stereoselectively,[8] producing **3ax** from **2ax** and **3eq** from **2eq**, respectively. If the interconversion of **2ax** and **2eq** is fast with respect to the reduction, both **1ax** and **1eq** will give identical ratios of **3ax** and **3eq**, but if the interconversion is slow, **1ax** and **1eq** will lead to different product ratios.

The results of the reductive decyanations of **1ax** and **1eq** are shown in Table 1.[17] The most important observation is that under each of the experimental conditions, **1ax** and **1eq** lead to different product ratios (e.g., entries 1 and 2, Table 1). Thus reduction of the radicals **2ax** and **2eq** is faster than their interconversion. Reduction by either Li/NH_3 or lithium di-*tert*-butylbiphenylide (LiDBB) in THF followed by protonation gave the same ratio of products. Some radical interconversion is observed in each reaction, but it can be minimized by lowering the temperature. Overall, the reduction proceeds primarily with retention of configuration. This result stands in stark contrast to the reductive decyanation of cyanohydrin acetonides, where both epimers give the cis diastereomer of the acetonide with excellent stereoselectivity.[18]

Reductive decyanations are admittedly highly specialized examples of radical reductions. Are nonequilibrium intermediates important in more common radical reactions? The reductive decarboxylation of *N*-hydroxypyridine-2-thione esters **4ax** and **4eq** were examined to answer this question, and the results are shown in Table 2.[17] Compounds **4ax** and **4eq** prefer the axial ester

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(2) For a few representative examples, see: (a) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716−7. (b) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1461−3. (c) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 945−54.

(3) For α- to β-glycoside strategy based on the generation and *inversion* of anomeric radicals, see: (a) Brunckova, J.; Crich, D.; Yao, Q. W. *Tetrahedron Lett.* **1994**, *35*, 6619−22. (b) Yamazaki, N.; Eichenberger, E.; Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623−6.

(4) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969−980.

(5) (a) Ando, T.; Yamanaka, H.; Namigata, F.; Funasaka, W. *J. Org. Chem.* **1970**, *35*, 33−8. (b) Gawronska, K.; Gawronska, J.; Walborsky, H. M. *J. Org. Chem.* **1991**, *56*, 2193−7.

(6) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996. (b) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley and Sons: New York, 1995; pp 19−30. (c) Kaplan, L. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vol. 2, pp 361−434.

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(8) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−84.

(9) The reductive lithiations of phenylthioethers are mechanistically related: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−61.

(10) The reductive decyanations of 2-cyanooxepanes lead to diverse stereochemical outcomes depending upon substitution: (a) Rychnovsky, S. D.; Dahanukar, V. H. *Tetrahedron Lett.* **1996**, *37*, 339−42. (b) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−9.

(11) Certain reductive lithiations of 2-phenylthiotetrahydropyrans appear to be too selective when the energy of each radical conformer is considered: Powers, J. P. Ph.D. Thesis, University of Minnesota, 1995.

(12) Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* **1978**, *100*, 6750−2.

(13) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 740−745.

(14) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2025−9.

(15) The pseudo-*A*-value for a 3-methyl substituent on a THP ring is 1.43 kcal/mol (ref 13).

(16) Molecular modeling (MM2) predicts that the axial nitrile conformations of **1ax** and **1eq** will be preferred by >1.5 kcal/mol. The chemical shifts and ring coupling constants for **1ax** and **1eq** are essentially invariant between −70 and 25 °C, suggesting that only a single ring conformation is populated under these conditions.

(17) The relative configurations of starting materials and products were assigned by coupling constant and NOE anaylsis as described in the Supporting Information.

(18) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550−1. Modeling (MM2 and AM1) suggests that only one of the two cyanohydrin acetonide diastereomers exists in a chair conformation. Reduction of both diastereomers lead to the cis product.

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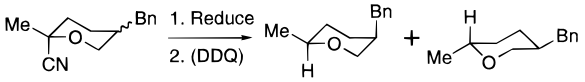
Table 1. Diastereoselectivity in Reductive Decyanation of **1ax** or **1eq**

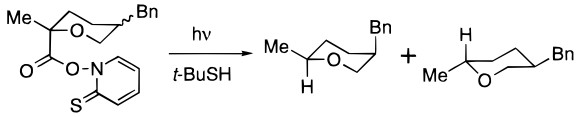


1ax or **1eq** **3ax** **3eq**

entry	substrate	conditions[a]	ratio (**3ax**:**3eq**)[b]
1	**1ax**	Li/NH_3 (−78 °C)	66:34
2	**1eq**	Li/NH_3 (−78 °C)	4:96
3	**1ax**	LiDBB (−78 °C)	66:34
4	**1eq**	LiDBB (−78 °C)	5:95
5	**1ax**	Li/NH_3 (−33 °C)	39:61
6	**1eq**	Li/NH_3 (−33 °C)	5:95
7	**1ax**	LiDBB (−95 °C)	71:29

[a] Reactions were carried out in THF and gave products in ca. 90% yield. Small amounts of dihydrobenzene from overreduction (ca. 5%) were oxidized by DDQ before analysis. [b] Product ratios by GC.

Table 2. Radical Decarboxylation of **4ax** or **4eq**



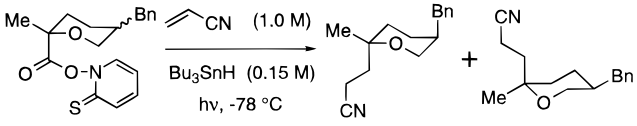
4ax or **4eq** **3ax** **3eq**

entry	substrate	conditions[a]	ratio (**3ax**:**3eq**)[b]
1	**4ax**	−78 °C, (0.1 M)	18:82
2	**4eq**	−78 °C, (0.1 M)	14:86
3	**4ax**	−78 °C, (0.5 M)	54:46
4	**4eq**	−78 °C, (0.5 M)	5:95
5	**4ax**	−78 °C, (1.0 M)	63:37
6	**4eq**	−78 °C, (1.0 M)	4:96
7	**4ax** or **4eq**	−78 °C, (0.1 M)	12:88
8	**4ax**	−20 °C, (1.0 M)	22:78
9	**4eq**	−20 °C, (1.0 M)	11:89
10	**4ax** or **4eq**	25 °C, (0.1 M)	15:85

[a] Reactions were carried out in toluene to give products in ca. 70% yield. The *t*-BuSH concentration is given in parentheses. [b] Product ratios by GC.

conformation[19] and should generate radical intermediates **2ax** and **2eq**, respectively. The reductive decarboxylations were carried out by photolysis in the presence of *t*-BuSH as an H-atom donor.[20] With high concentrations of *t*-BuSH and low temperatures, **4ax** and **4eq** lead to different product ratios of **3ax** and **3eq** (entries 5 and 6, Table 2). Differences are still observed at −20 °C, but the effect is small (entries 8 and 9, Table 2).[17] With lower concentrations of *t*-BuSH, radical equilibration is nearly complete even at −78 °C. The predicted enthalpies of 2,5-dimethyl-2-tetrahydropyranyl conformers, models for **2ax** and **2eq**, favor the equatorial C5 methyl isomer by ca. 1 kcal/mol.[21] The calculated energy difference is roughly consistent with the observed equilibrium product ratios, keeping in mind that the reduction of **2ax** to **3ax** may not be completely stereoselective. The product ratios in the reductive decarboxylation reaction at high thiol concentrations (entries 5 and 6, Table 2) are similar to those observed for the reductive decyanation reactions at the same temperature (entries 1 and 2, Table 1). Differences in the intrinsic stereoselectivity of the reductions would be expected to produce slightly different product ratios even if the rates of reduction were identical. These experiments demonstrate that Barton reductive decarboxylations can proceed through nonequilibrium radical intermediates under experimentally accessible conditions.

Scheme 1



4ax or **4eq**

Starting Material	**5ax**		**5eq**
4ax	62	:	38
4eq	4	:	96

Remarkably, nonequilibrium trapping of radicals was also observed with reactive olefins. Thus, decarboxylation of **4ax** or **4eq** in the presence of 1.0 M acrylonitrile leads to very different product ratios at −78 °C (Scheme 1). The **4ax** precursor gave a 62:38 product ratio favoring the **5ax** isomer,[22] while the **4eq** precursor gave a 4:96 product ratio favoring the **5eq** isomer.[17] These ratios are essentially the same as those observed in the *t*-BuSH trapping reaction.

The preceding studies show that slow conformational interconversion of radical intermediates can be an important factor in the stereoselectivity of radical reactions. The effect will be important not just in six-membered rings but also in medium ring compounds that show comparable conformational barriers.[23,24] Manipulating the conformation of a radical precursor should allow one to influence the stereoselectivity of radical reactions. Nonequilibrium radical reactions present new opportunities for stereoselective synthesis.

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Supporting Information Available: Preparation, characterization and configurational assignment of compounds **1ax**, **1eq**, **3ax**, **3eq**, **4ax**, **4eq**, **5ax**, and **5eq** (11 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980857K

(19) MM2 modeling of the methyl esters corresponding to **4ax** and **4eq** shows a >1.0 kcal/mol preference for the axial ester conformation.

(20) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901−24.

(21) For 2,5-dimethyl-2-tetrahydropyranyl radicals, the axial C5 methyl conformer is less stable than the equatorial conformer by 0.73 kcal/mol (MP2/6-31G(d)//MP2/6-31G(d)) or 1.41 kcal/mol (B3LYP/6-31G(d)//B3LYP/6-31G(d)).

(22) The **5ax** isomer adopts the conformation with the benzyl equatorial, but is drawn with the benzyl axial to emphasize its origins.

(23) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 762−769.

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