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Diverging Chemoselective Reactions of Separable Amide Rotational Isomers

Xiben Li and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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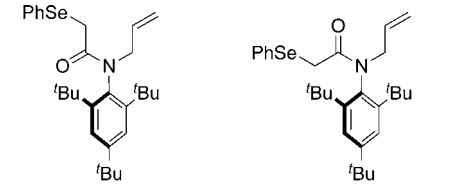
ABSTRACT



Diverging chemoselective reactions of a pair of amide rotamers have been observed by separating the rotamers and then reacting them individually. Reduction of (*Z*)-*N*-allyl-2-(phenylselanyl)-*N*-(2,4,6-tri-*tert*-butylphenyl)acetamide with tributyltin hydride at room temperature provides only the product of 5-*exo* cyclization, 4-methyl-1-(2,4,6-tri-*tert*-butylphenyl)pyrrolidin-2-one. In contrast, reduction of the corresponding (*E*) amide rotational isomer under identical conditions provides only the reduced product, (*E*)-*N*-allyl-*N*-(2,4,6-tri-*tert*-butylphenyl)acetamide. Such diverging reactions of rotamers may be common in transformations involving reactive intermediates (carbenes, radicals, organometallic intermediates) that have low barriers to onward reactions relative to amide rotation.

Amides with two different substituents on nitrogen generally exist as pairs of *E*/*Z* rotamers,[1,2] and selective reactions of these rotamers are therefore possible.[3] For example, directed metalations of amides typically occur on the substituent *cis* to the carbonyl oxygen,[4] and rotamer features of proline-containing amides in peptides and proteins can dictate their shape and therefore reactions in biological settings.[5] There can also be rotamer preferences when amide-containing small molecules bind to larger molecules.[6]

In many amide transformations, a reactive rotamer undergoes a binding or reaction event, while an unreactive rotamer does not.[7] Instead, the unreactive rotamer converts to the reactive one, then the binding or reaction event shifts the equilibrium. In other words, both rotamers give the same product. Figure 1, scenario "a", illustrates one such possibility: the selective reaction of R^B in one of the rotamers. This scenario is very common in intramolecular reactions such as metatheses[8] or Diels−Alder reactions[9] between an amide C−N substituent (here R^B) and the acyl substituent R to make a ring.

Reactions of amide C(O)−N rotamers with diverging selectivity have also been postulated.[10] That is, under

(1) (a) Stewart, W. E.; Slidell, T. H. Nuclear Magnetic Resonance Studies of Amides. *Chem. Rev.* **1970**, *70*, 517–551. (b) Oki, M. Recent Advances in Atropisomerism. In *Top. Stereochem.*; Allinger, N. L., Eliel, E., Wilen, S. H., Eds.; 1983; Vol. 14, pp 1−81. (c) Oki, M. *The Chemistry of Rotational Isomers*; Springer-Verlag: New York, 1993.

(2) The descriptors *E* and *Z* are used here to name amide C(O)−N rotamers by analogy to the usual *E*/*Z* nomenclature for alkenes.

(3) Wolf, C. *Dynamic Stereochemistry of Organic Compounds*; RSC Publishing: Cambridge, UK, 2008.

(4) (a) Seebach, D.; Wykypiel, W.; Lubosch, W.; Kalinowski, H.-O. *Helv. Chim. Acta* **1978**, *61*, 3100–3102. (b) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512–526. (c) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145–8153.

(5) Etzkorn, F. A.; Travins, J. M.; Hart, S. A. *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Jai Press: Stamford, CT, 1999; Vol. 2, pp 125−163.

(6) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398–6401.

(7) Both scenarios in Figure 1 and other variants are described in detail by Curtin−Hammett Winstein−Holness kinetics: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–135.

(8) For example: (a) Rodriguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185–1192. (b) Colombo, L.; Di Giacomo, M.; Vinci, V.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501–4513.

(9) Roush, W. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513.

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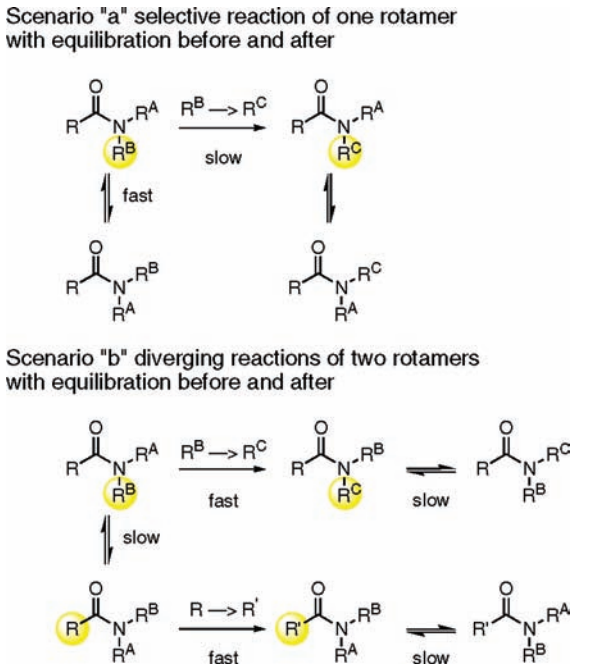


Figure 1. Two scenarios for reactions of amide rotamers.

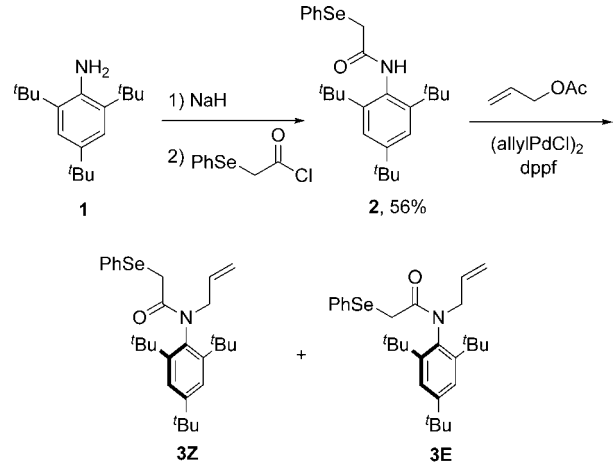
identical reaction conditions, the *E*-rotamer gives one product, while the *Z*-rotamer gives another. Assorted selectivities are possible. Figure 1, scenario "b", illustrates the case where one of the rotamers undergoes a reaction on the amide substituent (here $R^B \rightarrow R^C$), while the other reacts on the acyl group ($R \rightarrow R'$). These reactions typically occur through reactive intermediates (not shown) whose barriers for onward reaction must be lower than their barriers for amide rotation.

The case for rotational selectivity is generally built on circumstantial evidence. For example, it is argued that identical ratios of rotamers in a precursor and a pair of different products is not likely coincidence but instead transpires because each rotamer gives one of the products and not the other.[10] Building this kind of circumstantial case is usually necessary because amide bond rotation of both the precursors and the products takes place on the time scale of the experiments and analysis.

Here we catch two amide rotational isomers in the act of diverging chemoselective reactions. This demonstration builds on the long-known[11] but little recognized[4a,b,6] property that some amide rotamers are stable enough to be separated, on a recent stereoselective synthesis of such amides by Kitagawa[12] and on the speed and efficiency of tin hydride mediated cyclizations of α-amidoyl radicals with *N*-allyl substituents.[10c−e,13]

Amide rotational isomers **3*Z*** and **3*E*** were synthesized in two steps as shown in Scheme 1. Acylation of the sodium salt of 2,4,6-tri-*tert*-butylaniline **1** with 2-phenylselanyl acetyl chloride provided 2-(phenylselanyl)-*N*-(2,4,6-tri-*tert*-butylphenyl)acetamide **2** in 56% yield. Palladium-catalyzed N-allylation according to Kitagawa and co-workers[12] occurred under kinetic control to provide a 76/24 mixture of **3*Z***/**3*E*** in 69% yield. The stereostructures were assigned by characteristic features in the ^{1}H NMR spectra.[1,12]

Scheme 1. Stereoselective Syntheses of Amide Rotamers **3*Z***/**3*E***



conditions	yield	3Z/3E
kinetic (Pd allylation)	69%	76/24
thermodynamic (heat)	100%	9/91

Isomers **3*Z*** and **3*E*** could not be separated over standard silica gel; however, prolonged heating of the 76/24 mixture in refluxing toluene established equilibrium at a ratio of 9/91. In a more careful experiment, the ratio of isomers was followed as a function of time, and the data were processed in the usual way to provide the rotation barrier. At 70 °C, k from *Z* to *E* is 6.6×10^{-5} s^{-1}, and $\Delta G^{\ddagger} = 26.8$ kcal/mol. At room temperature, the half-life for isomerization from *Z* to *E* is about four months.

Figure 2 shows the mechanistic framework for the ensuing chemoselective radical reductions of **3*Z*** and **3*E***. Abstraction of the phenylselanyl group from the precursors **3** by tin radical provides radicals **4*Z*** and **4*E*** which, like their precursors, are rotational isomers. Radical **4*Z*** is poised to undergo 5-*exo* cyclization followed by hydrogen atom transfer to give lactam **5**.

In contrast, **4*E*** is geometrically prohibited from cyclizing and can only give reduced acetamide **6*E***.[10c−e] If all these

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(11) (a) Mannschreck, A. *Tetrahedron Lett.* **1965**, *6*, 1341–1347. (b) Staab, H. A.; Lauer, D. *Tetrahedron Lett.* **1966**, *7*, 4593–4598. (c) Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297–2303. (d) Staab, H. A.; Lauer, D. *Chem. Ber.* **1968**, *101*, 864–878.

(12) (a) Ototake, N.; Taguchi, T.; Kitagawa, O. *Tetrahedron Lett.* **2008**, *49*, 5458–5460. (b) Otatake, N.; Nakamura, M.; Dobashi, Y.; Fukaya, H.; Kitagawa, O. *Chem.—Eur. J.* **2009**, *15*, 5090–5095.

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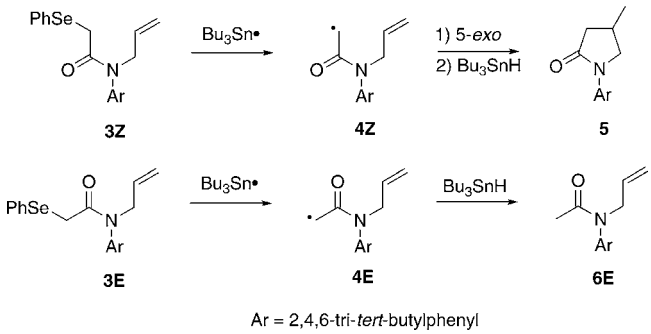

Figure 2. Mechanistic framework for diverging reactors of radicals **4*Z***/**4*E***.

reactions are faster than amide bond rotations, then the ratios of the products **5** and **6*Z*** should match the ratio of precursors **3*Z*** and **3*E***. Loss of chemoselectivity could occur by interconversion of either the precursors **3** or the intermediate radicals **4**. Assuming that the 5-*exo* cyclization is fast relative to reduction, the mechanism does not allow for the formation of the *Z*-rotamer of the reduced product **6*Z*** (not shown). However, in principle, this could be formed after the fact by amide bond rotation. In practice, none of these rotations was observed.

Data for the reductions of mixtures of **3*Z***/**3*E*** are summarized in Table 1. Reduction of both *Z*-rich and *E*-rich mixtures of **3** with tributyltin hydride at room temperature under standard conditions (0.05 M, Et_3B, air, toluene) provided products **5** and **6*E*** in ratios that matched the precursors within experimental error (entries 1 and 2). In an attempt to erode this selectivity by promoting crossover of the radicals **4**, we also conducted a pair of related experiments at 90 °C in toluene (AIBN initiation). But again, the product ratios reflected those of the precursors in each experiment (entries 3 and 4).

Table 1. Product Yields and Ratios from Tin Hydride Reductions of Isomers of **3**

entry	ratio **3*Z*/3*E***	temp	ratio **5/6*E***[a]
1	76/24	25 °C	75/25
2	9/91	25 °C	9/91
3	76/24	90 °C	75/25
4	9/91	90 °C	9/91
5	**3*Z*** only	25 °C	**5** only
6	**3*E*** only	25 °C	**6E** only

[a] Products ratios were determined by ^{1}H NMR analysis of the crude products; isolated yields of products in entries 1, 5, and 6 were nearly quantitative.

These results are already an advance over prior experiments because we could measure product ratio from two different starting material compositions (kinetic and thermodynamic) rather than one. This rules out coincidental matching of precursor and product ratios. Finally, in surveying various separation options, we discovered that **3*Z*** and **3*E*** could be conveniently separated on a Whelk-O1 column.[14] Though this chiral column is usually used for enantiomer separation, it served well here for preparative separation of the diastereomers. Indeed, room temperature reduction of isomerically pure **3*Z*** provided only lactam **5** with no directly reduced product (entry 5), whereas an identical reduction of **3*E*** provided only directly reduced product **6*E*** without detectable amounts of constitutional isomer **5** (entry 6).

In summary, we have directly observed diverging chemoselective reactions of a pair of amide rotamers by separating them and then reacting them individually under identical conditions. Different products were formed with no detectable crossover. Such reactions are probably rather rare in direct thermal reactions of amides because the reaction barriers are higher than those of amide rotation. However, they are probably rather common in transformations involving reactive intermediates (carbenes, radicals, organometallic intermediates) that have low barriers to onward reactions relative to amide rotation.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We tried this column because we had previously observed separations of amide *E*/*Z* rotamers during resolutions of axially chiral anilides. See: Guthrie, D.; Geib, S. V.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 15492–15500.