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# Automatic Chiral Selection in a Thermodynamically Predisposed Metathesis Reaction

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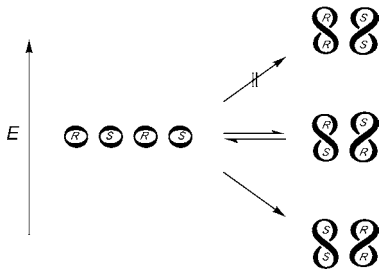
## ABSTRACT




**Tryptophan-derived azoninoindole imines select partners of the same chirality for dimerization to helical macrocycles.**

Chemical reactions that occur under thermodynamic control can show unexpected selectivity when a pronounced free energy minimum is achieved which excludes competing, kinetically accessible processes. This has recently been demonstrated where fairly rigid components participate in macrolactonization reactions, and the phenomenon, called "predisposition", has been likened to a covalent version of the molecular proofreading mechanisms of noncovalent assemblies.[1]

Our interest in hydrogen-bonding azamacrocycles led us to consider whether an intramolecular relationship between helical and tetrahedral asymmetry could predispose a macrocyclization reaction toward a single product. The process in question is the imine metathesis reaction of diazoninoindole **2**, which is known to give dimer **4**, presumably via intermediate **3**, in about 35% yield.[2] The mass balance of the reaction is accounted for by a highly insoluble, apparently polymeric material which we suggest stems from alternative products of the thermal azide decomposition reaction from which **2** is derived (Scheme 1).[3,4] When a single enantiomer of **1** (*S* at the amino ester center) is submitted to the reaction conditions, a single macrocyclic product, *SS*-**4**, results. If racemic **1** were, however, to undergo thermolysis, three products, *RR*-, *SS*-, and *meso*-**4**, are possible, assuming dimerization between *R*-**2** and *S*-**2** is not kinetically disallowed. This assumption is supported by semiempirical (PM3, AM1) and molecular mechanics (MM2*, MM3*, AMBER*,

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(1) For an excellent review of dynamic covalent chemistry, see: Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898 and references therein.

(2) (a) Mascal, M.; Moody, C. J.; Morrell, A. I.; Slawin, A. M. Z.; Williams, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 813. (b) Mascal, M.; Wood, I. G.; Begley, M. J.; Batsanov, A. S.; Walsgrove, T.; Slawin, A. M. Z.; Williams, D. J.; Drake, A. F.; Siligardi, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2427.

(3) Imine **2** is not directly observed but dimerizes spontaneously under the reaction conditions. We invoke the existence of **2** based on an analogous azide decomposition reaction where the product imine is substituted at the azomethine carbon and is stable and isolable: Mascal, M.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 823.

(4) The same reaction is observed by photolysis of azide **1** at 254 nm at room temperature in dry acetonitrile. Alternative "nitrene" migration products have been directly observed in this reaction; see ref 3.

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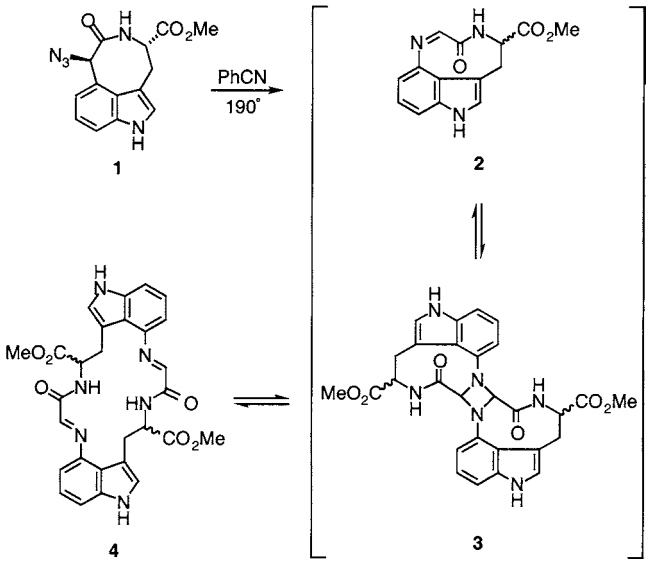
**Scheme 1**




MMFF*, OPLS*) calculations, which show that the intermediates *SS*-**3** and *RS*-**3** are within about 2 kcal mol$^{-1}$ of each other. In addition to this, no argument can be made for the ester group of either enantiomer of **2** obstructing the formation of *RS*-**3** when minimized structures are docked.[5]

If the reaction were under kinetic control, the statistical encounters between *R*-**2** and *S*-**2** should lead in any case to a 50% reduction in yield of *RR/SS*-**4**, whether or not *RS*-**4** is actually isolated. On the other hand, under thermodynamic control, a distribution of *RR/SS*-**4** and *RS*-**4**, as well as, in principle, higher oligomers, should arise.[6] If, however, the reaction is reversible but under the influence of a thermodynamic predisposition toward the matched *RR/SS* products, *the same result should be observed as in the case where a single enantiomer of* ***2*** *is present*, except that the material will be racemic. This in fact is demonstrated by the outcome of the reaction using *rac*-**1**, the yield of which (33%) is within experimental error of that using homochiral **1**, the isolated product being chromatographically and spectroscopically ($^1$H NMR, $^{13}$C NMR, IR, MS) indistinguishable from nonracemic **4**.[7,8]

Under these circumstances, imine **2** practices "molecular natural selection," where species able to produce robust conjugates in effect single each other out from a mixture. *SS*-**4** is known to fold into a left-handed, double-helical secondary structure by virtue of two strong, transannular NH···N hydrogen bonds (Figure 1), both in solution and the solid state.[2b] In principle, six distinct products **4** are possible: *SSM*, *RSM*, *RRM*,[9] and their enantiomers. A rationale for why *RR*- and *SS*-**4** should be favored over the meso dimer is provided by modeling studies, which show that the asymmetric *RS* helixes are less stable than the *C*2 symmetric *SSM* (or *RRP*) homodimers by 12 kcal mol$^{-1}$.[10] The destabilization is principally the result of moving one ester group from an anti relationship to the indole ring to gauche. The other alternative, *RRM* (or *SSP*), has two such interactions and is about 22 kcal mol$^{-1}$ higher in energy than the observed product. Thus, the synergy between tetrahedral and helical chirality funnels the reaction toward the matched pair, whereas the mismatched product reverses back to *R*-**2** and *S*-**2**, which eventually find their way into the more stable, homodimeric macrocycles.

**Figure 1.** Stereoview (cross-eye) of the crystal structure of *SS*-**4**, with hydrogens omitted for clarity.

We are unaware of other examples of macrocyclizations which take advantage of topological asymmetry to predispose the reaction to a single product. This phenomenon, which is supported by the calculated free energy differences between the strereoisomers, adds a new dimension for the manipulation of equilibria in the budding fields of thermodynamically controlled macromolecule synthesis and dynamic combinatorial chemistry.[1]

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(5) AM1 and PM3 minimizations were performed using the Gaussian98 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.11; Gaussian, Inc.: Pittsburgh, PA (www.Gaussian.com). The molecular mechanics force fields were used as implemented in the MacroModel program within Maestro v. 3.0, Schrödinger, Inc.: New York (www.schrodinger.com).

(6) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901.

(7) Calculated vibrational frequencies and GIAO $^{13}$C NMR shifts (HF/6-31G**//HF/6-31G**) unambiguously distinguish *C*2 symmetric *SS*-**4** from the hypothetical, asymmetric *RS*-**4** product.

(8) The modest yield of the thermolysis reaction leaves room for speculation that *RS*-**4** could in fact be formed from *rac*-**1** and subsequently destroyed under the reaction conditions. But as noted, since this process would statistically consume 50% of the starting material, the only way to achieve the same conversion as for homochiral **1** would be to double the yield of the dimer derived from *rac*-**1**. The implausibility of this scenario, alongside failed attempts to racemize *SS*-**4** and the substantial synthetic challenge of preparing *RS*-**4** by an independent route, has led us to resist the proposition to thermolyze *RS*-**4**, which should evolve into *RR/SS*-**4**.

(9) *M* and *P* are designations of left- and right-handed helical chirality, respectively.

(10) HF/6-31G**//HF/6-31G** free energy difference calculated at the reaction temperature (463 K) using the Gaussian98 program (ref 5).