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Mechanical Reconfiguration of Stereoisomers

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Atropisomers are chiral molecules whose asymmetric structures are derived from hindered rotations about sterically congested bonds.[1] They have found utility in a broad range of applications, including asymmetric synthesis and catalysis, supramolecular and polymer chemistry, and chemical sensors.[2] Certain atropisomers, such as 1,1′-bi-2-naphthol (binol),[2a] 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap),[2d] and their derivatives, have isomerization barriers that typically exceed 30 kcal mol^{-1} and therefore do not readily undergo thermal equilibration.[1−3] Although these high energy barriers facilitate chiral resolution, stereoselective syntheses are currently required to access enantiopure forms of these molecules in the most efficient manner.[4] In view of the recent advances in mechanochemistry,[5] in which known or conceived reaction pathways may be activated or even biased to proceed in atypical directions,[6] we demonstrate here that thermally restricted isomerization barriers can be surmounted by force, thus establishing a new method for reconfiguring stereoisomers.

As shown in Scheme 1, we reasoned that planar intermediates[7] should be accessible by applying a tensile force to binol derivatives outfitted with polymer chains of sufficient molecular weight, ultimately converting one enantiomer to the other. To test this hypothesis, poly(methyl acrylate) (PMA) was grown from the bifunctional initiator (*S*)-1,1′-binaphthyl-2,2′-bis-(2-bromoisobutyrate) ($\boldsymbol{S}_\mathbf{I}$)[8] using Cu-mediated single-electron-transfer living radical polymerization (SET LRP)[9] ([methyl acrylate]$_0$/[$\boldsymbol{S}_\mathbf{I}$]$_0$ = 1160) in dimethyl sulfoxide (DMSO) followed by precipitation from CH_3OH. The resulting polymer ($\boldsymbol{S}_\mathbf{100K}$) exhibited a number-average molecular weight (M_N) of 98.7 kDa and a polydispersity index (PDI) of 1.03, as determined by gel-permeation chromatography (GPC).[10] After the optical profile of this material was measured using circular dichroism (CD) and UV−vis spectroscopies, $\boldsymbol{S}_\mathbf{100K}$ was dissolved in CH_3CN (0.75 mg/mL) and subjected to sonication[11] in a Suslick cell[12] placed in an ice bath.[13] As shown in Figure 1, CD analysis of aliquots[14] removed periodically from this solution revealed a smooth decrease in signal intensity over time. Comparison of the intensity of the signal measured at 230 nm after 24 h of sonication with that of the pre-sonicated $\boldsymbol{S}_\mathbf{100K}$ revealed that >95% of the material had undergone racemization.[15] Although the polydispersity of the post-sonicated material was slightly higher (PDI = 1.13) than that of the pre-sonicated $\boldsymbol{S}_\mathbf{100K}$, the M_N (97.2 kDa) was comparable. Likewise, the UV−vis and ^{1}H NMR spectra of the pre- and post-sonicated materials revealed no significant differences (see Figures S1 and S2 in the Supporting Information). Similar results were obtained when the aforementioned experiments were performed with $\boldsymbol{R}_\mathbf{100K}$, a polymer prepared from methyl acrylate and (*R*)-1,1′-binaphthyl-2,2′-bis-(2-bromoisobutyrate) ($\boldsymbol{R}_\mathbf{I}$) (see Figure 1 and Table 1).

Scheme 1. Mechanically Facilitated Reconfiguration Processes

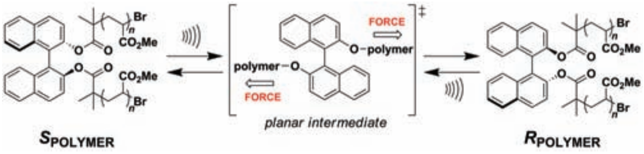

Table 1. Selected Molecular Weight and Polydispersity Data[a]

	pre-sonication		post-sonication	
polymer[b]	M_N (10^3 Da)[c]	PDI[c]	M_N (10^3 Da)[c]	PDI[c]
$\boldsymbol{S}_\mathbf{100K}$	98.7	1.03	97.2	1.13
$\boldsymbol{R}_\mathbf{100K}$	98.4	1.07	95.2	1.11
$\boldsymbol{S}_\mathbf{50K}$	48.8	1.16	48.4	1.16
$\boldsymbol{S}_\mathbf{25K}$	26.5	1.09	26.4	1.13
$\boldsymbol{S}_\mathbf{10K}$	9.66	1.03	9.58	1.21

[a] All of the materials were dissolved in CH_3CN (0.75 mg/mL) and subjected to sonication for 24 h. [b] The polymers were prepared in 88−99% isolated yield from methyl acrylate and $\boldsymbol{S}_\mathbf{I}$ using SET LRP. Nomenclature: the letter indicates the configuration of the binol unit embedded in the polymer chain and the subscripted number denotes the polymer's approximate molecular weight in kDa. [c] M_N refers to the number-average molecular weight of the polymer. The polydispersity index (PDI) was calculated using the equation PDI = M_W/M_N, where M_W is the weight-average molecular weight. M_N and M_W were determined using GPC.[10] The standard deviations for these measurements were calculated to be <1% on the basis of multiple experiments.

To support the observation of a mechanically facilitated isomerization, a series of control experiments was performed. Refluxing a solution of $\boldsymbol{S}_\mathbf{100K}$ in Ph_2O (bp = 257 °C; [$\boldsymbol{S}_\mathbf{100K}$]$_0$ = 10 mg/mL) for 72 h showed no decrease in its CD signal intensity (see Figure S3). This result is consistent with the high isomerization barriers

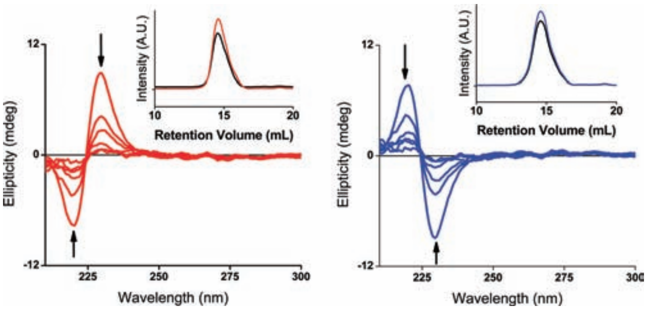

Figure 1. CD spectra of CH_3CN solutions of (red) $\boldsymbol{S}_\mathbf{100K}$ and (blue) $\boldsymbol{R}_\mathbf{100K}$ (0.1 mg/mL) as functions of time under the sonication conditions described in the text. Aliquots were removed 0, 2, 4, 8, 12, and 24 h after sonication commenced and then analyzed; the arrows indicate the direction of the spectra as they changed over time. The insets show gel-permeation chromatograms of $\boldsymbol{S}_\mathbf{100K}$ and $\boldsymbol{R}_\mathbf{100K}$ before (red and blue, respectively) and after sonication (black).

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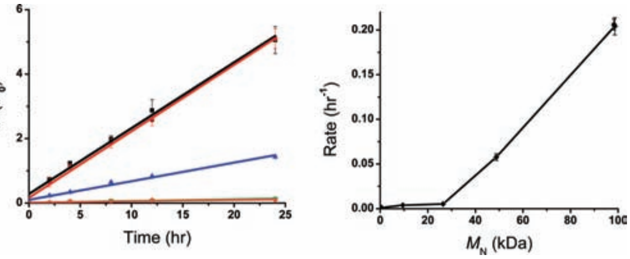

Figure 2. (left) First-order rate plots (logarithm of CD signal intensity loss as a function of time) for $\boldsymbol{S}_{\mathbf{100K}}$ (red), $\boldsymbol{R}_{\mathbf{100K}}$ (black), $\boldsymbol{S}_{\mathbf{50K}}$ (blue), $\boldsymbol{S}_{\mathbf{25K}}$ (green) and $\boldsymbol{S}_{\mathbf{10K}}$ (orange). Figure S9 shows the respective CD spectra. I_0 refers to the initial CD signal intensity (measured at 230 nm) of the material analyzed; I refers to the signal intensity of that same material taken at the time indicated in the x axis. (right) Plot of the rate coefficients of CD signal attenuation as a function of M_N.

observed for other binapthyl derivatives.[1−3] Additional support was obtained by sonicating for 24 h a CH_3CN solution of an appropriately end-functionalized PMA (M_N = 90.5 kDa, PDI = 1.02) prepared from methyl acrylate and (*S*)-1,1′-binapthyl-2-pivalate-2′-(2-bromoisobutyrate). The post-sonicated material showed no significant change in its CD signal or molecular weight (M_N = 89.9 kDa, PDI = 1.10) relative to the starting material (see Figure S4). Similar results were obtained when CH_3CN solutions of $\boldsymbol{S}_{\mathbf{I}}$ or a relevant small-molecule analogue devoid of bromine, (*S*)-1,1′-binaphthyl-2,2′-bis-(pivalate),[16] were sonicated for 24 h in the presence of 1 molar equiv of a 90.2 kDa (PDI = 1.03) PMA homopolymer (see Figures S5 and S6). These results indicate that the binol unit must be embedded within a polymer chain in order to undergo ultrasound-induced isomerization.

Previous reports have demonstrated that mechanically induced transformations are highly dependent on the length of the polymer chains connected to a putative mechanophore.[5,6d,h] Thus, to gain additional support for a mechanochemical reaction, a series of PMA polymers of various molecular weights were prepared from $\boldsymbol{S}_{\mathbf{I}}$ (see Table 1). After characterization of these materials by GPC and CD spectroscopy, they were individually subjected to sonication in CH_3CN and monitored over time as described above for $\boldsymbol{S}_{\mathbf{100K}}$. As shown in Figure 2, the CD signal intensities of these materials decayed with first-order kinetics, which permitted determination of the relative rates of racemization as a function of polymer molecular weight. The sharp increase in the observed rate between 25 and 50 kDa indicated that there is limited mechanical activation for polymers below a molecular weight threshold.[5] GPC analyses of the post-sonicated materials revealed no significant change in molecular weight with respect to the starting polymers, indicating that chain scission did not occur to a significant extent during sonication (see Table 1).

In conclusion, we have shown that ultrasound may be used to interconvert stereoisomers that have high thermal isomerization barriers. As shown by a series of control experiments and extensive characterization, the aforementioned isomerization reactions are consistent with mechanically facilitated processes that appear to proceed with minimal chain scission.[11] These results establish a novel concept in chemoselective activation (isomerization vs chain scission) and may create new strategies for manipulating asymmetric structures, including techniques for toggling the configurations of enantiomers other than those described above. The methodology reported herein is also expected to find applications in the resolution of atropisomers and other asymmetric molecules and may augment existing mechanochemical approaches used to map stresses in polymeric materials.[6a]

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

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(14) The removed aliquots were evaporated to dryness under high vacuum and then washed with excess methanol prior to analysis.
(15) Similarly, a polymer prepared from *rac*-1,1′-binaphthyl-2,2′-bis-(2-bromoisobutyrate) and methyl acrylate (M_N = 89.2 kDa, PDI = 1.26) exhibited no appreciable CD signal (see Figure S8).
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