Mechanochemistry

DOI: 10.1002/anie.201001360

Reconfiguration of Stereoisomers under Sonomechanical Activation**

Giancarlo Cravotto and Pedro Cintas**

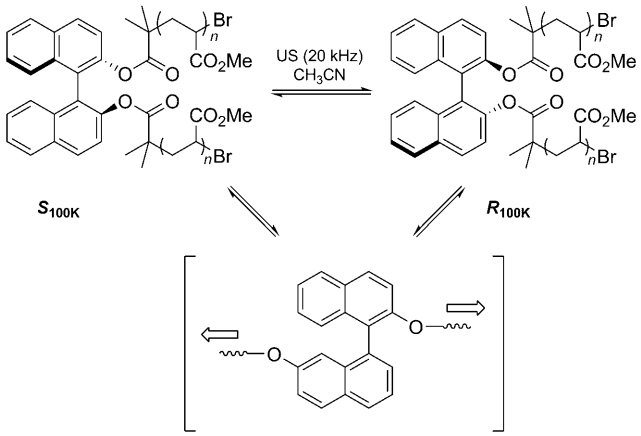
atropisomers · configurational inversion · mechanochemistry · sonochemistry

In Memory of José Manuel Concellón

Mechanochemistry has become an emerging and alternative tool in transformational chemistry, in which bond breaking and the subsequent chemically driven reactions are primarily induced by external forces. Several mechanisms can be identified ranging from purely mechanical (such as grinding, shearing, cracking, or friction) to others regarded as thermal processes (particularly those resulting from sonochemical activation). Part of the difficulty in ascertaining mechanochemical reactions is that they represent multiscale phenomena operating across multiple length scales, from supramolecular stages (e.g. crystals or polymers) to molecular scales of individual bonds.[1–3]

Among structures susceptible to mechanical forces, polymers exhibit a wide range of responses that can be controlled and amplified through their structure.[2] In this context, the concept of *functional mechanophore* represents a striking point. Thus, polymer-bound small molecules may experience forces transferred from the polymer chain segments. Two teams led by Moore and Bielawski have recently applied this approach to reconfigure atropisomers, which would otherwise be configurationally stable under thermal conditions.[4] (*R*)- and (*S*)-1,1′-bis-2-napthol (binol) derivatives,[5] have proven to be extremely versatile ligands and catalysts in asymmetric synthesis. With isomerization barriers exceeding 30 kcal mol^{-1},[6] these molecules displaying axial chirality do not undergo thermal isomerization and can therefore be resolved.

Bielawski and co-workers rightly reasoned that configurational inversion should proceed via planar intermediates, which could be generated by applying a tensile force to naphthyl rings by means of polymer chains with a critical molecular weight. Such a force would ultimately be able to surmount the restricted rotation, thereby converting one enantiomer into the other (Scheme 1). To verify this conjecture, a conveniently functionalized substrate, (*S*)-1,1′-binaphthyl-2,2′-bis-(2-bromoisobutyrate), was subjected to



Scheme 1. Configurational inversion of chiral atropisomers under ultrasound conditions. US = ultrasound.

single-electron transfer(SET)/living radical polymerization with methyl acrylate to yield a polymer with an approximate molecular weight of 100 kDa (referred to as $\boldsymbol{S}_{100K}$). Such a binaphthyl unit embedded in a polymer chain was then sonicated under Ar in CH_3CN (at 20 kHz, 12.8 mm Ti probe; power intensity = 10.1 $W cm^{-2}$). To avoid polymer degradation, pulsed irradiation was applied (1.0 s on and 1.0 s off) and an average temperature of ≤ 9 °C was maintained. Circular dichroism (CD) analyses showed a progressive decrease in intensity of the Cotton effect signal at 230 nm over time. After a sonication period of 24 hours more than 95 % of $\boldsymbol{S}_{100K}$ had undergone racemization. The postsonicated material showed almost identical spectroscopic characteristics (except the CD spectra) to that of presonicated $\boldsymbol{S}_{100K}$. Similar results were attained with a polymer having the opposite configuration at the binaphthyl unit ($\boldsymbol{R}_{100K}$).

It is remarkable that these researchers paid attention to power intensity optimization in this carefully executed sonochemical study. The applied intensity (10.1 $W cm^{-2}$) corresponds to 23 % power setting, although other instrument settings were also considered (20, 25, and 28 %). Sonication at 20 % revealed no decrease in the Cotton effect signal,

[*] Prof. Dr. G. Cravotto
Dipartimento di Scienza e Tecnologia del Farmaco
Università di Torino, Via Giuria 9, 10125 Torino (Italy)
Fax: (+39) 011-670-7687
E-mail: giancarlo.cravotto@unito.it
Prof. Dr. P. Cintas
Departamento de Química Orgánica e Inorgánica
Facultad de Ciencias-UEX, 06071 Badajoz (Spain)
Fax: (+34) 924-271-149
E-mail: pecintas@unex.es

[**] Support by the Spanish Ministry of Science and Innovation (Grant No. MAT2009-14695-C04-C01), the University of Turin, and MIUR (PRIN, Prot. 2008M3Y5WX) is gratefully acknowledged.

whereas irradiation at 28% showed appreciable chain scission. Results at 23 and 25% were comparable (>95% loss in CD signal intensity) and no change in molecular weight was observed.

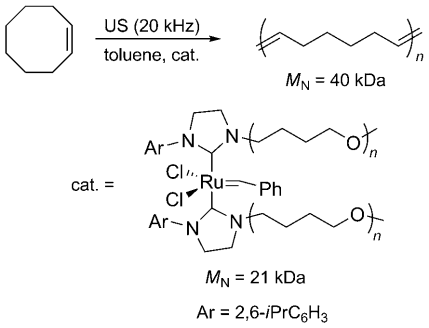
The role of ultrasound was crucial in promoting isomerization; as independent experiments carried out in solutions of $\boldsymbol{S}_{100K}$ at reflux in a high-boiling solvent (Ph_2O, b.p. = 257 °C) showed no change in its CD signal intensity. This result confirms the high isomerization barrier for such atropisomers (decomposition of $\boldsymbol{S}_{100K}$ occurred at 364 °C). If the monomeric substrate is sonicated in the presence of a poly(methyl acrylate) (PMA) homopolymer with a comparable molecular weight, the postsonicated material changed neither its CD spectrum nor molecular weight; a fact evidencing still further that only mechanophores covalently linked to a polymer chain will experience forces induced by ultrasound.

As mentioned above, mechanical activation of polymers appears to be largely dependent on their molecular weight. The authors observed that below a molecular mass threshold, the postsonicated materials exhibited no significant changes relative to the presonicated polymers. In other words, the polymer chain is too short to transfer the mechanical forces required for bond cleavage, though chain scission rates can be enhanced in the presence of weaker bonds at specific positions in the polymer backbone.[2] In contrast, high-molecular-weight polymers are prone to degradation upon sonication. When the binaphthyl core was incorporated into a methyl-acrylate-based polymer with a number-average molecular weight of $M_n = 2.8$ MDa, sonication under the same conditions caused significant degradation (final $M_n =$ 156 kDa) with minimal change in CD signals. Clearly, cleavage along the chain is faster than isomerization of the mechanophore.

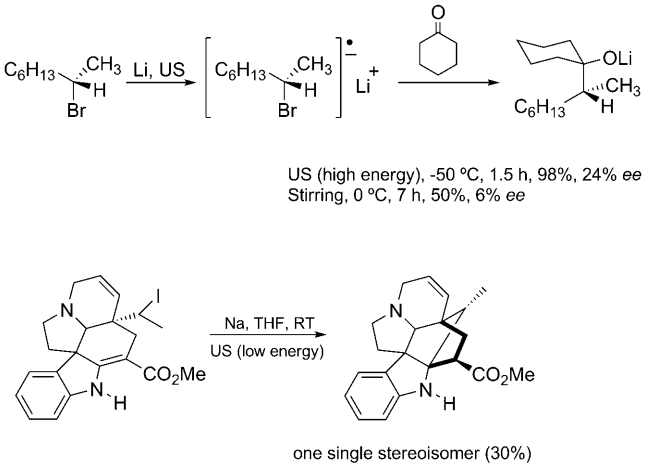
It is convenient to mention that recent related studies have also demonstrated the feasibility of this strategy, in which selective bond scission of the chain-centered mechanophore is triggered by mechanical force generated with ultrasound.[7] Polymer molecules become distorted and stretched as they undergo fast structural changes induced by cavitational collapse. At the final stage of this process the associated shock wave causes sufficient stress within the polymer to be responsible for bond scission.[8] Sijbesma and co-workers have, for example, applied the concept to activate catalysts that can further promote organic reactions. Here, a metal center is chelated by two N-heterocyclic carbenes (NHCs), each attached to a polymer chain. Sonication of longer polymers results in large shear forces in solution, which ultimately cleave the metal–ligand bond to generate an active catalyst. Under sonication, polymeric Ag– and Ru–NHCs catalyze transesterification and ring-opening metathesis polymerization, respectively (Scheme 2).[9] In a more impressive result, Moore and co-workers showed that mechanical stress applied to a polymer-bound benzocyclobutene circumvents the Woodward–Hoffmann rules.[10]

Although completely different from the mechanochemistry worked out by Bielawski and co-workers, it is noteworthy to highlight (in the present context) cases of stereoselective changes on small molecules that are induced by ultrasound. Documented results are varied and a satisfactory rationale is not always possible.[11] Stereoselective alterations can occur if sonication is able to change the energy difference of the transition states. Unlike polymers, shear forces in solution would hardly cause scission in small molecules; therefore salient examples are usually associated to reactions on activated surfaces. Thus, in an early case reported by Luche and co-workers, the Barbier reaction of enantiopure (*S*)-2-halo-octanes proved to be significantly dependent on the nature of the halide, and hence on the rate of C–X bond breaking.[12] A bromo derivative generates a reactive radical anion on the activated metal surface. As the rate-determining SET is sonication dependent, a more efficient irradiation increases the concentration of the radical ion and accelerates its addition to the carbonyl group in an *anti* orientation to the leaving bromide ion. Configuration inversion occurs in 24% *ee* and high yield, while conventional conditions give a product with very small enantioenrichment in a slower reaction (Scheme 3, top).

An outstanding result was also attained during the cyclization of 9-iodotabersonine to the alkaloid vindolinine, both having the core skeleton of terpenoid indole alkaloids. The ultrasonic energy largely determines the stereochemical outcome. Sonication with a high-energy probe produces four



Scheme 2. Proof of concept: a catalytic mechanophore becomes active under sonication only when the attached polymers reach a critical mass.



Scheme 3. Stereoselective transformations induced by sonication on activated metals.

diastereomers; on lowering the power intensity only two were obtained. A single stereoisomer was instead obtained with the lower power provided by an ultrasonic bath, although the yield was rather modest (Scheme 3, bottom).[13] Low-energy irradiation presumably drives the process on the metal surface where the enhanced stereoselectivity arises from the lower freedom of the adsorbed species. Higher energy favors desorption and random selection then occurs in the bulk solution.

Unlike reactions on surfaces or crystalline slurries,[14] homogeneous reactions do not usually exhibit a marked stereoselective bias caused by mechanical effects resulting from postcavitational collapse; this is because shear forces and shock waves will affect molecules randomly. Accordingly, the idea of employing polymers of appropriate length and molecular weight distribution is certainly appealing; they act as molecular tweezers that propagate and amplify mechanical forces induced by sonication, such as cutting or kneading.

In summary, the polymer-based ultrasound-induced reconfiguration strategy devised by Bielawski and co-workers represents an innovative protocol for enantiomer interconversion that overcomes the high barriers of configurationally stable stereoisomers. Using the chemoselective activation that balances isomerization versus polymer chain scission, further applications in asymmetric processes should be anticipated.

Received: March 7, 2010
Published online: July 20, 2010

[1] a) M. K. Beyer, H. Clausen-Schaumann, *Chem. Rev.* **2005**, *105*, 2921 – 2948; b) G. Kaupp, *Making Crystals by Design* (Eds.: D. Braga, F. Grepioni), Wiley-VCH, **2007**, pp. 87 – 148.

[2] M. M. Caruso, D. A. Davis, Q. Shen, S. A. Odom, N. R. Sottos, S. R. White, J. S. Moore, *Chem. Rev.* **2009**, *109*, 5755 – 5798, and references therein.

[3] A clear-cut distinction between mechanochemistry and mechanophysics, and their misleading association with solid-state processes in general, is lacking. Although the conflict may be largely semantic, for an illuminating perspective, see: G. Kaupp, *CrystEngComm* **2009**, *11*, 388 – 403.

[4] K. M. Wiggins, T. W. Hudnall, Q. Shen, M. J. Kryger, J. S. Moore, C. W. Bielawski, *J. Am. Chem. Soc.* **2010**, *132*, 3256 – 3257.

[5] Even though the *R*/*S* notation can be utilized for atropisomers, these substances are devoid of chiral centers and therefore, their axial chirality is best denoted by *M* and *P* descriptors (or alternatively *aR*, *aS*); see: E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 1119 – 1121, 1200.

[6] For configurational inversion to occur, isomerization barriers should be no greater than 23–24 kcal mol^{-1}; see: M. Ōki, *The Chemistry of Rotational Isomers*, Springer, Berlin, **1993**, Chapter 1.

[7] For representative examples of mechanotransduction of physical forces into chemical systems, see: a) J. M. J. Paulusse, R. P. Sijbesma, *Angew. Chem.* **2004**, *116*, 4560 – 4562; *Angew. Chem. Int. Ed.* **2004**, *43*, 4460 – 4462; b) K. L. Berkowski, S. L. Potisek, C. R. Hickenboth, J. S. Moore, *Macromolecules* **2005**, *38*, 8975 – 8978; c) O. Azzaroni, B. Trappmann, P. van Rijn, F. Zhou, B. Kong, W. T. S. Huck, *Angew. Chem.* **2006**, *118*, 7600 – 7603; *Angew. Chem. Int. Ed.* **2006**, *45*, 7440 – 7443; d) S. S. Sheiko, F. C. Sun, A. Randal, D. Shirvanyants, M. Rubinstein, H.-I. Lee, K. Matyjaszewski, *Nature* **2006**, *440*, 191 – 194; e) S. Karthikeyan, S. L. Potisek, A. Piermattei, R. P. Sijbesma, *J. Am. Chem. Soc.* **2008**, *130*, 14968 – 14969; f) J. M. Lenhardt, A. L. Black, S. L. Craig, *J. Am. Chem. Soc.* **2009**, *131*, 10818 – 10819; g) D. A. Davis, A. Hamilton, J. Yang, L. D. Cremar, D. Van Gough, S. L. Potisek, M. T. Ong, P. V. Braun, T. J. Martínez, S. R. White, J. S. Moore, N. R. Sottos, *Nature* **2009**, *459*, 68 – 72; h) M. J. Kryger, M. T. Ong, S. A. Odom, N. R. Sottos, S. R. White, T. J. Martinez, J. S. Moore, *J. Am. Chem. Soc.* **2010**, *132*, 4558 – 4559.

[8] A. M. Basedow, K. H. Ebert, *Adv. Polym. Sci.* **1977**, *22*, 83 – 148.

[9] A. Piermattei, S. Karthikeyan, R. P. Sijbesma, *Nat. Chem.* **2009**, *1*, 133 – 137.

[10] a) C. R. Hickenboth, J. S. Moore, S. R. White, N. R. Sottos, J. Baudry, S. R. Wilson, *Nature* **2007**, *446*, 423 – 427; for an extended commentary, see: b) G. Cravotto, P. Cintas, *Angew. Chem.* **2007**, *119*, 5573 – 5575; *Angew. Chem. Int. Ed.* **2007**, *46*, 5476 – 5478.

[11] For a review, see: J.-L. Luche, P. Cintas, *Advances in Sonochemistry*, *Vol. 5* (Ed.: T. J. Mason), JAI, London, **1999**, pp. 147 – 174, and references therein.

[12] J. C. de Souza-Barboza, J.-L. Luche, C. Petrier, *Tetrahedron Lett.* **1987**, *28*, 2013 – 2016.

[13] G. Hugel, D. Cartier, J. Levy, *Tetrahedron Lett.* **1989**, *30*, 4513 – 4516.

[14] T. Friščić, S. L. Childs, S. A. A. Rizvi, W. Jones, *CrystEngComm* **2009**, *11*, 418 – 426.

