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Pressure-dependent helix inversion of poly(quinoxaline-2,3-diyl)s containing chiral side chains in non-aqueous solvents†

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Poly(quinoxaline-2,3-diyl)s with chiral (*S*)-2-butoxymethyl side chains dissolved in 1,2-dichloroethane experience a reversible pressure-dependent helix inversion from *P*- to *M*-helical structures between 0.1 MPa and 200 MPa.

Pressure is one of the most fundamental thermodynamic parameters used to regulate molecular conformations and chemical reactions.[1,2] Since the pioneering work of Bridgman in 1914,[3] which demonstrated that high hydrostatic pressure is able to denature egg white proteins, much effort has been devoted to controlling the conformation of biomolecules such as DNA,[4] RNA,[5] and various proteins[6] in solution under hydrostatic pressure. In 1991, Barciszewski and co-workers demonstrated that DNA (poly(dGdC)·poly(dGdC)) exhibited a conformational change from the *B*- to the *Z*-form after having been exposed to 600 MPa for 19 h in an aqueous buffer solution,[4a] which was explained in terms of the pressure-induced dehydration of the DNA under these conditions. In general, hydration or dehydration processes, involving a large number of water molecules, play an important role in the conformational changes of such biomolecules in aqueous solutions.[7]

The quest for new classes of chiral functional materials has recently focused considerable attention on the control over the reversal of the screw sense of synthetic helical polymers bearing chiral side chains triggered by external stimuli.[8] To date, temperature,[9] light,[10] metal ions,[11] pH value,[12] and solvents[13] have been employed to control the helical chirality of polymer backbones. However, to the best of our knowledge, reports on the switch of the main-chain chirality of synthetic helical polymers by hydrostatic pressurization still remain elusive. One of our recent reports has demonstrated that the purely single-handed screw sense of poly(quinoxaline-2,3-diyl)s (PQXs) bearing (*S*)-2-butoxymethyl side chains is susceptible to a solvent-dependent helix inversion of the helical backbone between $CHCl_3$ (*M*-helix) and 1,1,2-trichloroethane (1,1,2-TCE, *P*-helix) without other conformational change.[14] It was furthermore possible to use these PQXs as effective chiral catalysts, and the solvent-dependent switch of helical chirality allowed a highly enantioselective synthesis of both product enantiomers in various asymmetric reactions.[15] This helical scaffold could also be used for the fabrication of solid polymer films exhibiting selective reflection of circularly polarized light (CPL) in the visible light region, whereby a switch of the handedness of the CPL could be induced.[16] Herein, we would like to disclose an *in situ* pressure-dependent helix inversion of PQXs bearing chiral side chains during high pressure circular dichroism (CD) measurements.

In a preliminary attempt to investigate the impact of hydrostatic pressure on the main-chain chirality, we measured the CD and UV-vis absorption spectra of PQX 40mer **1**, bearing (*S*)-2-butoxymethyl side chains, at ambient (0.1 MPa) and elevated (200 MPa) pressure (Table 1). The ambient temperature was set to 25 °C, and all measurements were carried out after adequate equilibration. The CD intensity was evaluated *via* Kuhn's dissymmetry factor g_{abs}, which is defined as the CD intensity normalized by the UV-vis absorbance to exclude errors originated from the compression of solvent at high pressure. Consistent with our previous reports, **1** adopted an absolute *M*-helical structure at 0.1 MPa (>99%), and showed no significant change in its CD spectrum at 200 MPa (entry 1). Although we also attempted to measure the CD and UV spectra of **1** in 1,1,2-TCE at 200 MPa, this was hampered by partial precipitation, which is most likely due to the low solubility of **1** in 1,1,2-TCE (entry 2). In order to improve the solubility of **1**, we subsequently employed solvent mixtures of $CHCl_3$ and 1,1,2-TCE. In mixtures containing 20–50% of 1,1,2-TCE, **1** adopted an *M*-helical conformation at 0.1 and 200 MPa (entries 3–5). Using 60% and 65% of 1,1,2-TCE, **1** adopted a *P*-helical conformation at 0.1 MPa, but an *M*-helical conformation at 200 MPa (entries 6 and 7). This pressure-dependent helix inversion was not observed for 1,1,2-TCE volume fractions >70% (entries 8 and 9). A series of

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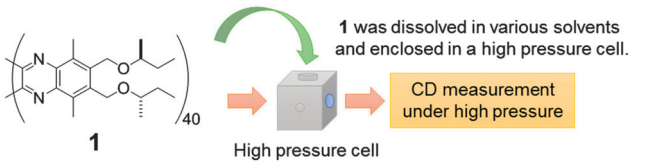
Table 1 Dissymmetry factor g_{abs} of **1** in various solvents at 0.1 or 200 MPa. Values for Δg_{abs} between 0.1 and 200 MPa are also displayed



Entry	Solvent	$g_{abs}/10^{-3}$ [a] 0.1 MPa	200 MPa	$\Delta g_{abs}/10^{-3}$
1	$CHCl_3$	−2.31 (*M*)	−2.31 (*M*)	0.00
2	1,1,2-TCE	+3.15 (*P*)	—[c]	—[c]
3	$CHCl_3$/1,1,2-TCE = 80/20	−2.45 (*M*)	−2.56 (*M*)	−0.11
4	$CHCl_3$/1,1,2-TCE = 60/40	−2.42 (*M*)	−2.67 (*M*)	−0.25
5	$CHCl_3$/1,1,2-TCE = 50/50	−2.07 (*M*)	−2.54 (*M*)	−0.47
6	$CHCl_3$/1,1,2-TCE = 40/60	−0.27 (*M*)	−1.85 (*M*)	−2.12
7	$CHCl_3$/1,1,2-TCE = 35/65	+1.15 (*P*)	−1.00 (*M*)	−2.15
8	$CHCl_3$/1,1,2-TCE = 30/70	+2.24 (*P*)	+0.60 (*P*)	−1.64
9	$CHCl_3$/1,1,2-TCE = 20/80	+2.72 (*P*)	+2.32 (*P*)	−0.40
10	Toluene	−2.02 (*M*)	−1.89 (*M*)	+0.13
11	CH_2Cl_2	−2.29 (*M*)	−2.35 (*M*)	−0.05
12	1,1,1-TCE	−2.24 (*M*)	−2.19 (*M*)	+0.05
13	THF	−2.22 (*M*)	−2.15 (*M*)	+0.07
14	1-BuCl	−1.14 (*M*)	+0.02 (*P*)	+1.16
15	1-BuCN	+1.10 (*P*)	+1.51 (*P*)	+0.41
16	1,2-DCE	+0.91 (*P*)	−1.30 (*M*)	−2.21
17	1,3-DCP	+1.26 (*P*)	+1.06 (*P*)	−0.20

[a] g_{abs} at 368.0 nm. [b] Δg_{abs} between 0.1 and 200 MPa at 368.0 nm. [c] g_{abs} could not be determined due to insufficient solubility.

$CHCl_3$–1,1,2-TCE solvent mixtures exhibited a negative difference for Kuhn's dissymmetry factor (Δg_{abs}; $\Delta g_{abs} = g_{abs/200MPa} - g_{abs/0.1MPa}$), *i.e.* hydrostatic pressurization induced an *M*-helical conformation. Assuming a constant solvent- and pressure-independent g_{max} value of 2.31×10^{-3} ($CHCl_3$, 0.1 MPa), the screw-sense excess (se) of **1** in a 35/65 mixture of $CHCl_3$/1,1,2-TCE can be estimated to be 50% (*P*) at 0.1 MPa and 43% (*M*) at 200 MPa.

In toluene, CH_2Cl_2, 1,1,1-trichloroethane (1,1,1-TCE), and tetrahydrofuran (THF), we could not observe any substantial changes of the main-chain chirality of **1** upon hydrostatic pressurization (entries 10–13). Although the screw sense of **1** was retained at 200 MPa, the CD intensities changed significantly in 1-BuCl and 1-BuCN (entries 14 and 15). For 1-BuCl and 1-BuCN, positive Δg_{abs} values were obtained, suggesting that static pressurization induced, in contrast to $CHCl_3$–1,1,2-TCE mixtures, the formation of a *P*-helical conformation in these solvents. In 1,2-dichloroethane (1,2-DCE), **1** showed a clear pressure-dependent helix inversion between 0.1 and 200 MPa (entry 16). Similar to $CHCl_3$–1,1,2-TCE mixtures, a negative Δg_{abs} value was observed in 1,2-DCE. Provided that the absolute g_{max} value in 1,2-DCE is comparable to that in $CHCl_3$ (2.31×10^{-3}), this helix inversion in 1,2-DCE corresponds to an se change from 39% (*P*, 0.1 MPa) to 56% (*M*, 200 MPa). In 1,3-dichloropropane (1,3-DCP), **1** adopted a *P*-helical conformation at 0.1 and 200 MPa (entry 17). These results suggested that a $CHCl_3$/1,1,2-TCE (v/v = 35/65) mixture or 1,2-DCE represents the most promising solvent for an effective hydrostatic pressure-induced helix inversion. In order to eliminate any potential ambiguity that might arise from a binary solvent system, we used 1,2-DCE for the subsequent studies.

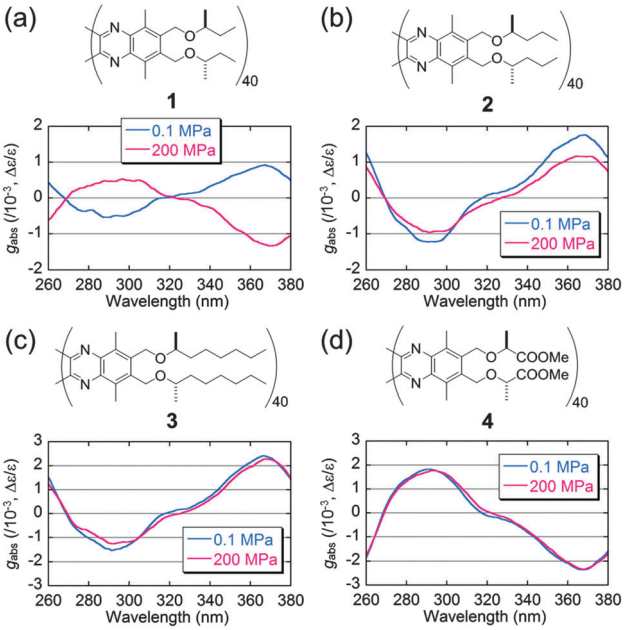


Fig. 1 CD spectra of **1–4** in 1,2-DCE at 0.1 or 200 MPa, whereby CD intensities are expressed in terms of $g_{abs}(\Delta\varepsilon/\varepsilon)$.

Following that, we carried out a screening of the effect of the chiral PQX side chains on the pressure-dependent helix inversion in 1,2-DCE (Fig. 1). As previously mentioned, the CD spectra of **1**, bearing (*S*)-2-butoxymethyl side chains, at 0.1 and 200 MPa are almost perfect mirror images of each other, which supports a pressure-dependent helix inversion (Fig. 1a). A series of 40mers bearing (*S*)-2-pentyloxymethyl (**2**), (*S*)-2-octyloxymethyl (**3**), or methyl L-lactate-derived side chains (**4**),[17] was examined in order to evaluate the effect of different side chains on potential hydrostatic pressure-induced changes of the chirality of the polymer backbone. A common feature of all these chiral side chains is the methyl-substituted *S*-stereogenic center at the γ-position. Although the side chain structure of **2** is similar to that of **1**, a pressure-dependent helix inversion was not observed between 0.1 and 200 MPa. Similarly, no helix inversion was observed between 0.1 and 200 MPa for (*S*)-2-octyloxymethyl-substituted **3**, even though **3** showed the most efficient screw-sense induction in our previous report.[14b] However, **4**, containing methyl L-lactate-derived side chains, adopted an *M*-helical structure in 1,2-DCE, while the absolute configuration of the stereogenic center in the chiral side chain was identical to the *P*-helical polymers of **1–3**. At high pressure, **4** still adopted an *M*-helical structure, and a switch of the helix chirality was not observed. Although we also prepared other polymers, bearing (*S*)-2-butoxy and (*S*)-3-octyloxymethyl groups, these polymers exhibited an insufficient solubility in 1,2-DCE. Based on these results, the use of (*S*)-2-butoxymethyl side chains was found to be of critical importance in order to gain sensitivity towards hydrostatic pressure. Although we also prepared polymers of **1** with higher degrees of polymerization (60mers, 100mers, and 200mers), bearing (*S*)-2-butoxymethyl side chains, these polymers were also found to be insoluble in 1,2-DCE at 200 MPa (see ESI†).

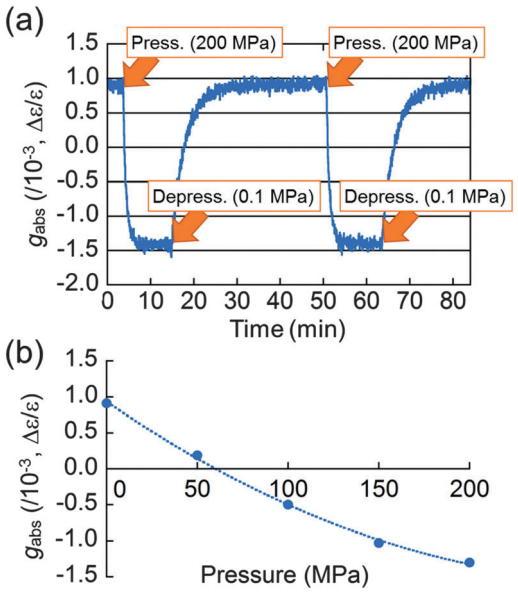


Fig. 2 (a) Time-resolved CD intensity change of **1** in 1,2-DCE at 368.0 nm exposed to pressurization (200 MPa) and depressurization (0.1 MPa) cycles. (b) Correlation between pressure and g_{abs} of **1** in 1,2-DCE at 368.0 nm.

Subsequently, we investigated the time-resolved CD intensity change of **1** in 1,2-DCE as a function of pressurization (0.1 to 200 MPa) and depressurization (200 to 0.1 MPa; Fig. 2a). The pressure-dependent helix inversion process was found to be reversible, and rate constants for the helix inversion reaction were determined as 2.40×10^{-2} s^{-1} (*P* to *M* at 200 MPa) and 5.41×10^{-3} s^{-1} (*M* to *P* at 0.1 MPa, see ESI†) by considering simple first-order reaction kinetics between *P*- and *M*-helices. The half-life values for the helix inversion were determined to be 29 s (*P* to *M* at 200 MPa) and 128 s (*M* to *P* at 0.1 MPa), which clearly demonstrated that the helix inversion proceeds faster at high pressure than at ambient pressure.

We also investigated the correlation between pressure and g_{abs} of **1** in 1,2-DCE (Fig. 2b), and found that pressurization induced a nonlinear decrease of g_{abs}. According to Hawley,[18] the Gibbs energy difference (ΔG) in an isothermal process before and after pressurization can be expressed as

$$\Delta G = \Delta V \times (P - P_0) - \Delta\beta/2 \times (P - P_0)^2, \quad (1)$$

where ΔV and $\Delta\beta$ represent the difference of the partial molar volume of the dissolved polymer and the compressibility factor, respectively. According to Green's theory,[19] ΔG of the helix inversion may also be expressed as

$$\Delta G = -2RT_0 \times \{\mathrm{atanh}(g_{abs}/g_{max}) - \mathrm{atanh}(g_{abs,0}/g_{max})\}, \quad (2)$$

wherein $g_{abs,0}$ and g_{abs} refer to the dissymmetry factor before and after pressurization, respectively, g_{max} is the dissymmetry factor for the purely single-handed polymer (*P*-helix, 100%), T_0 is the temperature (298.15 K), and *R* is the gas constant (8.314 J K^{-1} mol^{-1}). Due to the low solubility of **1** in 1,2-DCE, the corresponding g_{max} value could not be determined accurately, and therefore an assumed g_{max} value of 2.31×10^{-3} ($CHCl_3$; Table 1) was used at this stage in order to obtain approximate values for ΔV and $\Delta\beta$. A nonlinear least-square fitting of ΔG *versus P* was carried out in order to minimize the sums of the squares of the deviation by varying the two parameters ΔV and $\Delta\beta$. A convergence of these parameters at $\Delta V = -36.8$ cm^3 mol^{-1} and $\Delta\beta = -0.103$ cm^3 mol^{-1} MPa^{-1} was observed (see ESI†), and despite using a non-aqueous solvent, the observed ΔV value is comparable to ΔV values of pressure-induced protein unfolding.[20] As discussed by Green *et al.*, a conformational change of a helical polymer is induced by the cooperative accumulation of very small energy differences between *P*- and *M*-helices.[21] In the case of the present pressure-dependent helix inversion of PQXs, a minute molar volume change per repeat unit may cooperatively accumulate and become sufficiently large in order to enable the screw-sense inversion of the helical main chain even in organic solvents. While the reason was still not clear, **2**–**4** did not exhibit the pressure-dependent helix inversion in spite of their structures and the solvent effect similar to **1** in 1,2-DCE. It seems that an appropriate combination of the chiral side chain and the solvent is essential to obtain a large ΔV for the pressure-dependent helix inversion.

In summary, we have investigated the induction of a specific helical sense in the main chain of poly(quinoxaline-2,3-diyl)s, containing chiral (*S*)-2-butoxymethyl side chains, in various solvents when exposed to different levels of hydrostatic pressure. We observed a clear pressure-dependent helical sense inversion in 1,2-dichloroethane or $CHCl_3$–1,1,2-trichloroethane mixtures. For this high pressure-induced helix inversion to occur, the presence of (*S*)-2-butoxymethyl side chains was found to be of critical importance. Currently, an unequivocal clarification of the origin of the observed pressure effect, *e.g.* by molecular dynamics simulations, has still remained difficult due to the very small energy difference between conformations. Therefore, further studies, exploring potential applications of helical poly(quinoxaline-2,3-diyl)s with switchable chirality as a new class of chiral supporting materials, are currently being undertaken in our laboratory, alongside in-depth investigations into the origin and mechanism of this pressure-dependent helix inversion.

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