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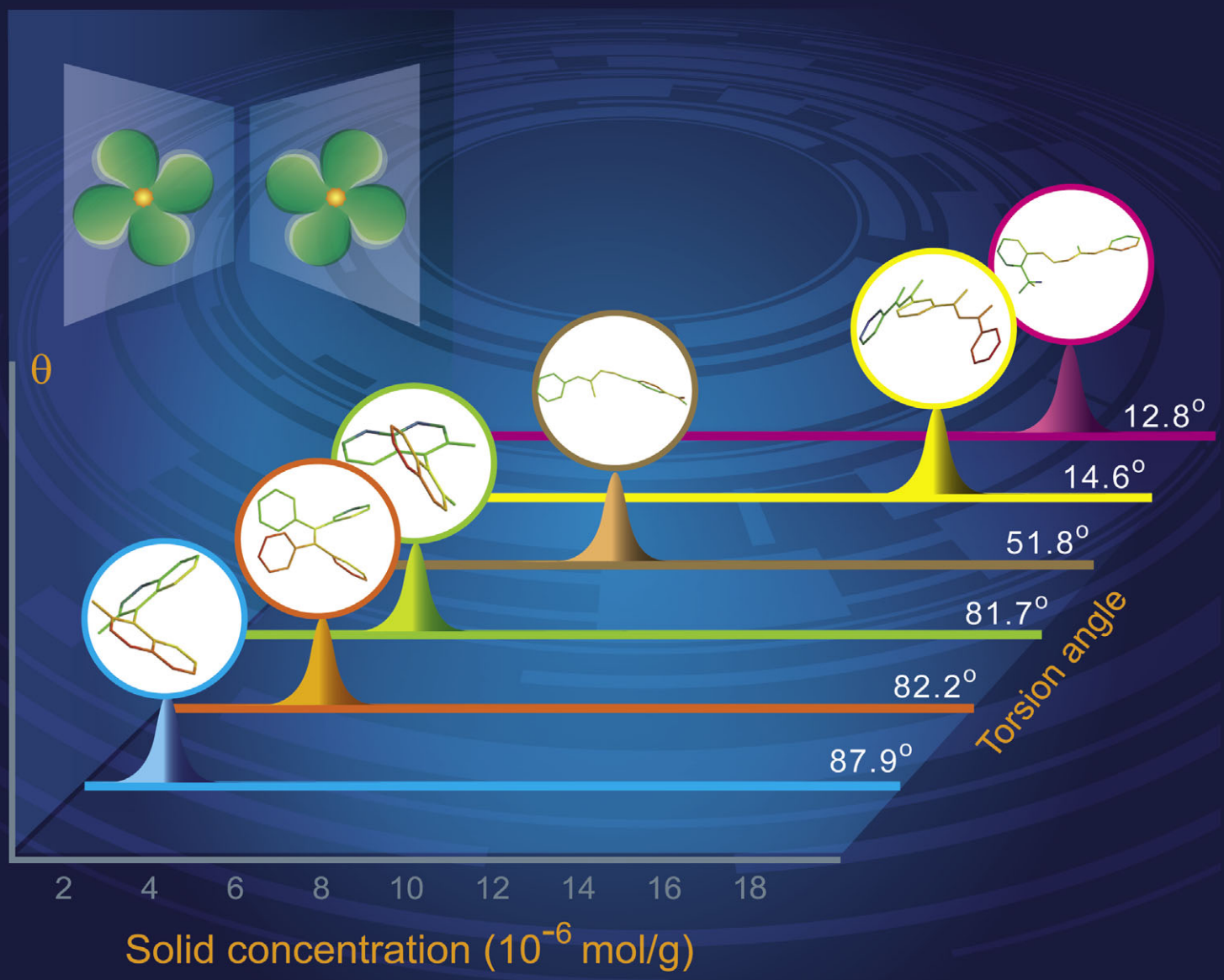

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PAPER

Concentration effects in solid-state CD spectra of chiral atropisomeric compounds

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Atropisomerism is one of the basic concepts in stereochemistry. Chiral crystals of stereochemically labile atropisomers that originated from Mirror Symmetry Breaking (MSB) can only be characterized by solid-state chiroptical techniques. Herein, solid-state circular dichroism and UV-Vis spectra of six atropisomeric compounds (most of them were obtained from MSB) have been studied. A concentration effect including a wavelength shift and inverse concentration-dependence has been found and preliminarily explained by the absorption flattening effect, scattering effect and the torsion in the molecular structures.

Introduction

Classical atropisomerism is a type of stereoisomerism that may arise when free rotation around a single bond is impeded to allow for the resolution of the enantiopure atropisomers at ambient temperatures.[1–3] A typical example is a class of *ortho*-substituted biphenyls[4] (or, more generally, biaryls), in which the steric congestion between substituents is too great to enable essentially free rotation around the sp^2–sp^2 carbon–carbon bond. In recent years, with the increasing disclosure of MSB phenomenon, more and more chiral crystals of atypical atropisomers have been found, in which chiral conformations resulting from the restricted rotation are locked in solid-state.[5–9]

Circular dichroism (CD) spectroscopy is a powerful chiroptical technique based on the differential interaction between the chiral sample and left- and right-circularly polarized light, and represents a versatile tool for analyzing chiral compounds with suitable CD chromophores.[10] The chiroptical properties of stereochemically labile atropisomers should be measured in solid-state due to their rapid racemization in solution. The measured solid-state chiroptical information can be correlated with that from other solid-state methods such as single-crystal X-ray diffraction, solid-state nuclear magnetic resonance (NMR) to assign the absolute configurations of the atropisomers.[10]

Typical CD spectroscopy was mainly applied in solution, which means perfectly isotropic samples, as opposed to solid samples which are often far from ideal in this respect. Thus, there are some factors, such as linear dichroism (LD), linear birefringence (LB), absorption flattening (AF) and scattering effect, that can impact the measurement of a true solid-state CD spectrum.[10–12] Although a few remarkable papers have pointed out these problems,[10–14] distorted solid-state CD spectra measured at unsuitable concentrations and parameters are still common in publications, even those published in mainstream journals.[4,15]

Herein, solid-state CD spectra of six atropisomeric compounds with aryl groups (Fig. 1) were studied by a microcrystalline pellet method. A blue shift of the CD maxima wavelength with the decreasing sample concentration was observed. It was also found that the intensity of the CD signal decreased continuously when the concentration was higher than a specific certain value, although the concentration was still in the linear range of the absorbance. All of these concentration effects were preliminarily explained.

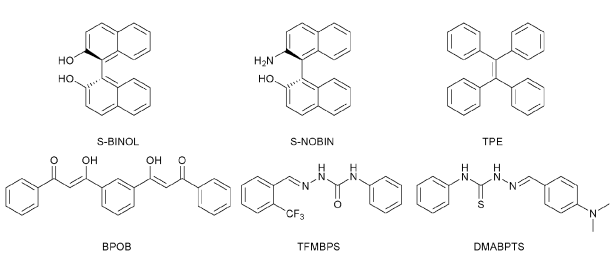

Fig. 1 Structures of atropisomeric compounds.

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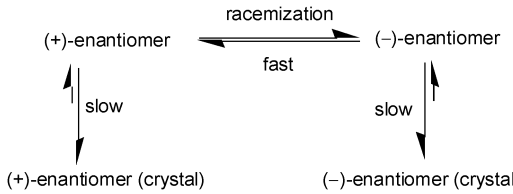

Scheme 1 Crystallization-induced asymmetric transformation of racemate.

Experimental section

S-1,1′-Bi-2-naphthol (*S*-BINOL) and *S*-2-amino-2′-hydroxy-1,1′-binaphthyl (*S*-NOBIN) were resolved from their racemates.[16,17] 1-[4-(Dimethylamino)benzylidene]-4-phenylthiosemicarbazide (DMABPTS), 1-[2-(trifluoromethyl)benzylidene]-4-phenylsemicarbazide (TFMBPS), 1,3-bis(3-phenyl-3-oxopropanoyl)-benzene (BPOB), and tetraphenylethylene (TPE) were prepared following reported methods.[9,18–21] The enantiopure single crystals of TPE were obtained from the spontaneous resolution. The chiral crystals of DMABPTS, TFMBPS and BPOB were synthesized from the crystallization-induced asymmetric transformation, known as total spontaneous resolution or absolute asymmetric synthesis (Scheme 1).[20,21]

As can be seen from Fig. 2, *S*-BINOL and *S*-NOBIN are typical atropisomeric *ortho*-substituted biaryls which are stereochemically inert in solution. For DMABPTS and TFMBPS, the rotation of the phenyl around the C–N bond axis is free in solution, but is restrained like the above biaryls in solid state. A similar situation exists in the chiral crystal of BPOB, in which the free rotation of the phenyl rings around the C–C bond is not permitted. In the crystals of TPE, the phenyl groups are twisted around the molecular axes and form the propeller conformations.

All the pellets of the same sample are derived from the same single crystal. The single crystal was mixed with 49 equivalent weight of KCl. The mixture was powdered. 50 mg of this powder was pressed to form a pellet whose concentration was 1/50 in weight. Another 50 mg of this powder was mixed with 50 mg KCl. Half of this mixture was used to form the pellet whose concentration was 1/100 in weight; the other half was mixed with additional 50 mg KCl. This process was repeated to obtain all the pellets. Each pellet was prepared using a KCl

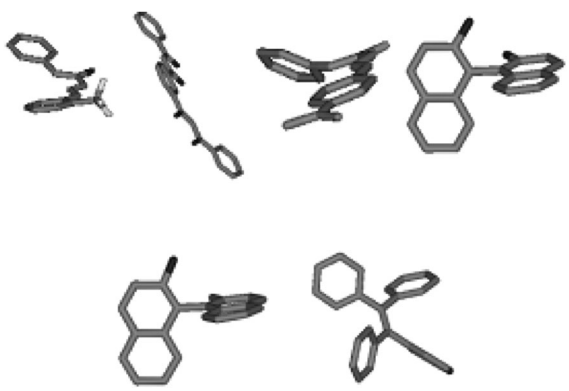

Fig. 2 Atropisomerism in the crystals of the compounds. From left to right: TFMBPS, BPOB, DMABPTS, BINOL, NOBIN and TPE.

matrix 13 mm in diameter and 50 mg in weight.[10] UV-Vis and CD spectroscopies were performed on a JASCO J-810 spectropolarimeter. The pellets were placed as close as possible to the photomultiplier tube sensitive surface in order to diminish the scattering effect.[11] Sample rotation around the incident-light axis (or z axis) and flip (180° rotation) around the vertical y axis were done to ensure that the presence of LD and LB can be ignored.[10] All measurements were performed using the following parameters: single scan, continuous scanning mode, 500 nm min^{-1} scanning speed, 4 nm SBW, 1 nm data interval, air baseline had been subtracted from UV-Vis and CD spectra.

Results and discussion

The CD and UV-Vis spectra of each compound are illustrated in Fig. 3 and 4. By comparing the CD spectra of the same sample in different concentrations, it is easy to see that the concentration has a great impact on these spectra, not only on the intensity but also the peak shape. The intensity of some specified CD bands are inverse concentration-dependent at a specific higher concentration range. So a maximum intensity can be found for each of them at a specific testing concentration.[22] When the testing concentration is higher than the maximum intensity concentration, the CD intensity decreases with further increase in concentration.

For TFMBPS (Fig. 4a), the positive Cotton effect (CE) at 342–330 nm and the negative CE at about 290 nm may be an exciton couplet pattern, corresponding to the phenyl conjugated azomethine π–π* transition band located at 310 nm in the UV-Vis spectrum. The negative CE at 290 nm has a maximum value when the concentration is 1/200. The CD signal at 342–330 nm almost remains unchanged when the concentration is decreasing from 1/50 to 1/200 but then is reduced when the concentration continues to decrease.

Similar to the TFMBPS, in the CD spectra of BPOB (Fig. 4b), the positive CE at 368 nm and the negative CE at 323 nm may also be an exciton couplet pattern, related to the phenyl conjugated diketone π–π* transition band located at 350 nm. When the concentration is 1/200, the positive CE and the negative CE both reach their maximum value.

For DMABPTS (Fig. 4c), the negative CE at about 382 nm is associated with the azomethine π–π* transition band located at 380 nm. The negative CE at 400–426 nm arises from the n–π* transition band at 405 nm. The maximum intensity of the bands at 382 nm and 400 nm is obtained when the concentration is 1/800, and the CD signal at 298 nm has a maximum value when the concentration is 1/400.

For *S*-BINOL and *S*-NOBIN (Fig. 4d and e), the positive CE from about 240 to 270 nm has a maximum intensity at 1/800 and 1/1600 concentrations, respectively, affiliated to the naphthalene π–π* transition band located at 240 nm in the UV-Vis spectrum.

In the CD spectra of TPE (Fig. 4f), the positive CE at 231 nm and the negative CE at 260 nm also looks like an exciton couplet pattern corresponding to the phenyl π–π* transition band located at 245 nm in its UV-Vis spectrum. But this pattern is an artefact. The real exciton couplet pattern among the phenyl π–π* transitions is located at the vacuum–UV range (<180 nm)[23] and is inaccessible for the

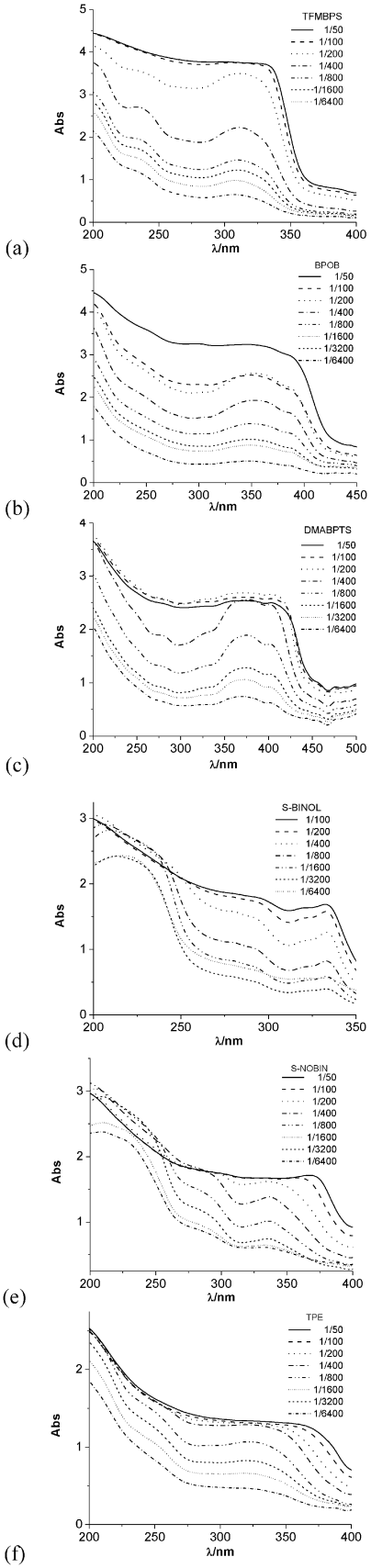

Fig. 3 UV-Vis spectra of atropisomeric compounds at different concentrations. (a) TFMBPS, (b) BPOB, (c) DMABPTS, (d) *S*-BINOL, (e) *S*-NOBIN, (f) TPE.

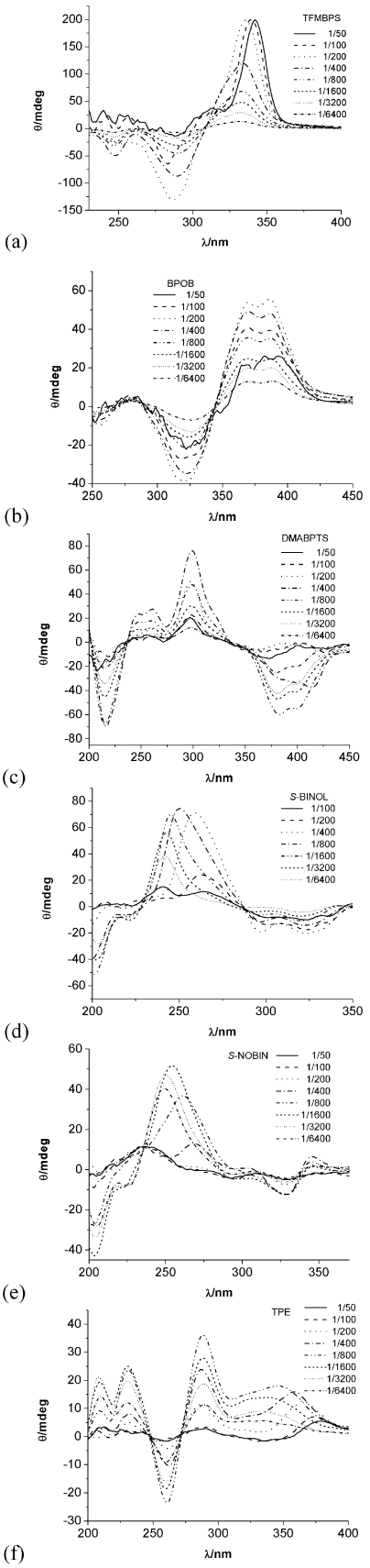

Fig. 4 CD spectra of atropisomeric compounds at different concentrations. (a) TFMBPS, (b) BPOB, (c) DMABPTS, (d) *S*-BINOL, (e) *S*-NOBIN, (f) TPE.

commercial CD spectrometer.[24] The negative CE at 260 nm and the positive CE at 288 nm and 330–380 nm all have a maximum intensity at 1/800 concentration. The maximum intensity of the positive CE at 231 nm appears at such a low concentration, 1/1600.

It is noted that a blue shift with the decreasing concentration is observed in some CD spectra. While the concentration of TFMBPS goes down from 1/50 to 1/6400, the positive CE blue shifts from 342 to 333 nm. The blue shift in the CD spectra of TPE is much more notable. Its maximum absorbance wavelength moves from 380 to 335 nm with the concentration dropping down from 1/50 to 1/6400. The CD spectra of *S*-BINOL is another remarkable example, whose positive CE shifts from 264 nm (1/100) to 242 nm (1/6400). Similarly, in the CD spectra of *S*-NOBIN, the positive CE shifts from 273 nm (1/50) to 249 nm (1/6400).

The blue shift of a CD band with the decreasing concentration can be explained by the AF effect.[13,14] The AF effect is derived from the nonhomogeneity of the pellets, which is inevitable for solid samples. Due to the nonhomogeneity of a pellet, photons are free to pass through it without interacting with the CD chromophores in a certain percentage. It will cause the AF effect in the UV-Vis spectra just as the name implies (Fig. 5a) or the wavelength shift in the CD spectra (Fig. 5b). The higher the concentration, the more serious the distortion of the UV-Vis and CD curves will be. By comparing the CD spectra of these atropisomeric compounds with the modeling CD spectra, it is easy to see that the blue shifts with the decreasing concentration in the CD spectra of TFMBPS, TPE, *S*-BINOL and *S*-NOBIN are derived from the AF effect, or essentially, from the inevitable nonhomogeneity of the pellets.

The AF effect can explain the departure of the linear relation between the CD signal and sample concentration. However, both the modeling (Fig. 5b) and experimental CD spectra[25] show that although the CD signal is reduced by the AF effect at a higher concentration, there is still an obvious stronger CD intensity than that at a lower concentration. Thus, the inverse concentration-dependent effect observed in the solid-state CD spectra of these atropisomeric compounds cannot be accounted for the AF effect only.

The scattering effect is another semi-possible reason for the inverse concentration-dependence. It is considered to be able to drastically distort the Nujol mull CD spectra (in which the scattering effect is much stronger than microcrystalline pellet CD).[12] In contrast, Castiglioni *et al*. reported that it can cause nearly no spectral distortions except for a very low attenuation of both absorbance and CD spectra.[13] In addition, it has been found to force the CD signal tend to roughly a constant at quite a high concentration ($>1/20$).[26] The attenuation of absorbance can be observed at high concentrations in all of the UV-Vis spectra (Fig. 6a). Absorbance curves corresponding to the points at the right of the red line are flat and rough. Thus, the inverse concentration-dependence at higher concentrations (the right region of the dashed line in Fig. 6b) may be considered to be the result of the scattering effect, or the combined effect of the scattering and AF effect.

For *S*-BINOL and *S*-NOBIN, it is remarkable that their absorbance curves at 200–250 nm are heavily distorted at higher concentrations, although the scattering effect is still low at a long wavelength. This can be considered as the

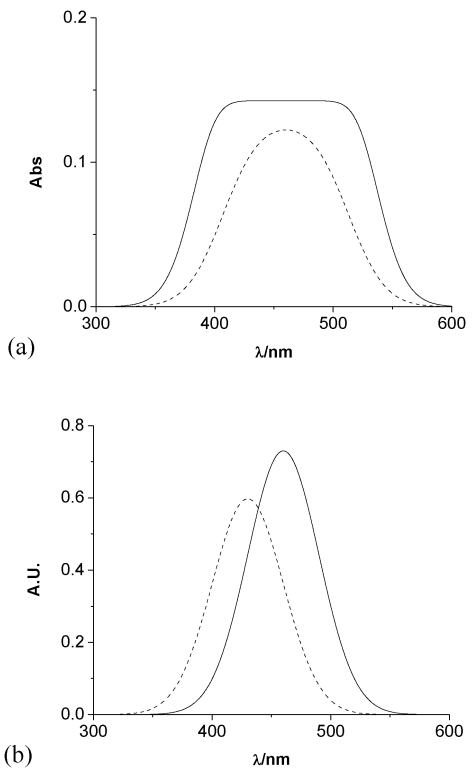

Fig. 5 Modeling the UV-Vis spectrum (a) and CD spectrum (b) distorted by the AF effect at different concentrations.[13] The solid line is at a higher concentration, dashed line is at a lower concentration.

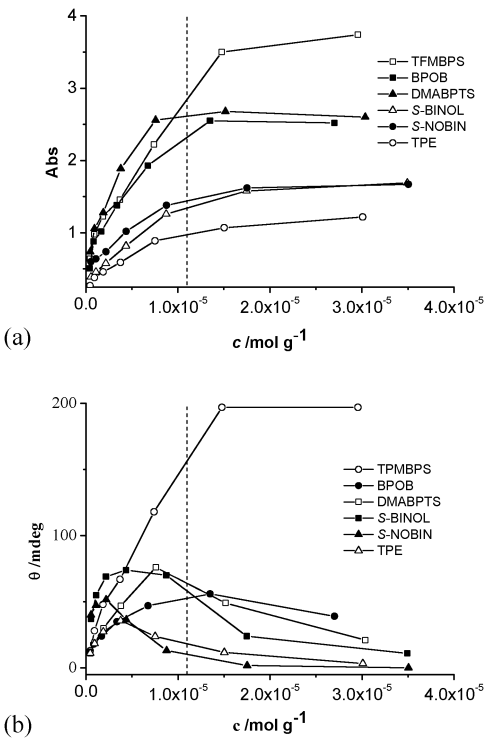

Fig. 6 Intensity of typical absorbance (a) and CD (b) bands of atropisomeric compounds at different concentrations.

Table 1 Torsion angle and maximum CD intensity concentration of atropisomeric compounds

Compound	Wavelength of the CE/nm	Concentration of the maximum intensity of the related CE/m m^{-1}	Concentration of the maximum intensity of the related CE (10^{-6} mol g^{-1})	Torsion angle/°
TFMBPS	333–342	1/200	14.8	12.8
BPOB	369	1/200	13.5	14.6
DMABPTS	299	1/400	7.59	51.8
BINOL	242–264	1/800	4.36	81.7
NOBIN	250–268	1/1600	2.19	87.9
TPE	288	1/800	3.76	82.2

affection of the stray-light when the absorbance is too high. A CD spectrometer measures CD as a ratio of an AC and a DC signal.[14] The DC signal carries the information on the sample absorption. The stray-light becomes the dominant part of the DC component at very high absorbance. This will force the CD signal to move toward zero. The decreasing of the positive CE around 250 nm at higher concentrations may come down for this reason.

However, it is still hard to explain why the maximum intensity of the bands in the CD spectra of TPE appears at quite a low concentration such as 1/800 (see the left region of the dashed line in Fig. 6b). The scattering effect at such low concentrations is too low to affect the linearity relation between the absorbance value and the concentrations. The affection of the stray-light is also trivial. Absorbance curves related to the points at the right of the dashed line are smooth and clear. According to the papers mentioned above, it is a little farfetched to consider this phenomenon to be derived from the scattering effect at such low concentrations. The influence of the AF effect has also been reduced by the decreasing concentration, let alone that in the previous paragraphs the AF effect has been considered to be unable to cause the inverse concentration-dependent effect solely by itself. It is remarkable that the torsion angle of these three atropisomeric compounds whose maximum intensity appears at lower concentrations is much larger than others (Table 1). It seems that a relation may exist between the molecular structures and the inverse concentration-dependent effect occurring at lower concentrations. Further investigation is being carried out in our lab.

Conclusions

In conclusion, a wavelength shift and an inverse concentration-dependence with the decreasing concentration have been observed in the solid-state CD spectra of six atropisomeric compounds. The wavelength shift has been fairly explained by the AF effect. The inverse concentration-dependence occurring at higher concentrations has been considered to be the result of the scattering effect, or the combined effect of the scattering and AF effect. For *S*-BINOL and *S*-NOBIN, such effects occurring at lower concentrations can be considered as the affection of the stray-light when the absorbance is too high. For TPE, it cannot be simply explained by these effects. Perhaps it may be related to the torsions in some special molecular structures.

As a summary and reflection of our works in the past years,[16,21,27–32] several points are essential for obtaining CD spectra of solid samples by the microcrystalline pellet method: (1) measure the sample at suitable concentration as low as possible to provide acceptable CE. (2) Collect the transmission absorption spectra of the same pellet simultaneously with CD spectra to confirm whether the scattering effect occurred. (3) Measure the sample at a series of different concentrations to ascertain if a wavelength shift or inverse concentration-dependence appeared.

Acknowledgements

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