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# Hydrophilic carotenoids: facile syntheses of carotenoid oxime hydrochlorides as long-chain, highly unsaturated cationic (bola)amphiphiles

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ABSTRACT

Stable cationic carotenoid aggregates — predominantly of the *J*-type — develop when the hydrochlorides of carotenoid aldoximes and ketoximes are exposed to water. The oxime hydrochlorides are obtained by simple syntheses from commercially available food color carotenoids. Bluish-purple, unstable transient compounds were observed during hydrochlorination performed at liquid nitrogen temperature.

## 1. Introduction

The first study of hydrophobic, highly unsaturated polyenic carotenoids in water dates back to 1931 (von Euler et al., 1931). Since then, nearly all investigations of carotenoids in aqueous solutions have been hampered by their low hydrophilicity, water-soluble crocin being an extraordinary exception (Nalum Naess et al., 2006). The inherent low water-affinity of carotenoids poses a serious obstacle for application in medicine and food technology and, consequently, elaborate formulation processes have been invented to circumvent their hydrophobicity (Horn and Rieger, 2001; Lockwood et al., 2003; Lüddecke et al., 1999). Recently, increasing attention has been paid to the synthesis of hydrophilic carotenoids, which can be dissolved or dispersed in water (Foss et al., 2003, 2005c, 2006). Water-soluble carotenoids are immediately reactive as antioxidants and $^1O_2$-quenchers, whereas dispersions of self-aggregating carotenoids are more inert. Such aggregates can withstand harsh conditions and typically will only operate as antioxidants and quenchers when contacting a (biological) milieu in which the aggregates are disrupted (Sliwka et al., 2007; Jackson et al., 2004; Foss et al., 2004; Nadolski et al., 2006; Cantrell et al., 2003). Since self-aggregating and therefore self-formulating carotenoids capture significant interest as potential food colorants and pharmaceuticals, a simple chemical method to change inherent hydrophobicity into hydrophilicity would be useful. We looked for a facile modification of carotenoids with small hydrophilic groups and presumed that the syntheses of carotenoid oxime hydrochlorides would present a straightforward way to hydrophilicity. The reaction of aldehydes and ketones with hydroxylamine to aldoximes and ketoximes is known to proceed in many cases quantitatively (Bryant and Smith, 1935). While oximes can be less soluble than the corresponding carboxyl compounds — as found for some carotenoid oximes (Entschel and Karrer, 1958; Sliwka and Liaaen-Jensen, 1993) — the hygroscopic nature of oxime hydrochlorides was recognized in early investigations (Janny, 1883; Beckmann, 1909). Contradictory results have been reported on the stability of oxime hydrochlorides in water. On the one hand they seem to hydrolyze slowly when dissolved, while on the other hand, water is used for recrystallization of oxime hydrochlorides; dissociation into oxime and HCl does not occur before ~100 °C (Janny, 1883; Petraczek, 1883; Brady and Dunn, 1923; Kitano et al., 1983). Oxygen protonated oximes are unstable (Saito et al., 1964). Neither protonation of carotenoid oximes — although prepared to introduce hydrophilicity — nor of related annulene oximes has been reported (Entschel and Karrer, 1958; Benade, 2001; Ojima et al., 1985).

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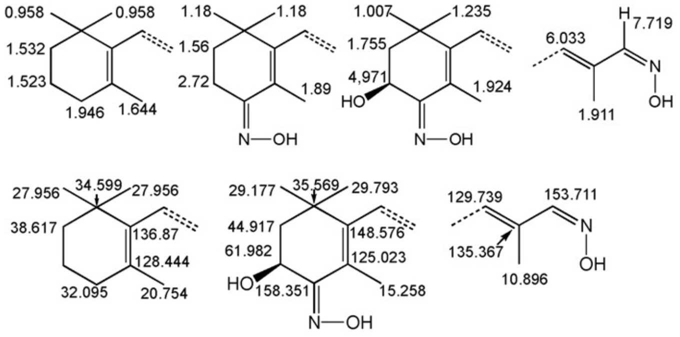
## 2. Experimental procedures

### 2.1. Synthesis of oximes

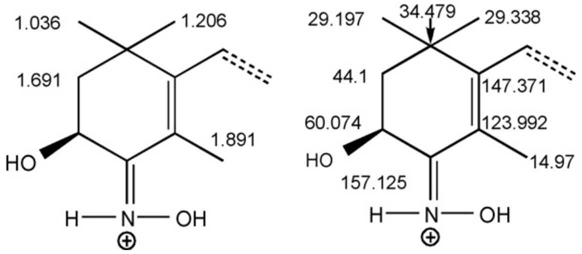
Ald **1**, Ech **2**, Cant **3** and Ast **4** (ca. 20 mmol) were reacted in pyridine (2 ml) with hydoxyamine hydrochloride (ca. 10 time molar excess) and stirred at 60 °C until the reaction was completed (TLC evidence). Representative reaction times: Ald 4 h, Ech 24 h, Cant 48 h, and Asta 3 h. $CH_2Cl_2$ (50 ml) was added and the organic phases were washed three times with water (50 ml) and sat. NaCl-solution. The organic phase was dried over $MgSO_4$ and the solvent evaporated, giving the dark colored Carox. IR (film on NaCl plates) showed the disappearance of the C=O group. UV–VIS ($\lambda_{max}$, $CH_2Cl_2$, nm): Aldox 456, Echox 463, Cantox 462, Astox 456; Aldox 448 (THF), Astox 467 (THF). MS (EI, $M^+$): Aldox 431 $M^+$, 414 $M^+$-OH, 339 $M^+$-92 (toluene); Echox 565 $M^+$, 534 $M^+$-31 (NOH), 573 $M^+$-92; Cantox 594 $M^+$, 577 $M^+$-OH, 563 $M^+$-31; Astox 626 $M^+$, 595 $M^+$-31. HRMS: Aldox, calc. for $C_{30}H_{41}NO$ 431.3188 $[M]^+$; found 431.3167. AldoxH$^+$, calc. for $C_{30}H_{42}ClNO$ 467.2955 $[M]^+$, $Cl^-$ 34.9694; found 431.3191, $Cl^-$ 34.9699. Echox, calc. for $C_{40}H_{55}NO$ 565.4284 $[M]^+$; found 565.4269. EchoxH$^+$, calc. for $C_{40}H_{56}ClNO$ 601.4050 $[M]^+$, $Cl^-$ 34.9694; found 565.4211, $Cl^-$ 34.9698. Cantox, calc. for $C_{40}H_{54}N_2O_2$ 594.4185 $[M]^+$; found 594.4178. CantoxH$_2^{2+}$, calc. for $C_{40}H_{56}Cl_2N_2O_2$ 666.3719 $[M]^+$, $Cl^-$ 34.9694; found 594.4164, $Cl^-$ 34.9698. Astox, calc. for $C_{40}H_{54}N_2O_4$ 626.4084 $[M]^+$; found 626.4076. AstoxH$_2^{2+}$, calc. for $C_{41}H_{59}$ $Cl_2N_2O_4$ 698.3617 $[M]^+$, $Cl^-$ 34.9694; found 626.4074, $Cl^-$ 34.9698.

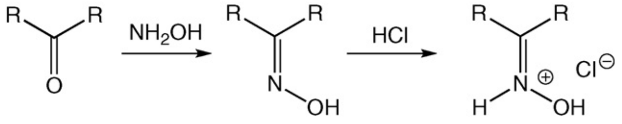
$^1H$ NMR, $^{13}C$ NMR (600 or 300 MHz, DMF-$d_7$ or DMSO-$d_6$): polyene chain signals at 6–6.8 and 125–140 ppm.



### 2.2. Synthesis of oxime hydrochlorides

The oximes were dissolved in THF and HCl–gas was bubbled into the solution. The end of the reaction was identified after a few seconds when the color of the solution suddenly increased in intensity. The solution was flushed with nitrogen and slightly warmed to facilitate the evaporation of the solvent. UV–VIS ($\lambda_{max}$, $CH_2Cl_2$, nm): AldoxH$^+$ 456, EchoxH$^+$ 462, CantoxH$_2^{2+}$ 467, AstoxH$_2^{2+}$ 468. $^1H$ NMR, $^{13}C$ NMR (600 or 300 MHz, DMF-$d_7$ or DMSO-$d_6$): AldoxH$^+$ broad peaks from charge delocalization, representative example for resolved peaks AstoxH$_2^{2+}$(DMSO-$d_6$): polyene chain signals at 6–6.8 and 125–140 ppm.





**Scheme 1.**

Capillary electrophoresis (Beckman P/ACE MDQ) with detection at wavelengths between 300 and 500 nm showed a strong peak for AldoxH$^+$ and CaroxH$_n^+$, accompanied by a second minor peak in the case of CantoxH$_2^{2+}$ and AstoxH$_2^{2+}$.

### 2.3. Critical solvent concentration $c_{H_2O}$ and $c_{MeOH}$

The oxime hydrochlorides CaroxH$_n^+$ were each dissolved in MeOH or dispersed in $H_2O$. Then $H_2O$ or MeOH was added, respectively, in 50, 100 or 200 μl-amounts with a syringe and the absorption was measured. Between 40 (AstoxH$_2^{2+}$) and 120 (AldoxH$^+$) additions of MeOH or $H_2O$ were monitored for aggregate or monomer absorption, respectively. The spectra were corrected for the concentration changes arising from solvent addition. The critical solvent concentration $c_{H_2O}$ and $c_{MeOH}$ was taken from the absorption spectra showing equal parts of monomer and aggregates.

### 2.4. Aggregate size

Dynamic light scattering measurements were performed using an ALV DLS/SLS-5022F compact goniometer and an ALV-5000/E multiple τ-digital correlator (ALV, Langen, Germany). The light source was a 22 mW He–Ne laser (Uniphase, Witney Oxon, UK). The temperature of the sample in a 9% MeOH–water dispersion was 25 °C, and the scattering angle was set to 30°. The samples were carefully filtered through a 0.8 μm filter. Data analysis was performed with the CONTIN method available in the ALV software package.

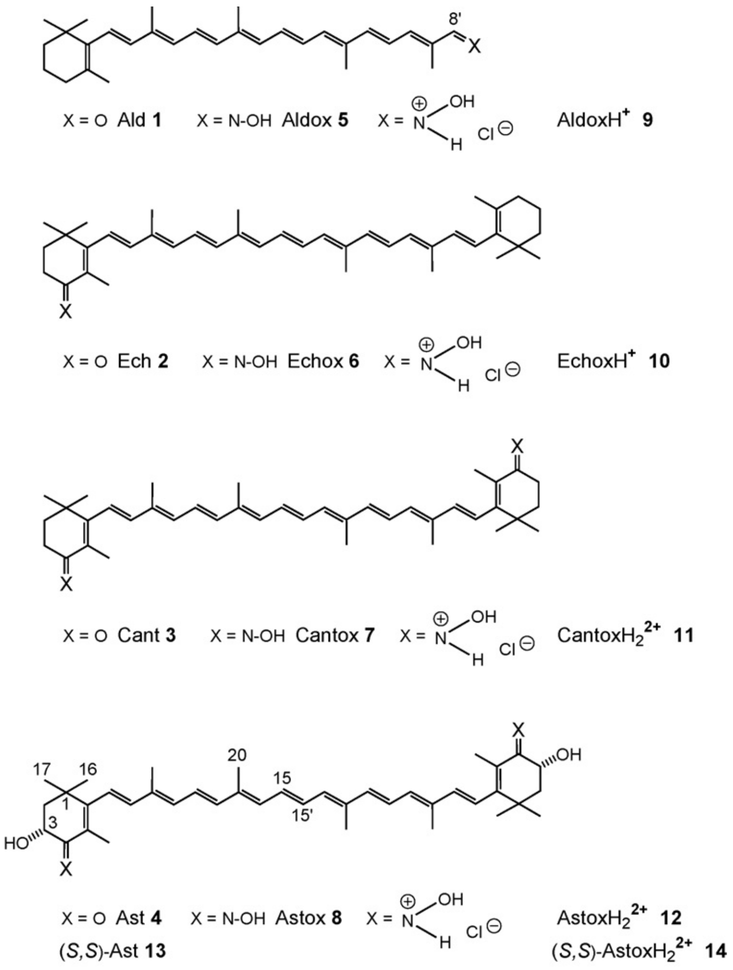
## 3. Results and discussion

### 3.1. Synthesis

The food color carotenoids (Car) C30-aldehyde (E 160e, Ald **1**), canthaxanthin (E 161g, Cant **3**) and astaxanthin (E 161j, Ast **4**) and related echinenone (Ech **2**), were reacted with hydroxylamine to the corresponding oximes Aldox **5**, Echox **6**, Cantox **7** and Astox **8** (Schemes 1 and 2). The oximes were then dissolved in THF and HCl gas was rapidly passed through the solutions until a sudden change in color intensity indicated the end of the reaction. The solutions were flushed with $N_2$ removing HCl and solvent. After drying the residues in high vacuum, amphiphilic oxime hydrochlorides AldoxH$^+$ **9** and EchoxH$^+$ **10**, and bolaamphiphilic CantoxH$_2^{2+}$ **11** and AstoxH$_2^{2+}$ **12** were obtained (Scheme 2).

Capillary electrophoresis identified pure AldoxH$^+$ **9** and EchoxH$^+$ **10**; CantoxH$_2^{2+}$ **11** and AstoxH$_2^{2+}$ **12** were accompanied by some minor cationic impurities. In order to test the stability against hydrolysis AldoxH$^+$ **9** was stirred in water for 2 days at room temperature. Subsequent azeotropic drying resulted in a product that had the same retention time in the electropherogram as AldoxH$^+$ **9** before treatment with water.

The $\lambda_{max}$ of the four CaroxH$_n^+$ — and also of the four Carox (Kuhn and Grundmann, 1932) — appeared at lower wavelengths than their parent compounds, the hypsochromic shift being more pronounced for the dioximes (Table 1, Fig. 1). An increase in absorption after protonation of unsaturated oximes has rarely been observed (Mukai, 1960; Pearson and Watts, 1955). In contrast, protonated



**Scheme 2.**

Schiff bases of carotenoids are blue (Kolsouzidis, 2004). When HCl was introduced to Astox **8**, dissolved in acetone/3-methylpentane 1:1 and cooled with liquid $N_2$, the solution turned bluish-purple. The color was specific for the reaction with the oxime, since HCl gas, introduced to a cooled solution of Ast **4** did not result in a bluish product. Warming-up of the bluish solution gave orange AstoxH$_2^{2+}$ **12**. Cationic, blue carotenoids can be very stable at room temperature (Carr and Price, 1926; Kildahl-Andersen et al., 2006). The $^1$H NMR spectra of AldoxH$^+$ **9** — the functional group is in-plane of the polyene chain — presented broad, irresolvable signals suggesting charge delocalization, nonetheless without a bathochromic effect in the VIS-spectra. In the NMR spectrum of AstoxH$_2^{2+}$ **12** — the functional group is out-of-plane of the polyene chain —proton signals were significantly shifted upfield for H-C2, H-C17, H-C20 and notable upfield shifts of carbon signals were recorded for C1, C3 and C20 (Fig. 2). Within the polyene chain of AstoxH$_2^{2+}$ **12** the shift changes are small ruling out charge delocalization.

**Table 1**
Absorption of Car, Carox and CaroxH$_n$$^+$.

| | λ (nm) $CH_2Cl_2$ | | λ (nm) $CH_2Cl_2$ |
|---|---|---|---|
| Ald | 465 | Cant | 480 |
| Aldox | 455 | Cantox | 460 |
| AldoxH$^+$ | 455 | CantoxH$_2^{2+}$ | 465 |
| Ech | 470 | Ast | 485 |
| Echox | 460 | Astox | 455 |
| EchoxH$^+$ | 460 | AstoxH$_2^{2+}$ | 470 |

### *3.2. Aggregation and surface tension*

VIS-spectroscopy of EchoxH$^+$ **10** in water showed a broad absorption maxima at $\lambda \approx 540$ nm. Aggregation resulting in bathochromic shifts are commonly, but not necessarily correctly, associated with the formation of *J*-(head to tail) aggregates (Horn and Rieger, 2001; Spano, 2009). Dropwise addition of MeOH to the aqueous EchoxH$^+$-dispersion disrupted the aggregates and a

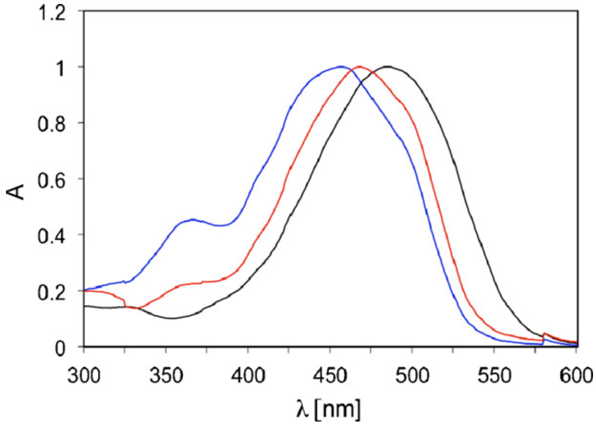


**Fig. 1.** VIS-spectra of Ast (—) (485 nm), Astox (—) (455 nm) and AstoxH$_2^{2+}$ (—) (470 nm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

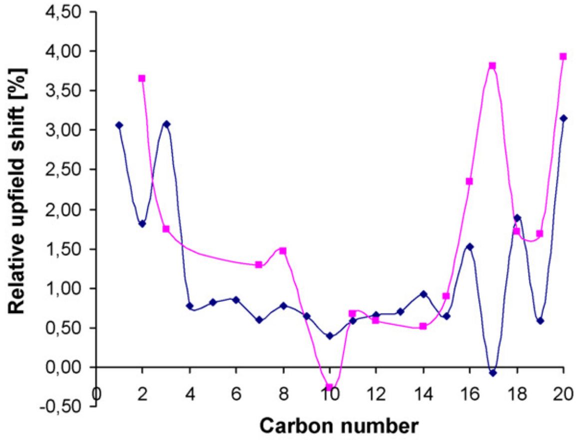


**Fig. 2.** Upfield proton (——) and carbon (——) shift of Astox$H_2^{2+}$ **12** in relation to Astox **8**.

monomolecular solution of Echox$H^+$ was obtained with $\lambda \approx 450$ nm (Fig. 3a). Conversely, when water was added to a solution of Echox$H^+$ **10** in MeOH ($\lambda = 450$ nm) *J*-aggregates were formed with $\lambda \approx 525$ nm (Fig. 3b). Aldox$H^+$ **9** and Cantox$H_2^{2+}$ **11** demonstrated similar behavior. Likewise, adding MeOH to the aqueous *J*-aggregate dispersion of Astox$H_2^{2+}$ **12** ($\lambda \approx 530$ nm) resulted in an Astox$H_2^{2+}$-solution with $\lambda = 460$ nm (Fig. 4a). Surprisingly, when water was added to a methanolic Astox$H_2^{2+}$-solution, *H*-aggregates were obtained with $\lambda = 400$ nm (Fig. 4b). As observed and noted before, the aggregation of hydrophilic carotenoids is not predictable, neither from the molecule structure, nor from the nature of the hydrophilic group or from the experimental conditions (Foss et al., 2005b,a; Billsten et al., 2005). Since Astox$H_2^{2+}$ **12** has more hydrophilic groups than the other compounds we attempted to measure the surface parameters of this dicationic bolaamphiphile. However, it was neither possible to reach the critical aggregate concentration $c_M$ in water nor the Krafft point (warming did not clarify the turbid Astox$H_2^{2+}$ dispersion). Instead, we determined the solvent concentration (water/MeOH) at which the four Carox$H_n^+$ started to aggregate. Adding water to methanolic solutions of the Carox$H_n^+$ had no immediate effect on the VIS-spectra (Figs. 3a and 4a). However, when a particular water concentration was reached aggregates were formed and the absorption maxima of the monomers were shifted to the absorption of the aggregates. The midpoint of the concentration range for monomer/aggregate conversion was taken as the *critical solvent concentration for aggregation*, $c_{H_2O}$ or $c_{MeOH}$. Conversely, when the four Carox$H_n^+$ were dispersed in water and methanol was added, a comparable discontinuity in $\lambda_{max}$ was detected between disruption of aggregates and formation of monomers. For the three ketoxime hydrochlorides Echox$H^+$ **10**, Cantox$H_2^{2+}$ **11** and Astox$H_2^{2+}$ **12** $c_{H_2O}$ and $c_{MeOH}$ were quite similar. Shorter Aldox$H^+$ **9** with its polar group attached at the chain end had slightly different and less accurate values, i.e. the sum of $c_{H_2O}$ and $c_{MeOH}$ had the highest deviation from 100% (Table 2). The determination of $c_{H_2O}$ and $c_{MeOH}$ for the Carox$H_n^+$ is shown in Fig. 5 with Astox$H_2^{2+}$ **12**. In general, the UV–VIS-spectra and, consequently, the CD spectra of aggregates deviate from those of the monomer spectra (Foss et al., 2005a). (*S*,*S*)-Astox$H_2^{2+}$ **14** in MeOH displays one broad negative Cotton effect centered at 270 nm within the region 215–350 nm. The spectrum of the aggregates differs

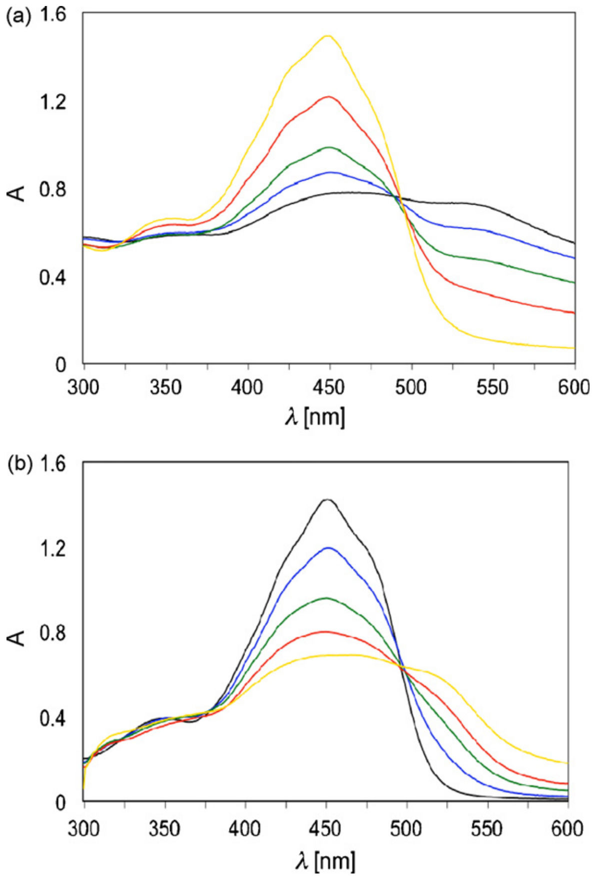


**Fig. 3.** (a) Echox$H^+$ in water adding MeOH: *J*-aggregate disrupted (long-wavelengths tail disappearing). Concentration range 35–85% MeOH, cf. Fig. 4a. (b) Echox$H^+$ in MeOH (450 nm) adding water: *J*-aggregate formed (long-wavelengths tail appearing). Concentration range 0–50% $H_2O$, cf. Fig. 4b.

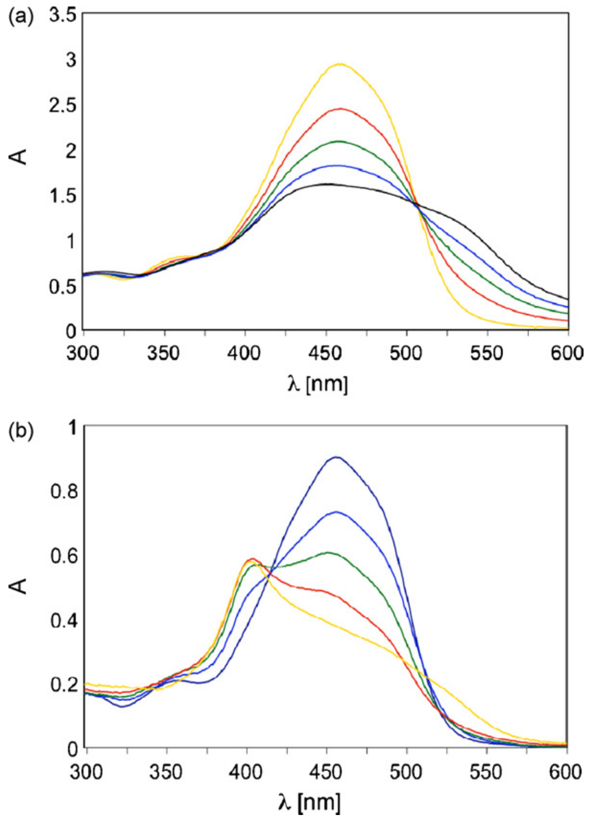


**Fig. 4.** (a) Astox$H_2^{2+}$ in water adding MeOH: *J*-aggregate disrupted (long-wavelengths tail disappearing). For concentration range see Fig. 5a. (b) Astox$H_2^{2+}$ in MeOH (450 nm) adding water: *H*-aggregate formed (short-wavelength peak). For concentration range see Fig. 5b.

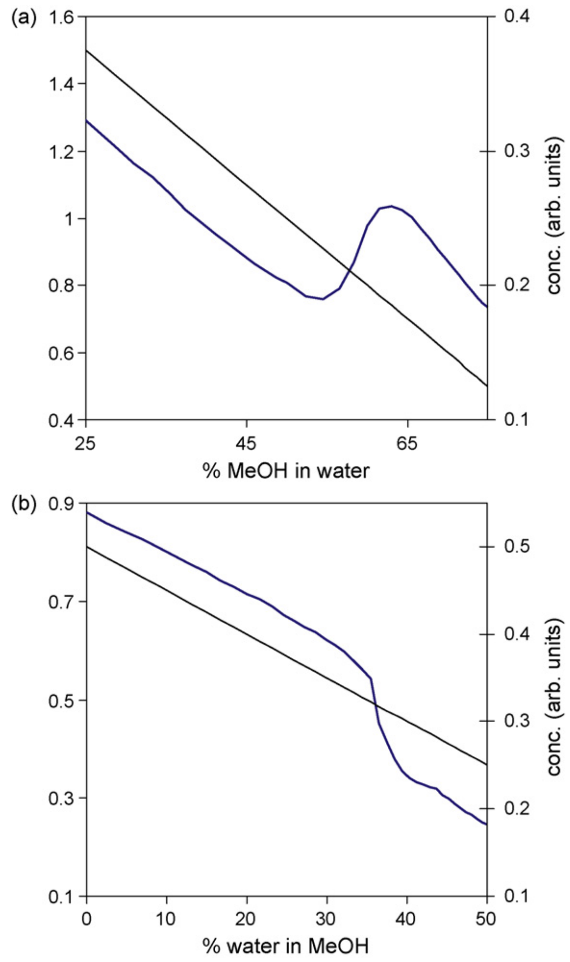


**Fig. 5.** (a) Determination of $c_{H_2O}$: $AstoxH_2^{2+}$ in water adding MeOH. (b) Determination of $c_{MeOH}$: $AstoxH_2^{2+}$ in MeOH adding water.

from that of the monomer with two negative chiroptical absorption bands at 255 and 320 nm; within the aggregates the chromophoric molecules interact expressing supramolecular chirality, Fig. 6.

### *3.3. Aggregate size*

The size of the aggregates in an aqueous solution with 9% MeOH were determined by dynamic light scattering (DLS). Short-chain monopolar $AldoxH^+$ **12** formed aggregates with the smallest equivalent hydrodynamic radius $r_H$ whereas monopolar $EchoxH^+$ **10** gave aggregates with the largest $r_H$ (Fig. 7).

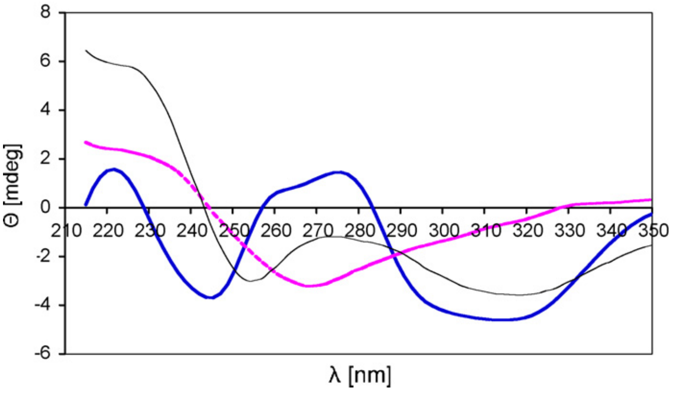


**Fig. 6.** CD spectrum of (*S*,*S*)-Ast **13** in MeOH (——) and of (*S*,*S*)-$AstoxH_2^{2+}$ **14** in MeOH (– – –) and water (—). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

**Table 2**
Critical concentrations of $CaroxH_n^+$.

| | $H_2O$ to $CaroxH_n^+$-solution in MeOH $c_{H_2O}$ (% in MeOH) | MeOH to $CaroxH_n^+$-dispersion in $H_2O$ $c_{MeOH}$ (% in $H_2O$) |
|---|---|---|
| $AldoxH^+$ | 38 | 61 |
| $EchoxH^+$ | 38 | 62 |
| $CantoxH_2^{2+}$ | 39 | 62 |
| $AstoxH_2^{2+}$ | 32 | 72 |

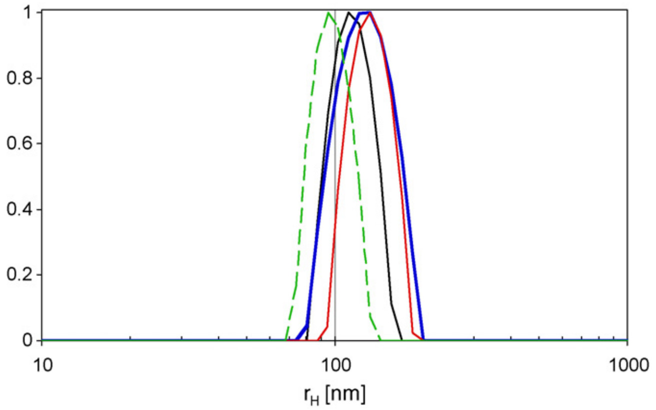


**Fig. 7.** Aggregate size of $CaroxH^+$ in $H_2O$–MeOH 10:1, determined by DLS: (– – –) $AldoxH^+$ **9** $r_H$ = 95 nm, (—) $AstoxH_2^{2+}$ **12** $r_H$ = 110 nm, (——) $CantoxH_2^{2+}$ **11** $r_H$ = 125 nm and (——) $EchoxH^+$ **10** $r_H$ = 130 nm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

## 4. Conclusion

The synthetically prepared $CaroxH_n^+$ did not possess the distinct hydrophilicity of previously synthesized carotenoid derivatives (Foss et al., 2006). Nevertheless, the four $CaroxH_n^+$ compounds were dispersible in water with a minor amount of MeOH. In contrast, the parent compounds are non-dispersible in water and, with the exception of Ald **1**, also poorly soluble in MeOH. Oximation and subsequent hydrochlorination of the commercially available carotenoids C30-aldehyd **1**, canthaxanthin (**3**), astaxanthin (**4**) and, analogously, of citranaxanthin, represents a straightforward way to study carotenoid aggregates, otherwise prepared with xenobiotic detergents (Burke et al., 2001). As an example: the optimal water content for the formation of carotenoid triplets ($^1O_2$-quenching) and carotenoid cation radicals (antioxidant ability) was determined with $AldoxH^+$ **9** (Sliwka et al., 2007).

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