



## Electron uptake by classical electron donators: astaxanthin and carotenoid aldehydes

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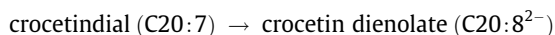
Electron transfer

### ABSTRACT

Carotenoids are prime examples for antioxidants: they donate electrons to noxious radicals. Density functional calculations anticipate the possibility of electron uptake by carotenoids. This prediction has been confirmed experimentally: carbonyl carotenoids, including the super-antioxidant astaxanthin, easily take up electrons and react as antireductants.

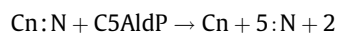
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The electron rich polyenic carotenoids (Car) are eminent electron donators to reactive radicals. This specific property of providing electrons to noxious radicals and converting them into benign homologs made carotenoids legendary as antioxidants.<sup>1</sup> The antioxidant qualities of carotenoids culminate in astaxanthin (Ast), the excellent class 1 super-antioxidant.<sup>2–4</sup> The uptake of electrons by Car has not yet been observed in nature, although the scavenging of superoxide anion radicals  $O_2^{\bullet-}$  occurs by electron release to Car.<sup>5,6</sup> Cyclic polyenes such as annulenes and benzenoids straightforwardly attract electrons (Birch reduction).<sup>7,8</sup> Contrastingly, oblong polyenes defy capturing electrons. Procedures with alkali metals are quite elaborated,<sup>9</sup> producing  $Car^{\bullet-}$  and  $Car^{2-}$  electrochemically, with laser or nuclear radiation, requires specific instruments.<sup>10–12</sup> Nevertheless, it has been predicted theoretically that Car could favorably act as electron acceptors.<sup>13</sup> It was then found in a simple bench-top experiment that a specific carotenoid dialdehyde accepted electrons from the electron donator alkaline  $DMSO = DMSO^- = H_3C(S=O)CH_2^-$ .<sup>14</sup> In this trial, the electron uptake reaction

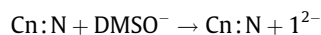


was confirmed spectroscopically and by analyzing secondary products. We have now synthesized several homologous carotenoid

dialdehydes  $C_n$  ( $n$  = number of carbon atoms) with  $N$   $C=C$  bonds:  $C_n:N$  (Fig. 1). The electron transfer reactions of these aldehydes and diketone Ast were systematically investigated experimentally and by molecular modeling. The dialdehydes were synthesized with Wittig salt C5P [Scheme 1, Figs. 2, and 1S in the Supplementary data].<sup>15</sup>



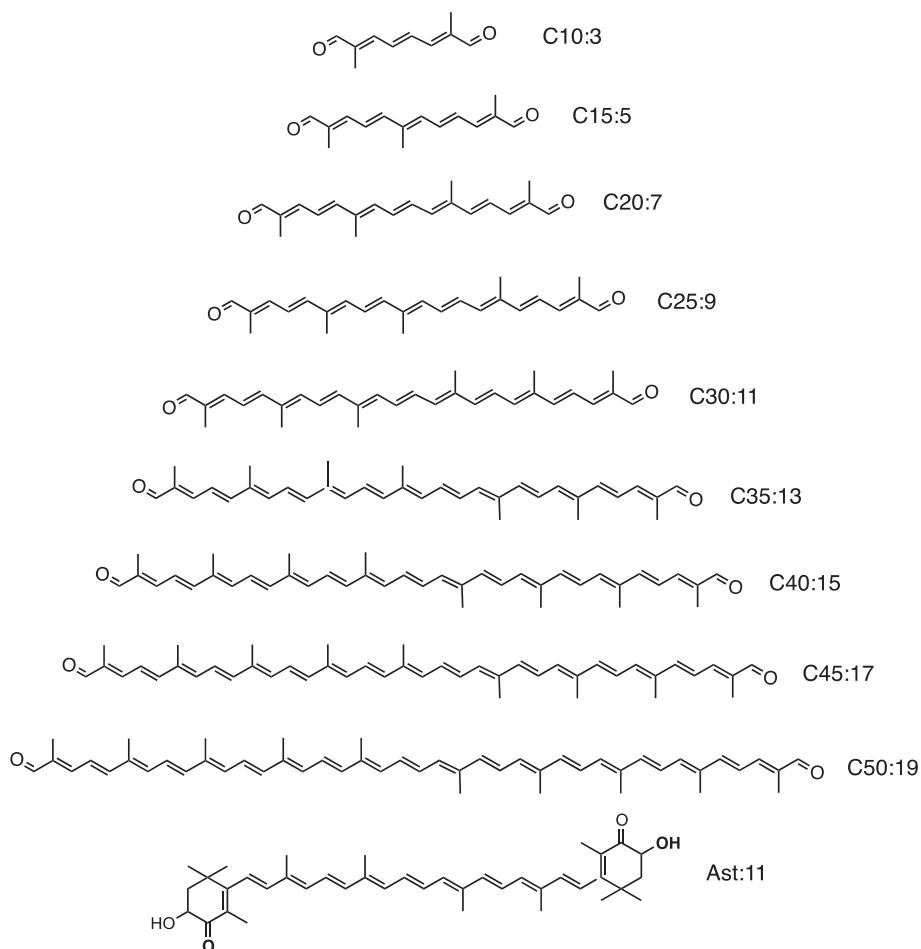
The dialdehydes were dissolved in DMSO and filled in a quartz cuvette; under nitrogen a minute amount of  $DMSO^-$  was injected resulting in an immediate bathochromic color change indicating the formation of dienolates with an additional double bond (Scheme 2, Figs. 3, and 2S):



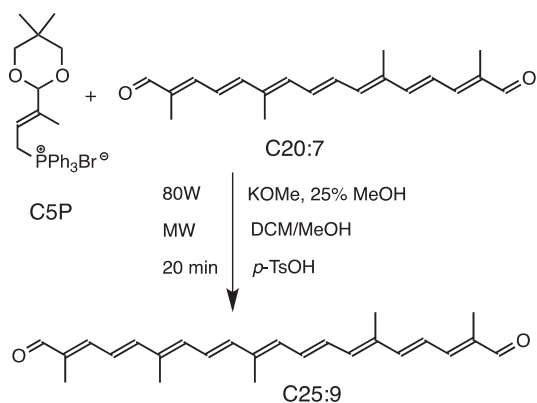
The limiting solvation in DMSO was reached for the elongation reaction with  $C_{45}:17$  and with  $C_{50}:19$  for spectra recording. The observed color conversion of Ast:11 represents an analogous reaction to Ast:12<sup>2-</sup> (Table 1S Supplementary data). Despite extensive investigations the role of  $DMSO^-$  in the electron transfer reaction remains ambiguous, especially concerning structure and fate of the electron donator species.<sup>16</sup> Since the reaction occurs in the presence of  $N_2O$  ( $Car^{\bullet-}$  scavenger)<sup>17</sup> a direct two-electron uptake (one electron to each of the  $C=O$  groups) is probable (Scheme 2) precluding a consecutive one-electron uptake via  $C_n^{\bullet-}$ . There was no obvious difference in the reaction of  $C_n$  and Ast; an exception is  $C_{10}:3$ , which showed a retarded color change. The  $DMSO^-$  reaction reminds of electron transfer from sodium to  $C=O$  groups (Bouveault-Blanc reduction).

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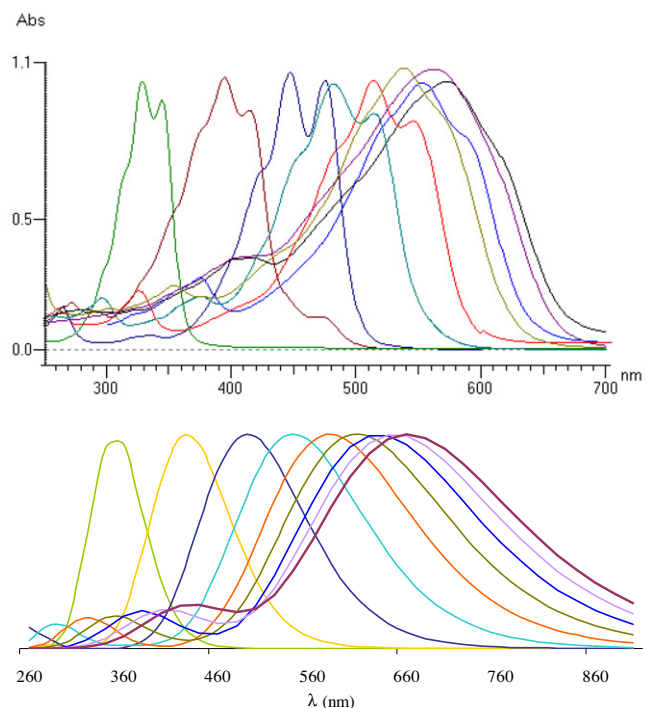


**Figure 1.** Schematic representation of the investigated carotenoids.

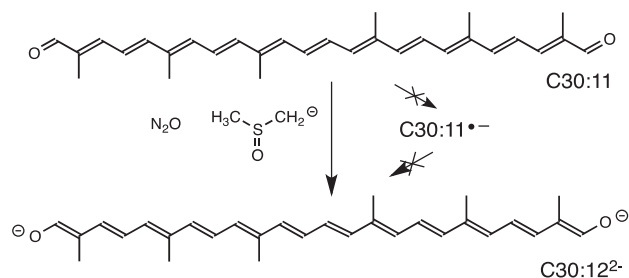


**Scheme 1.** Representative dialdehyde synthesis.

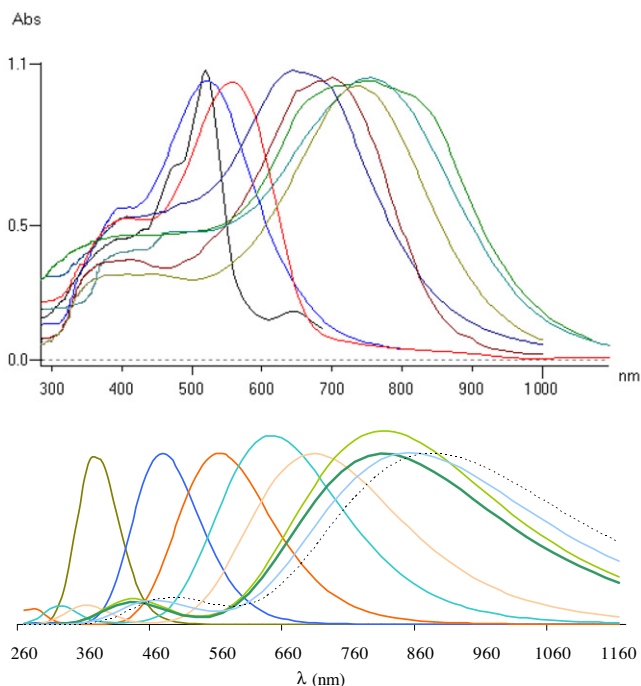
The electron transfer from and to Cn and Ast in relation to N was validated by quantum chemical calculations, which correspondingly established the molecular structure, simulated the absorption spectra, and determined the reaction energy. C10:3, C15:5, and C20:7 are straight polyenes; the other molecules become increasingly bended with extended N (Fig. 3S). The shape of Cn<sup>2-</sup> and Ast<sup>2-</sup> was similar to the neutral molecules showing the characteristic alteration of bonding character: the formal C=C bonds (central C=C in C50:19 *l* = 0.138 nm) convert into formal C–C bonds (central C–C in C50:20<sup>2-</sup> *l* = 0.144 nm), the equalized bond lengths express conjugation and charge delocalization. The



**Figure 2.** Experimental and theoretical (arbitrary units for absorption) spectra of dialdehydes Cn in DMSO: C10:3 (—), C15:5 (—), C20:7 (—), C25:9 (—), C30:11 (—), C35:13 (—), C40:15 (—), C45:17 (—), C50:19 (—) (See Fig. 1S).

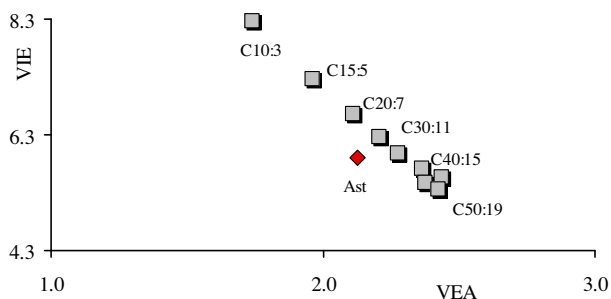


**Scheme 2.** Representative dienolate synthesis by direct two-electron uptake.

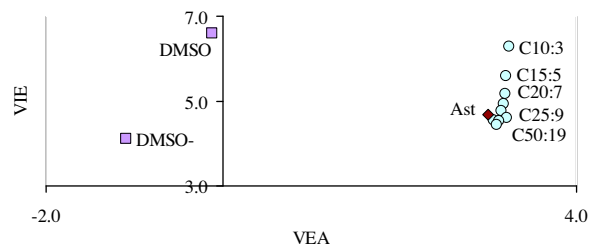


**Figure 3.** Experimental and theoretical (arbitrary units for absorption) spectra of dienolates  $\text{Cn}^{2-}$  in DMSO: C10:3 (—), C15:5 (—), C20:7 (—), C25:9 (—), C30:11 (—), C35:13 (—), C40:15 (—), C45:17 (—), C50:19 (···) only calculated value, see Supplementart data.

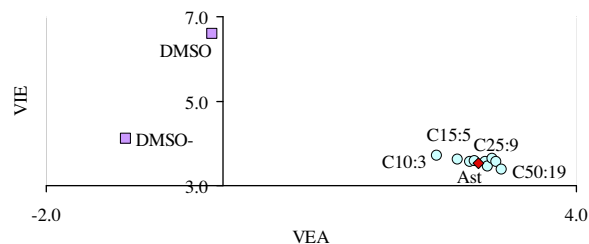
$\lambda_{\text{max}}$  for Cn,  $\text{Cn}^{2-}$ , Ast, and  $\text{Ast}^{2-}$  were computed with time-dependent density functional theory (TD-DFT) using the M06-2X<sup>18</sup> and 6–311 g basis sets<sup>19</sup> with the associated polarized continuum model.<sup>20</sup> While there is a variance in experimental and calculated  $\lambda_{\text{max}}$  for both Cn and  $\text{Cn}^{2-}$  the predictive reliability of the calculation is expressed by the relative low  $\lambda_{\text{calc}}/\lambda_{\text{exp}}$  ratio (Table 1S). The experimental and calculated Cn and  $\text{Cn}^{2-}$  spectra asymptotically reached a limiting value (Figs. 2 and 3)



**Figure 4.** VIE and VEA (in eV) of Cn and Ast in the gas phase.



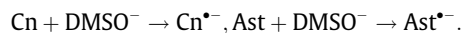
**Figure 5.** VIE and VEA (in eV) of Cn, Ast, DMSO, and  $\text{DMSO}^-$  calculated in DMSO.



**Figure 6.** VIE and VEA (in eV) of  $\text{Cn}^{2-}$ ,  $\text{Ast}^{2-}$ , DMSO, and  $\text{DMSO}^-$  calculated in DMSO.

The electron donor-acceptor capacity of a molecule is conveniently determined by relating the vertical electron affinity (VEA) with the vertical ionization energy (VIE),<sup>21–24</sup> (see Fig. 4S, Ref. 23). The VEA and VIE of Cn and Ast were initially obtained in the gas phase. The one-electron uptake ability  $\text{Cn} + e^- \rightarrow \text{Cn}^{\bullet-}$  is remarkably linear and increases with expanding chain length (Fig. 4). The best and worst one-electron acceptors in the gas phase are C50:19 and C10:3, respectively.

The calculations for the experimental conditions (see Fig. 5) place  $\text{DMSO}^-$  in the good electron donor region, thus  $\text{DMSO}^-$  transfers an electron to Cn and Ast:

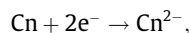


The electron-uptake ability is similar for all Cn independent of N (nearly constant VEA-values) and, therefore, controlled by the C=O groups (Fig. 5, Table 2S). The VIE values for  $\text{Cn}^{\bullet-}$  and  $\text{Ast}^{\bullet-}$  are comparable gathering at the right bottom of the electron acceptor section of Figure 6.

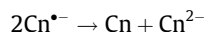
The electron transfer from  $\text{DMSO}^-$  to  $\text{Cn}^{\bullet-}$  (and  $\text{Ast}^{\bullet-}$ ) is therefore obstructed:



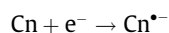
The values of the calculated energy differences  $\Delta E$  favor the experimentally observed two-electron transfer



a disproportionation<sup>9</sup>



would be energetically possible for the larger Cn, whereas the one-electron uptake reaction



is energetically disfavored (Table 1). The calculations also reflect the electron donor property, which increases with N (best antioxidant C50:19).

Natural and commercial carotenoid syntheses deliver various carbonyl carotenoids. Our concordant experimental and

**Table 1**

Energy differences for disproportionation and one- and two-electron uptake reactions (in DMSO)

Car:N	$\Delta E$ (kcal/mol) $2\text{Car}^{\bullet-} \rightarrow \text{Car}^{2-} + \text{Car}$	$\Delta E$ (kcal/mol) $\text{Car} + 2\text{e}^- \rightarrow \text{Car}^{2-}$	$\Delta E$ (kcal/mol) $\text{Car} + \text{e}^- \rightarrow \text{Car}^{\bullet-}$
C10:3	85.5	-77.0	13.79
C15:5	13.31	-146.6	15.10
C20:7	8.97	-149.3	15.93
C25:9	8.56	-150.3	15.63
C30:11	3.11	-151.6	17.67
C35:13	1.48	-152.9	17.84
C40:15	1.93	-151.6	18.25
C45:17	-1.68	-153.5	19.13
C50:19	-5.39	-154.6	20.44
Ast:11	2.94	-147.7	19.75

theoretical results demonstrate that these carotenoids can react contradictorily to the exclusively expected property as electron donating (super) antioxidants. Even if alkaline DMSO may not mirror natural conditions (neither do many antioxidant assays<sup>25</sup>), the presented reaction is a convenient method to investigate the electron uptake reaction of carbonyl carotenoids without relying on typical intricate methods such as pulse radiolysis or electrochemistry.

## Conclusion

Astaxanthin and other carbonyl carotenoids are superior compounds insofar as they both release and attract electrons; these carotenoids can react as antioxidants as well as antireductants.

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## Supplementary data

Supplementary data (experimental and computational details, optimized structures and theoretical results) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.06.029>.

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