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New Colours for Carotenoids – Synthesis of Pyran Polyenes

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In memory of Professor Dr. Hans-Dieter Martin

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A new type of carotenoid has been synthesized with a 2*H*-pyran ring placed in the polyene chain. This compound was successively elongated by Wittig reactions. The pyran-carotenoids obtained show a significant increased $\lambda_{\max}$ compared with carotenoids lacking the pyran ring. A further remarkable bathochromic shift was observed upon protonation to pyranium-carotenoids. The pyranium ring is the distinctive feature of anthocyanidin dyes and has now become an internal part of carotenoids.

Introduction

Carotenoids (in-chain methylated uncharged polyenes built up from oligomerized isoprene units) are important examples for the effect of linearly conjugated double bonds on the wavelength of the main absorption peak $\lambda_{\max}$.[1] The light absorption properties of carotenoids play crucial roles in many biological photoactive systems and in non-linear photonic materials.[2,3] Shifting the absorption to longer wavelengths is often synonymous with increasing activity. However, extending the π system by augmenting the number of double bonds, in particular, beyond the natural boundary (14 C=C)[4] does not lead to a linear rise in $\lambda_{\max}$. There is a limiting value of $\lambda_{\max}$ that cannot be exceeded regardless of the number of double bonds. Different absorption limits have been calculated or extrapolated for hydrocarbon carotenoids, for example, λ_∞ = 608, 665, 700, 910 or 990 nm. The latter value was reduced to a "real" λ_∞ = 825 nm, predicted to be reached with 33 C=C bonds.[5–9] Other equations yield substantially different values of λ_∞.[10,11] Nonetheless, linear-conjugated compounds at λ_∞ probably combine the properties of polyenes, carotenoids and cyanine dyes.[12,13] Whatever the exact value of λ_∞, a carotenoid approaching the absorption limit has not yet been obtained. Synthesis and work-up procedures become more and more complicated as the chain length is extended and the stability of the highly unsaturated compounds is precariously affected. The longest carotenoid so far synthesized includes 23 conjugated double bonds and decomposes even at low temperatures under argon.[9] With unsubstituted polyenes the same degree of (in)stability is reached with 10 C=C bonds.[14] (The degree of conjugation in stable polymer polyenes is too low to be relevant in this context.)[15] Because of the practical limitations of chain elongation, other methods have been employed to approach λ_∞ (Scheme 1): attaching an aldehyde group to the polyene chain,[16] introducing quinone or cyclopentenedione rings,[17,18] transforming carotenones to carotenethiones,[19] replacing the O in the cyclopentenone ring of carotenoids with S[20] or substituting a keto with a dicyanomethylene group.[20,21] The increase in $\lambda_{\max}$ to 630 nm for a carotenoid bearing two pentenedione end-rings and an isopropylidene-norbornadiene moiety in the centre of a common carotenoid chain with seven C=C bonds can be considered an outstanding achievement.[22] A cyclohexene triketone carotenoid would certainly manifest an even larger $\lambda_{\max}$ if it could ever be isolated.[23] The underlying causes of the pronounced bathochromism in the given examples are not directly apparent and cannot be explained in terms of empirical Woodward–Fieser increments.[1,24–26]

Some may object that carotenoids with norbornadiene and polyketone rings are no longer omniconjugated[27] and therefore should not be compared with those compounds with full conjugation between all connected moieties. However, most chemists will classify the compounds shown in part a of Scheme 1 as carotenoids doped with permissible auxochromes. Some doubts may be articulated as to the carotenoid character of a push–pull polyene combining pyridoquinoline and thiobarbituric acid end-groups with $\lambda_{\max}$ = 647 nm (Scheme 1, b).[28] However, a carotenoid with julolidine and thiobarbituric donor/acceptor groups certainly boosts $\lambda_{\max}$ to extremely high values.[12]

As might be expected, the world champion carotenoids in absorption were obtained by elaborate reaction sequences. We present here a reaction, which increases $\lambda_{\max}$

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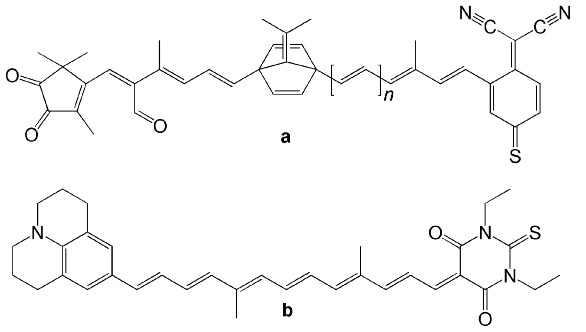


Scheme 1. a) Hypothetical carotenoid molecule, which assembles known auxochromes, b) push–pull carotenoid with the longest λ_{max} known to date.

values of carotenoids without relying on preformed auxochromes or push–pull groups. Our approach is based on the prediction that certain heterocyclic (mesoionic) rings placed within the polyene chain might act as a donor–acceptor spacer, replacing several C=C bonds.[29,30]

Results and Discussion

When yellow apocarotenoid **1** (C_{10} dialdehyde) and $AlCl_3$ were dissolved in dry CH_2Cl_2 the solution immediately turned red. After stirring overnight, a purple compound was isolated. The ^{1}H and ^{13}C NMR spectra revealed the polyenic nature of the product through the signals at 6.6–7.0 and 137–148 ppm, respectively. The aldehydic proton and carbon atoms were identified by the signals at 9.5 and 194 ppm, respectively. The number of protons on the carbon atoms and the direct connectivities were determined by DEPT 90, DEPT 135 and HSQC experiments. The relative positions were assigned precisely by iterative interpretation of the spectra obtained by different 2D NMR techniques: $^{1}H,^{1}H$ COSY (proton–proton correlations), HMBC (long-range H–C correlations), H2BC (isolate different spin systems) and ROESY (relative orientation of the protons). The NMR spectroscopic data combined with the MS and UV/Vis spectra (Figure 1) established the 4-methyl-2*H*-pyran structure **2** connected to a heptatrienal and a pentenedienal chain at C-2 and C-6, respectively. When purple C_{20}-pyran dialdehyde **2** was treated with Wittig salt **3**, the blue C_{30} dialdehyde **4** was obtained. Further elongation of **4** with salt **3** gave green C_{40}-pyran carotenoid **5**. Addition of a small amount of CF_3COOH to solutions of the pyran carotenoids **2**, **4** and **5** in CH_2Cl_2 resulted in strong bathochromic shifts: purple **2** became blue **2^+**, blue **4** changed to pale-grey **4^+** and green **5** turned into colourless **5^+** (Scheme 2 and Scheme 3).

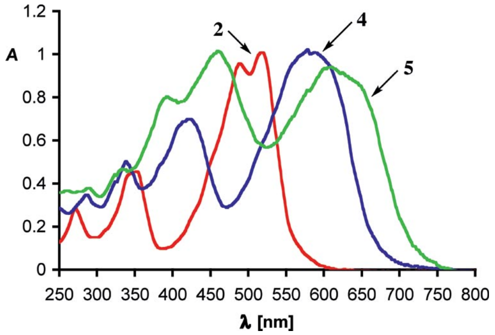
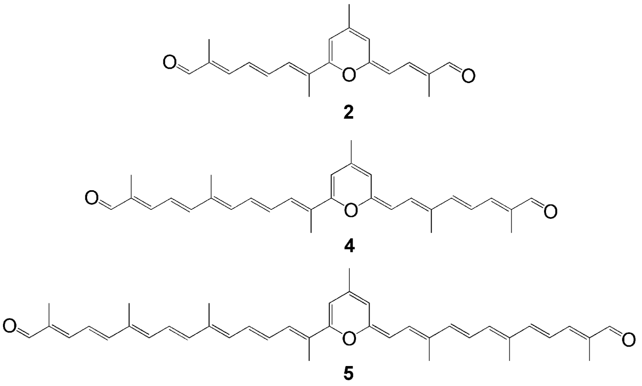
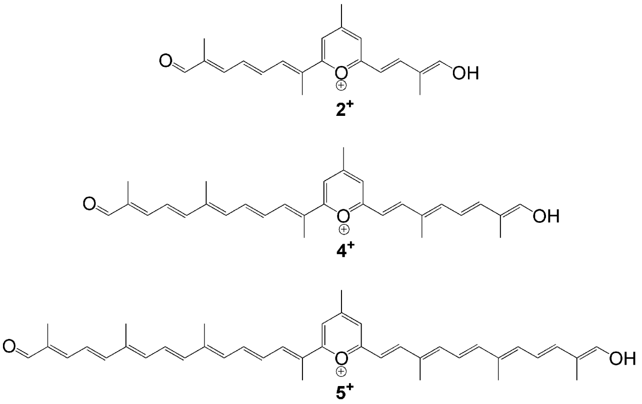


Figure 1. Absorption spectra of pyran carotenoids **2**, **4** and **5** in CH_2Cl_2.

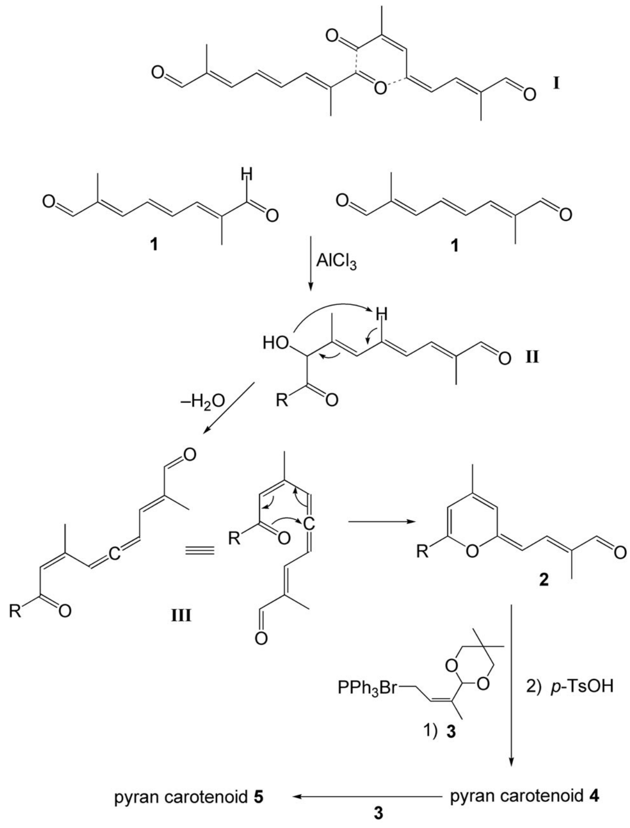


Scheme 2.

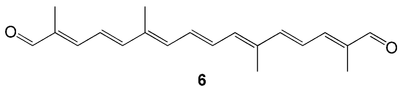


Scheme 3.

Pyran carotenoid **2** appears, at first glance, to be a condensation product of two C_{10} aldehyde molecules **1** (Scheme 4, **I**). Such a reaction seems to be a rather unusual synthesis of 2*H*-pyran and has, to the best of our knowledge, not been reported previously. The mechanism of the carbon–carbon linking sequence between the aldehyde molecules remains unclear. Nevertheless, some similarities with reported metal-catalyzed aldehyde reactions might be considered.[31–34] $AlCl_3$ clearly assists the reaction, C–C bond formation and hydride transfer, to intermediate **II**. Subsequent elimination of H_2O leads to the transient allene **III**, which immediately rearranges to vinylogue α-pyranone **2**. Pyranones and ketene aldehydes have been found to be interchangeable isomers.[35,36] The reaction steps outlined are mentioned only as a tentative mechanism as viable evidence is lacking. Especially intriguing is the observation that pyran formation only proceeds with C_{10} aldehyde **1**; C_{20} aldehyde **6** (Scheme 5) did not react, nor did two molecules of C_{20}-pyran dialdehyde **2** yield directly a C_{40}-dipyran carotenoid.

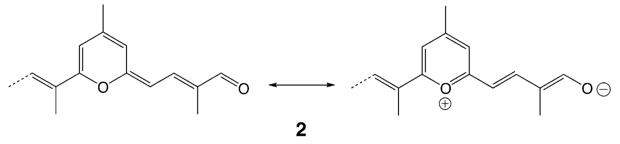


Scheme 4.



Scheme 5.

Compounds **2**, **4** and **5** can be regarded as carotenoids with two *cis* bonds or as a 2*H*-pyran connected to two different polyenal chains. The molecule can also be viewed as a polyene, whose linear conjugation is blocked by an oxo barrier, which results in a deviation of the conjugation through the *cis* bonds. The increase in $\lambda_{\max}$ is illustrated by comparing C_{20}-pyran carotenoid **2** with *trans*-C_{20} dialdehyde **6** (see Table 1). The increase becomes even more accentuated in view of the fact that di-*cis*-carotenoids are generally hypsochromically shifted.[37] The potential conjugation of the oxygen lone-pair electrons with the shorter chain (Scheme 6) may create a one-sided, particularly bathochromically shifting HOMO–LUMO topology[38] (Figure 2), similar to the separated orbital regions in postulated mesoionic polyenes.[29] An irregular orbital localization could again be regarded to be in variance with normal carotenoid conjugation characterized by regular HOMO and LUMO extension. However, a possible different orbital orientation would not prevent the classification of compounds **2**, **4** and **5** as carotenoids because peridinin and pyrroxanthin, including an almost auxochrome-ineffective 2-furanone ring, are definitely carotenoids.[39] The 2*H*-pyran structure is found in many natural compounds and a few 6-polyene-2*H*-pyranones have been isolated.[40]



Scheme 6.

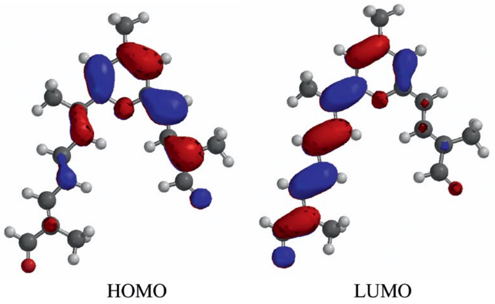


Figure 2. Topology of the HOMO and LUMO in the C_{20}-pyran carotenoid **2** (determined by HF/6-31G*/CH_2Cl_2 in Spartan 08, Wavefunction Irvine CA 92612).

The importance of the pyran ring for the bathochromic shift becomes evident when acid is added to solutions of **2**, **4** or **5** to form the cations $\mathbf{2}^+$, $\mathbf{4}^+$ and $\mathbf{5}^+$ with a proaromatic pyranium (pyranylium, pyrylium) ring in which the charge is assumed to be delocalized along the conjugated chain. The absorption of $\mathbf{2}^+$ is therefore found at a significantly higher $\lambda_{\max}$ than that of the comparable cation without the pyran ring, for example, protonated C_{20} dialdehyde $\mathbf{6}^+$ (Figure 3, Table 1). Transition-energy calculations of a 2-hexadienyl-2*H*-pyranium compound (one polyene chain only) yielded $\lambda_{\max}$ = 652 nm.[41] In fact, the pyranium ring is the crucial chromogen in anthocyanidins.

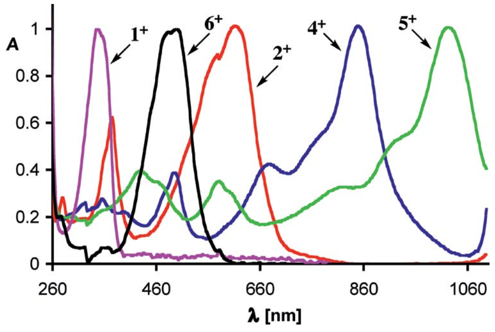


Figure 3. Absorption spectra of carotenoid cations $\mathbf{1}^+$ and $\mathbf{6}^+$ and pyran carotenoid cations $\mathbf{2}^+$, $\mathbf{4}^+$ and $\mathbf{5}^+$ in CH_2Cl_2.

The $\lambda_{\max}$ values of longer-chain pyran carotenoids are required to establish whether compounds **2**, **4** and **5**, and $\mathbf{2}^+$, $\mathbf{4}^+$ and $\mathbf{5}^+$ display the expected non-linear and linear increases in $\lambda_{\max}$, respectively (Figure 4).

Table 1. Absorption of carotenoids and carotenoid cations in CH_2Cl_2 solutions.

	C=C	λ_{max} [nm]
C_{10} **1**	3	330, 350
C_{20} **7**	7	450, 475
C_{20}-pyran **2**	7	350, 520
C_{30}-pyran **4**	11	425, 590
C_{40}-pyran **5**	15	465, 615
C_{10}^+ **1**$^+$	3	350
C_{20}^+ **7**$^+$	7	500
C_{20}-pyran$^+$ **2**$^+$	7	620
C_{30}-pyran$^+$ **4**$^+$	11	855
C_{40}-pyran$^+$ **5**$^+$	15	1030

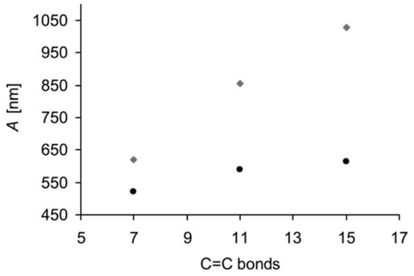


Figure 4. Absorption of the pyran carotenoids **2**, **4** and **5** (●) and the pyranium carotenoids **2**$^+$, **4**$^+$ and **5**$^+$ (♦).

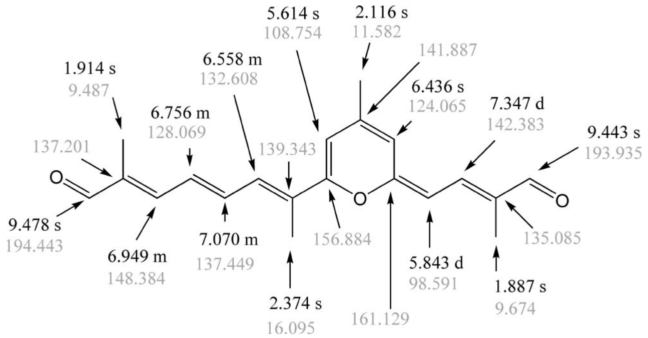
Conclusions

Although the introduction of a pyran ring into the polyene chain does not challenge the records set with norbornadiene or push–pull modifiers for increasing λ_{max}, the pyran carotenoids described are more easily accessible. 2*H*-Pyran represents an effective auxochrome and a mesoionic-like push–pull initiator for polyenes. Pyran carotenoid **5** with 15 C=C bonds clearly outperforms dodecapreno-β,β-carotene with 19 C=C bonds.[42] The merits of the pyran auxochrome become evident after protonation; the formation of the aromatic pyranium ring results in a distinct bathochromic shift. Finally, it has to be emphasized that the pyranium compounds **2**$^+$, **4**$^+$ and **5**$^+$ combine the structural characteristics of the important natural pigments carotenoids and anthocyanidins.

Experimental Section

General: NMR spectra were recorded in $CDCl_3$ with 0.05% TMS on Bruker Avance DPX 400 MHz and 600 MHz instruments. UV/Vis spectra were obtained with a single-beam Helios γ (Thermo Spectronic) and mass spectra (EI, ESI) with a MAT 95XL (ThermoQuest Finnigan). Solvents of spectroscopic quality were used for spectra recording. Solvents for reactions and elutions were of p.a. quality. Carotenoids **1**, **6** and salt **3** were gifts from BASF AG, Ludwigshafen Germany.

C_{20}-Pyran Carotenoid 2: C_{10}-dial (**1**; 500 mg, 2.66 mmol) and $AlCl_3$ (355 mg, 2.66 mmol) were dissolved in dry CH_2Cl_2 (25 mL) and stirred at room temperature under N_2 for 12 h. The reaction mixture was extracted with H_2O (25 mL) and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (hexane/acetone, 8:2, $R_f = 0.27$). Yield: 62%. HRMS: calcd. for $C_{20}H_{22}O_3$ 311.1647 $[M + H]^+$; found 311.1653. UV/Vis: see Figure 1 and Table 1. For ^1H and ^{13}C NMR see Scheme 7.



Scheme 7. Structure and ^1H and ^{13}C NMR data for C_{20}-pyran carotenoid **2**.

C_{30}-Pyran Carotenoid 4: An excess of C_5 Wittig salt **3** (100 mg, 0.22 mmol) and CH_3OK (25%, 69 µL, 0.23 mmol) were dissolved in dry MeOH (5 mL) and stirred at room temperature for 30 min. Carotenoid **2** (5 mg, 0.016 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added and heated at reflux under N_2 for 20 h. H_2O (1 mL) was added and the reaction mixture concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and extracted with H_2O (3×10 mL) and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), a crystal of *p*-toluenesulfonic acid was added and the solution was stirred at room temperature under N_2 for 30 min. The reaction mixture was washed with 5% $NaHCO_3$ (3×10 mL) and H_2O (3×10 mL) and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (hexane/acetone, 8:2, $R_f = 0.28$). HRMS: calcd. for $C_{30}H_{34}O_3$ 443.2581 $[M + H]^+$; found 443.2583. UV/Vis: see Figure 1 and Table 1.

C_{40}-Pyran Carotenoid 5: Carotenoid **4** (4 mg, 0.009 mmol) was treated as described above with an excess of C_5 Wittig salt **3** (100 mg, 0.22 mmol) and CH_3OK (25%, 69 µL, 0.23 mmol) to yield carotenoid **5**. HRMS: calcd. for $C_{40}H_{46}O_3$ 575.3520 $[M + H]^+$; found 575.3508. UV/Vis: see Figure 1 and Table 1.

The pyran compounds were treated and stored as usual for carotenoids (under N_2 and avoiding sunlight) and appeared to be as stable as other carotenoids of the same chain lengths.

Pyranium Carotenoids: Pyranium carotenoids **2**$^+$, **4**$^+$ and **5**$^+$ were obtained by adding trifluoroacetic acid in an amount up to 1% to **2**, **4** and **5** in CH_2Cl_2. UV/Vis: see Figure 3 and Table 1. The addition of pyridine, tributylamine or other bases to the cationic solutions regenerated the uncharged carotenoids. The cationic solutions, stored in closed vials at room temperature, were stable for several months.

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