



## Thiocarbonyl polyenes: monomers, trimers, and thiopyrans

Eugenia M. Sandru, Jan Sielk, Jens Burghaus, Christer L. Øpstad, Nebojsa Simic, Susana Villa Gonzales, Hans-Richard Sliwka <sup>\*</sup>, Vassilia Partali

Department of Chemistry, Norwegian University of Science and Technology, 7491 Trondheim, Norway

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### ABSTRACT

Polyunsaturated conjugated thiocarbonyl compounds (thioxocarotenoids) occur as monomers or react instantaneously to give polyene substituted trithiacyclohexanes and 2*H*-thiopyrans.

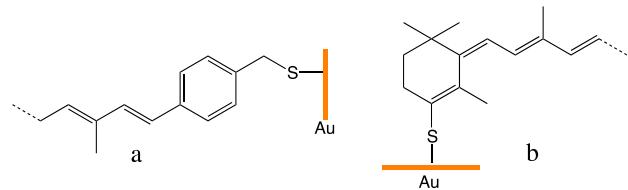
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The preparation of self-assembled monolayers (SAMs) is associated with the reaction of Au surfaces with saturated thiols, thiocyanates, thioesters, thiosulfates, acyclic disulfides, or thiranes.<sup>1</sup> The SAM is formed via a thiolate–Au bond by expelling residual atoms at S (H, CN, CH<sub>3</sub>C=O, SO<sub>3</sub>, and SR) or by breaking the thirane structure. Molecular wire studies require unsaturated SAMs. Polyunsaturated SAMs connected by conjugation via sulfur to Au cannot evolve like saturated SAMs because of instability problems with alkenethiols or thiirenes. Consequently, polyene SAMs were previously connected to gold via an insulating methylene group (Fig. 1a).<sup>2,3</sup> We have found that a long chain unsaturated thionekone assembled via a conjugated polyenolate bonding on Au (Fig. 1b).<sup>4</sup>

Long chain unsaturated aldehydes and ketones are daily digested in the diet as natural ingredients or as added food colors, for example, C30 aldehyde **1** E160e, rhodoxanthin (**5**) E161f, canthaxanthin (**10**) E161g, astaxanthin (**14**) E161j, and citranaxanthin (**18**) E161i (Schemes 1–3 and 5). How do these food colors behave when associated with sulfur? Carotenoids in the presence of sulfur-containing compounds display an often desired color deepening.<sup>5</sup> On the other hand, the occurrence of sulfides accelerates the photodegradation of carotenoids.<sup>6,7</sup> Nonetheless, it was verified that VIS and CD spectra, and, hence, the stability of carotenethiols, were not affected by the –SH group.<sup>2,8–10</sup> While the characteristic color (mostly red or violet with low intensity strength) of saturated thiones can be durable (e.g., thioacetone),<sup>11</sup>

the unsaturated counterparts bear the stigma of ‘too reactive even at low temperature’.<sup>12</sup> For certain, simple thials are unstable, whether they are saturated or unsaturated, cyclic or acyclic; they all trimerize immediately to thiacyclohexanes (1,3,5-trithianes),<sup>13–19</sup> or, rarely, they dimerize to dithianes or dithiacyclobutanes (1,3-dithietanes).<sup>20,21</sup> In contrast, the outcome of a thionekone synthesis is not always predictable. Acyclic thiones are stable or unstable, they may dimerize or trimerize;<sup>14,22,23</sup> cyclic thiones are stable, including  $\alpha,\beta$ -unsaturated cyclohexenethiones, or unstable.<sup>12</sup> The present study was undertaken with the aim of extending our previous investigations with thioxopolymers.

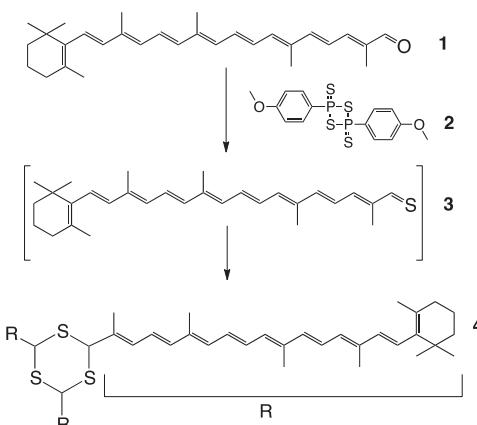
When C<sub>30</sub>-aldehyde **1** was reacted with Lawesson's reagent **2**,<sup>24</sup> the orange toluene solution changed to yellow (Fig. S1 in the Supplementary data). The absence of the C=O band in a IR spectrum together with NMR and MS data suggested instant trimerization of intermediate C<sub>30</sub>-thioaldehyde **3** to propeller-shaped trithiane **4** in the preferred *eq, eq, eq*-conformation<sup>25,26</sup> [(29:3)<sub>3</sub>-trithiane, (29:3)<sub>3</sub>-6S3 in crown ether nomenclature (Scheme 1 and Fig. 2).<sup>27</sup>



**Figure 1.** (a) Polyene connected to Au via an ‘insulator to metal’ arrangement,<sup>2</sup> (b) polyene connected to Au via a conjugated enethiolate bond.<sup>4</sup>

\* Corresponding author. Tel.: +47 73595600; fax: +47 73596255.

E-mail address: hrs@nvg.ntnu.no (H.-R. Sliwka).

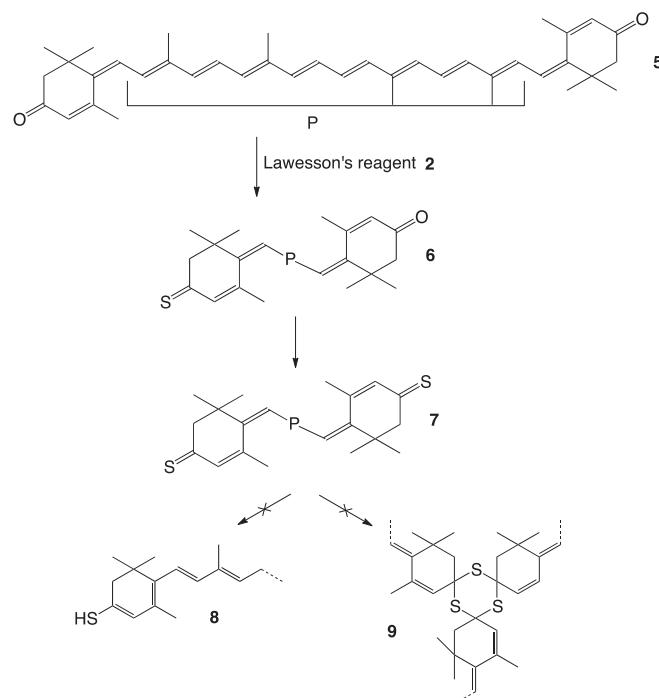
**Scheme 1.**

The reaction of **1** to trithiane **4** via transient thioaldehyde **3** is in line with observations on retinethial and other intermediate thiocaldehydes.<sup>13,28</sup> We suppose that other carotenals like C<sub>30</sub>-aldehyde **1** would similarly react to trithianes.<sup>29</sup>

Trithianes react with Ag and Au salts to give complexes with the intact ring; the ring is also integrally adsorbed on Ag surfaces.<sup>30–32</sup> It is probable that trithiane **4** similarly assembles on Ag or Au surfaces without ring dissociation. Thus, the anticipated solidity of polyenyl trithianes would prevent the formation of nonstop conjugated monolayers on Au. Retinethial not only trimerized to the related trithiane but also formed at lower temperature polyene substituted 4-methyl-2H-thiopyran.<sup>28,33</sup>

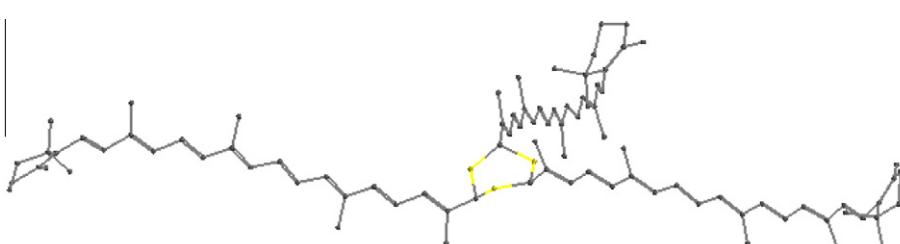
The initial reaction of diketones rhodoxanthin (**5**) and canthaxanthin (**10**) with Lawesson's reagent **2** gave monothiones **6** and **11** with a distinct bathochromic shift in the VIS spectra, similar to the shift of thioechinenone **12** (Schemes 2 and 3).<sup>34</sup> Rhodoxanthin dithione **7** and canthaxanthin dithione **13** were prepared by extending the reaction time, carefully controlling product formation and decomposition (visual evidence). The two thione groups increased  $\lambda_{\max}$  and noticeably decreased the stability of **7** and **13** (Fig. S2 in the Supplementary data). In contrast, a less stable monothione and a more stable dithione were found with the cyclopentenone carotenoid 2,2'-dinor-canthaxanthin.<sup>35</sup> Fading of the characteristic thione color to the shade of the starting compound or to even lighter colors was not observed; therefore, carotenoid monothiones **6** and **11** did not noticeably tautomerize over time to labile enethiols<sup>36,37</sup> for example **8**; nor did they trimerize to trithiane **9** (Scheme 2).<sup>21,23</sup> Since canthaxanthin monothione **11** self-assembled with an enethiolate bond on gold (Fig. 1b)<sup>4</sup> it can be predicted that other cyclohexenethiones<sup>29</sup> will react analogously. Thus, carotenyl cyclohexenethiones are potential candidates for fully conjugated monolayers on Au. Hydroxyketones such as astaxanthin (**14**) (Scheme 3) failed to form thioketones.

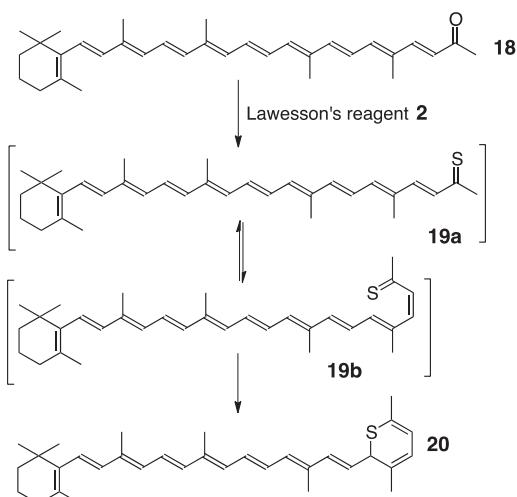
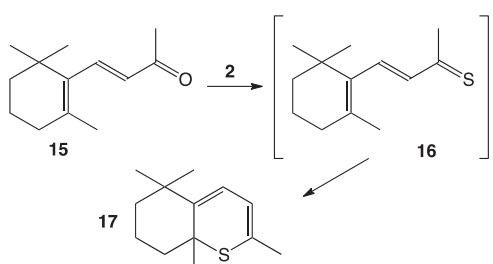
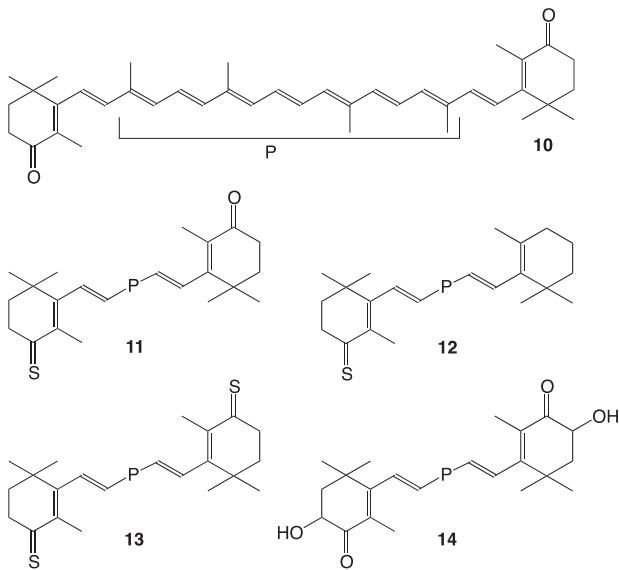
The reaction of sulfur reagent **2** with  $\beta$ -ionone (**15**) (Scheme 4) gave a product, whose mass spectra indicated the replacement of O

**Scheme 2.**

by S. In addition to 1D <sup>1</sup>H and <sup>13</sup>C NMR spectra, the structure of **17** was established by HSQC, COSY, and HMBC spectra, leaving initially just one doubt—the location of one of the two Me groups on the sulfur ring. A 2D NOESY experiment showed no correlation between the allocated Me group at C5 (1.36 ppm) with the non-allocated Me group (1.97). Therefore, the only possible place for the Me group at 1.97 was C-2. Additional proof was attained by running the experiments in DMSO-d<sub>6</sub>, which allowed distinction between protons H-3 and H-4 (in CDCl<sub>3</sub> the shifts coincided). Their vicinal position was then confirmed by COSY and their relative arrangement in the molecule by HMBC. Establishing the 5H-thiocromene structure **17** corroborated the hitherto just once reported reaction of thione **16**.<sup>38</sup> The increase in absorption (25 nm) of thiocromene **17** compared to  $\beta$ -ionone **15** demonstrates imminent auxochrome properties of the 2H-thiopyran ring caused by conjugation of the double bonds with the sulfur orbitals (Figs. S3 and S4 in the Supplementary data).<sup>39,40</sup> Such an auxochrome effect has also been observed in 2H-pyran-carotenoids.<sup>41</sup>

When Lawesson's reagent **2** was reacted with citranaxanthin (**18**), a fading of the color was seen similar to C<sub>30</sub>-aldehyde **1** (Scheme 5, Fig. S5 in the Supplementary data). The frequently reported trimerization to a trithiane was, therefore, anticipated. Yet, mass spectroscopy data of the product pointed to the uptake of only one sulfur atom. The precise assignments of proton and carbons, achieved by iterative interpretation of spectra from different

**Figure 2.** Structure of *eq,eq,eq*-trithiane **4** (MMFF/SYBYL, Spartan 08).



NMR techniques, established the formation of 2-carotenyl-3,6-dimethylthiopyran **20** by 1,6-intramolecular cyclization of intermediate 8'-*cis*-(Z)-thioketone **19b** derived from 8'-*trans*-(E) **19a** (Scheme 5). Chemical shifts of protons and carbons in the polyene chain were in accordance with published NMR data.<sup>42</sup> Other shifts, divergent from the polyene values, indicated the occurrence of an additional structural moiety in the molecule. Particularly the

HMBC experiment undoubtedly pointed to a 6-membered heterocycle including sulfur.

Intuitively, the trimerization of *trans*-thione **19a** to the corresponding trithiane seems more plausible than cyclization of *cis*-thione **19b** to 2*H*-thiopyran, which is not a stable structural unit when lacking stabilizing substituents.<sup>43</sup> Nevertheless, the spontaneous cyclization of polyene thiones **16** and **19** to **17** and **20** could represent pioneering examples of a general approach to 2,6-disubstituted 2*H*-thiopyran polyenes. It is probable that not only citranaxanthin (**18**) but also other alkyl-carotenyl ketones<sup>29</sup> cyclize to 2*H*-thiopyran polyenes. The thiopyran ring lacks an auxochromic influence in **20** due to conjugation interruption between the polyene chain and the perpendicularly oriented sulfur ring (Fig. S6).<sup>45</sup> An auxochromic effect is likewise not seen after protonation of **20**; the resulting color change originates merely from the octaenylum chain, which is not coplanar with the aromatic thiopyrylium chromophore.<sup>41,44</sup> If carotenyl 2*H*-thiopyrans were to assemble by ring breaking on Au, a conjugated monolayer might result.

In summary, unsaturated aldehyde **1** reacted upon thionation to give trithiane, in accordance with trithiane formation from saturated aldehydes. Polyene substituted cyclohexenones form thiones. The polyenyl cyclohexenethiones are processible under normal conditions at laboratory conditions without special precautions.<sup>8</sup> Polyene diones preferentially afforded mono-thiones; dithiones decomposed quickly. In contrast to saturated thiones, methyl-polyenyl thiones cyclized to 2*H*-thiopyrans. The 1,6-cyclization of transient polyene thiones to 2*H*-thiopyrans can be added to the common spontaneous reactions of thiocarbonyl compounds. Polyenyl cyclohexenethiones are promising candidates for assembling conjugated monolayers on Au. Whether molecules **17** and **20** self-assemble on gold surfaces with the intact thiacycle or by dissociative chemisorption is yet to be ascertained.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.10.012>.

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44. The thionation reaction is exemplified with citranxanthin (**18**): 11'-apo-11'-(3,6-dimethyl-2*H*-thiopyran-2-yl)- $\beta$ -carotene (**20**). Lawesson's reagent **2** (70 mg, 0.17 mmol) was dissolved in CS<sub>2</sub> at reflux. Citranxanthin (**18**, 100 mg, 0.218 mmol) was added and refluxed under N<sub>2</sub> for 12 h. The reaction was monitored by TLC on Al<sub>2</sub>O<sub>3</sub> using hexane:toluene:acetonitrile 72:25:3. The crude product was purified by flash chromatography on Al<sub>2</sub>O<sub>3</sub> with hexane:toluene:acetonitrile 94.3:5:0.7 to afford 65 mg **20** (63%);  $\lambda_{\text{max}} = 416 \text{ nm}$  (CH<sub>2</sub>Cl<sub>2</sub>, Fig. S5 in the Supplementary data). HRMS (EI): Calcd: 472.3164, found: *m/z* = 472.3152 (M<sup>+</sup>). The synthesis of other unsaturated and saturated thioxo compounds is reported in Supplementary data.
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