PAPER

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6-*endo* or not 6-*endo*, that is the question: correcting an erroneous structural assignment and mechanistic presumption†

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Careful reading of a published article uncovered a specious structural assignment, which has so far remained unchallenged. An alternate structure has been suggested and the experimental procedure repeated. Subsequently, a more rigorous analytical characterization confirmed the true structure to be a cyclic dimer of the structure proposed in the original paper, thereby negating their singular claim of an otherwise unobserved type of 6-*endo* cyclization.

Introduction

Cyclizations of 5-hexenyl radicals and congeners (Scheme 1) are known to strongly favor the 5-*exo* path,[1] but 6-*endo* products have been isolated, and in some cases may even dominate.[2] As such, 6-*endo* radical cyclizations, though of lesser importance, are useful enough to have found application in target syntheses.[3] During the preparation of a review[4] on syntheses of lactams and lactones by carbon–carbon bond-forming radical cyclizations, one report in the literature stood out as the single case of a 6-*endo* radical cyclization of an allylic α-carbamoylalkyl radical or α-carbalkoxyalkyl radical. In 1983, a short paper by Nagashima *et al.* was published,[5a] wherein it was reported that methallyl trichloroacetate (**4**) reacted with cuprous chloride in acetonitrile at 140 °C (Scheme 2) to afford both 5-*exo* and 6-*endo* products **5** and **6** in 38% and 29% isolated yield, respectively. Unfortunately, their brief communication did not contain spectral data or analyses for either product.

In a follow-up paper,[5b] the authors revisited their earlier results, this time including their characterization‡ of the product, which had been assigned the structure of δ-lactone **6**, along with the following observations and conclusions:

"Interestingly, an ^{1}H NMR spectrum of the formed δ-lactone showed the existence of two conformational isomers. Two methyl signals appeared at 1.85 and 1.87 ppm in $CDCl_3$, and at 1.18 and 1.20 ppm in C_6D_6, respectively. Two methylene protons, which were split to AB patterns, were also observed as two sets. Coupled and decoupled spectra of ^{13}C NMR also showed two sets of signals, which have close chemical s[h]ifts. These conformational isomers derived from β-chlorine, which is located at the axial and equatorial positions in equal amounts. No collapse was observed on ^{1}H NMR signals between room temperature to 100 °C in toluene-d_8, which suggests a high energy barrier for the interconversion of these two isomers."

Such NMR splitting, as a result of non-interconverting ring conformations, has not been reported for other examples of δ-lactones, even at room temperature, and failure to observe peak coalescence at 100 °C would be unprecedented.

Results and discussion

MP2/6-31G* calculations§ on the δ-lactone **6** structure predict four conformational minima, with barriers to ring inversion in the range of 6–26 kJ mol^{-1}, which are consistent with experimentally determined barriers for six-membered rings,[6] and inconsistent with distinct peaks in the ^{1}H and ^{13}C NMR spectra at 100 °C or even room temperature. Besides the evidence provided by the *ab initio* computations, a substantial number of reports[7] of cyclizations of allylic α-carbamoylalkyl radicals and allylic α-carbalkoxyalkyl radicals, in particular those bearing a substituent at the internal position of the double bond, explicitly state that no traces of either δ-valerolactams or δ-valerolactones formed by 6-*endo* cyclization could be detected.

To make a case for an erroneous structural assignment in the literature, it is imperative to propose an alternative structure for the mis-identified compound that is consistent with the physical data in the original reports. A solution to this problem has been suggested by Barth and O-Yang,[8] who showed that cyclizations of similar allylic esters conducted at comparable concentrations produced good yields of cyclic dimers and trimers rather than monomeric lactones. The minor product in the cyclization of methallyl trichloroacetate seemed almost certain to be the twelve-membered cyclic dilactone **7**, which would be expected to form as a 50 : 50 mixture of non-equilibrating *cis*/*trans* diastereomers (Scheme 3). These could easily have been co-eluted during flash chromatographic isolation and, having the same empirical formulae as **6**, the mixture of *cis*-**7** and *trans*-**7** would give the same combustion analysis as

† Electronic supplementary information (ESI) available: spectrograms of compounds **5** and **7**, along with Cartesian coordinates and computed total energies for all conformations of **6** reported on herein. See http://www.rsc.org/suppdata/nj/b4/b418256a/

‡ Characterization of **6** transcribed from ref. 5b with [corrections], "^{1}H NMR (270 M[H]z, $CDCl_3$) 1.85 (s, 3 H), 1.87 (s, 3 H), 3.23 (d, 1 H, J = 7.3 Hz, C*H*CCl_2), 3.28 (d, 1 H, J = 7.3 Hz, C*H*CCl_2), 3.40 (d, 1 H, J = 15.6 Hz, C*H*CCl_2), 3.52 (d, 1 H, J = 15.6 Hz, C*H*CCl_2), 4.06 (d, 1 H, J = 12.7 Hz, C*H*O), 4.12 (d, 1 H, J = 12.7 Hz, C*H*O), 4.27 (d, 1 H, J = 4.4 Hz, C*H*O), 4.31 (d, 1 H, J = 4.4 Hz, C*H*O); ^{13}C NMR (67.8 [M]Hz, $CDCl_3$) 28.8, 29.5 (q, J = 131 Hz, CH_3), 53.4 (t, J = 139 Hz, $CCCl_2$), 64.6, 65.2 (s, *C*Cl), 71.4, 71.8 (t, J = 154 Hz, *C*O), 80.7 (s, CCl_2), 164.0, 164.2 (s, *C*=O); IR (Nujol) 1760; mp 164–165.5 °C. Anal. Calcd. for $C_6H_7O_2Cl_3$: C, 33.14; H, 3.25. Found: C, 33.33; H, 3.14."

§ Computations performed with MacSpartan Pro v. 1.0.4 on a PowerPC G4/400 desktop.

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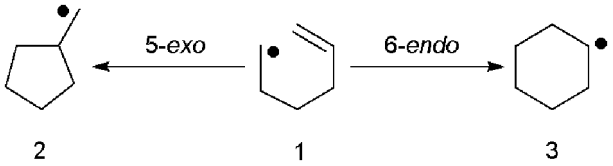
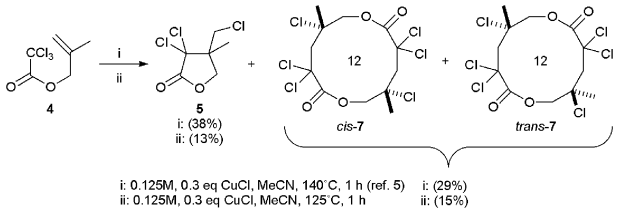


Scheme 1



Scheme 3

reported for **6**. Furthermore, the ^{1}H NMR, ^{13}C NMR, and IR spectra reported‡ are more consistent with a mixture of *cis*-**7** and *trans*-**7** than with **6**. Unfortunately, HR-MS data was not included in the original reports.

A conclusive demonstration of the structural mis-assignment required the repetition of the cyclization as described by Nagashima, *et al.*, with subsequent acquisition of the missing mass spectral data. Expectations were borne out and the cyclization of methallyl trichloroacetate **4** does, in fact, produce the mixture of products depicted in Scheme 3. The lesser overall conversion of the present cyclization is presumably due to the lower reaction temperature. The mixture of *cis*-**7** and *trans*-**7** gave ^{1}H and ^{13}C NMR spectra identical to those reported by Nagashima (*cf.* present experimental section and data in the footnote‡) and erroneously assigned to δ-lactone **6**, while the mass spectrogram indicated the molecular ion's mass to be the expected value for the dimers. As a final proof, the two dimers were themselves partially separated by flash chromatography, and ^{1}H NMR and HR-MS spectra of the individual *cis* and *trans* diastereomers were obtained. Thus, it appears certain that δ-lactone **6** was not synthesized as indicated in Scheme 2 and 6-*endo* cyclization of **4**, as claimed by Nagashima *et al.*, did not occur. Structural, spectral, and reaction databases need to be amended accordingly.

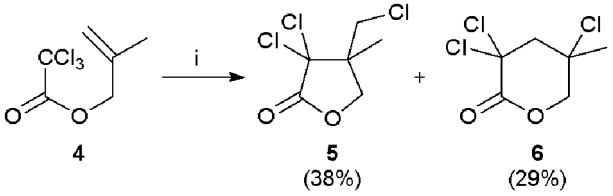
Experimental

General

^{1}H NMR spectra were obtained in $CDCl_3$ using Fourier-transform spectrographs at 300 MHz for ^{1}H and 125 MHz for ^{13}C, reported in ppm relative to the internal standard, TMS. All boiling points are uncorrected. Reagents were used as supplied by the manufacturer, except as indicated. TLC was carried out on Merck Silica Gel 60 F-254 pre-coated glass plates. Flash chromatography was performed by the method of Still, Kahn, and Mitra[9] using Merck silica gel 60 (230–400 mesh ASTM).

Synthesis of methallyl trichloroacetate (4)

Freshly distilled methallyl alcohol (1.18 ml, 14.0 mmol) and Et_3N (3.2 mL, 23 mmol) were dissolved in dry ether (30 ml, distilled from sodium metal). CCl_3COCl (1.90 ml, 17.0 mmol) was added dropwise *via* syringe at 0 °C. After stirring for 3 h, the solution was filtered and the filtrate washed with 0.1 M HCl, saturated $NaHCO_3$, and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled to provide the product in 79% yield, bp 75 °C at 10 mm Hg. ^{1}H NMR: δ 1.83 (s, 3 H, CH_3), 4.77 (s, 2 H, CH_2), 5.06 (s, 1 H, olefinic), 5.13 (s, 1 H, olefinic).



Scheme 2

Cyclization of methallyl trichloroacetate

CuCl (0.27 g, 2.7 mmol) was measured into an Ace Glass pressure tube fitted with a screw cap. Methallyl trichloroacetate (1.96 g, 9.0 mmol) dissolved in freshly distilled acetonitrile (72 ml) was added. The resultant mixture was heated at 125 °C for 1 h. The contents of the tube were concentrated to dryness, then the residue was spotted onto a TLC plate and developed with hexanes–ethyl acetate. The plate was sprayed with 10% *p*-toluidine in ethanol, dried, and irradiated with a low pressure UV lamp at 254 nm, revealing the eluants as brown spots. Purification by column chromatography afforded three products: **5** (13% yield) and *cis*-**7** plus *trans*-**7** (15% combined yield). Subsequently, diastereomers *cis*-**7** and *trans*-**7** were partially separated by flash chromatography with hexanes–ethyl acetate.

5: ^{1}H NMR δ 1.49 (s, 3 H, C*H*$_3$), 3.70 (d, 1 H, J = 10.9 Hz, C*H*Cl), 3.77 (d, 1 H, J = 10.9 Hz, C*H*Cl), 4.18 (d, 1 H, J = 8.9 Hz, C*H*O), 4.47 (d, 1 H, J = 8.9 Hz, C*H*O).

7a + **7b** (mixture of *cis*-**7** and *trans*-**7**): ^{1}H NMR δ 1.86 (s, 3 H), 1.88 (s, 3 H), 3.25 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 3.28 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 3.41 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 3.49 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 4.07 (d, 1 H, J = 12.6 Hz, C*H*O), 4.13 (d, 1 H, J = 12.6 Hz, C*H*O), 4.29 (d, 1 H, J = 12.6 Hz, C*H*O), 4.31 (d, 1 H, J = 12.6 Hz, C*H*O); ^{13}C NMR (decoupled) δ 29.1, 29.8 (*C*H$_3$), 53.8 (*C*CCl$_2$), 65.0, 65.6 (*C*CH$_3$), 71.7, 72.1 (*C*O), 81.1 (*C*Cl$_2$), 164.4, 164.6 (*C*=O).

7a (diastereomer with higher R_f value): ^{1}H NMR δ 1.86 (s, 3 H, C*H*$_3$), 3.28 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 3.41 (d, 1 H, J = 15.0 Hz, C*H*CCl$_2$), 4.13 (d, 1 H, J = 12.6 Hz, C*H*O), 4.29 (d, 1 H, J = 12.6 Hz, C*H*O); HRMS calc'd for $C_{12}H_{14}Cl_6O_4$ 431.9023; found 431.9028.

7b (diastereomer with lower R_f value): ^{1}H NMR δ 1.88 (s, 3 H, C*H*$_3$), 3.25 (d, 1 H, J = 14.5 Hz, C*H*CCl$_2$), 3.49 (d, 1 H, J = 14.5 Hz, C*H*CCl$_2$), 4.07 (d, 1 H, J = 12.7 Hz, C*H*O), 4.31 (d, 1 H, J = 12.7 Hz, C*H*O); HRMS calc'd for $C_{12}H_{14}Cl_6O_4$ 431.9023; found 431.9028.

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