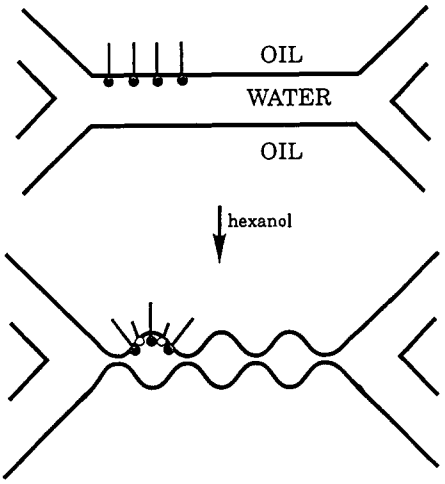

Figure 2. Proposed mechanism for water droplet formation from a polyaphron. Undulation is induced by the presence of *n*-hexanol (represented by the open circles attached to short tails).

polyaphron. The resulting reorganization of the system was then photographed with a Polaroid camera and ISO 3000 film.

Upon exposure to hexanol, the dodecane compartments fuse at the edge of the polyaphron, and the dodecane flows outside the original boundaries of the polyaphron sample (Figure 1B). The fluorescent water, initially present as an encapsulating film, is seen to form droplets that diffuse outwardly into the dodecane. These water droplets are rapidly reduced to submicroscopic size as the water-in-oil microemulsion forms spontaneously.[7] Only a fluorescent cast from the fully formed microemulsion gives any evidence for the 50–500-Å dye-bearing microdroplets residing in the continuous oil phase.

Figure 2 depicts the key step in which an aqueous film disintegrates into water droplets. Interfacial stability[8,9] depends on the oil–water interfacial tension, $\Upsilon_{o/w}$, and on the two-dimensional pressure, π. When hexanol gravitates to the oil–water interface, it lowers the $\Upsilon_{o/w}$ and, in addition, increases π by molecular crowding. The summation of the two effects creates a transiently unstable condition of $\pi > \Upsilon_{o/w}$. Curvature, in the form of a corrugated interface (Figure 2), resolves the instability by reducing π. According to Vrij–Overbeek theory,[10] corrugations can grow spontaneously in amplitude if their wavelength exceeds a critical value. Since this critical value is diminished by addition of cosurfactants,[10] hexanol induces large-amplitude vibrations. Apparently, adjacent oil compartments of the polyaphron must touch and fuse, thereby enclosing the water droplets that we have observed microscopically.[11]

Ultimately, the water droplets disappear into the dodecane to form water-in-oil microemulsions. Note that a droplet does not divide into two, then into four, and so on. Instead, a droplet continuously decreases in radius as water molecules (or submicroscopic water particles) are expelled into the dodecane.

The experiments just described were carried out with four mundane compounds: water, dodecane, surfactant, and hexanol. It is organization and cooperativity, not molecular structure, that make the subject interesting.

Acknowledgment. This work was supported by the National Institutes of Health.

(7) The sequence of events seen under the microscope was reproducible over many repeat experiments.

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(11) Equations describing polyaphron film behavior have been developed by one of the authors (E.v.d.L) and will be published in due course. Bending moduli, surface tension, spontaneous interfacial curvature, and thickness of the oil/water layers are all taken into account.

Thioketene Formation from α-Haloalkenyl 2-Nitrophenyl Disulfides: Models for Biological Reactive Intermediates of Cytotoxic S-Conjugates[1]

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Elucidation of the relationship between enzymatic reactive intermediate formation and xenobiotic-induced cell damage and death remains an important goal. Elaboration of the bioactivation mechanism of chloroalkene-derived cysteine S-conjugates **1** revealed that α-chlorovinyl thiols are putative, proximate metabolites whose formation is associated with the geno-, cyto-, and nephrotoxicity of the parent haloalkenes.[2] Although the chemistry of α-chlorovinyl thiols or thiolates **2** has apparently not been explored, such compounds may lose HCl to give thioketenes **3** or may tautomerize to thioacyl chlorides **4** (Scheme I). Cysteine S-conjugate derived thioacylating agents can be trapped with nucleophiles to give substituted thioacetamides,[3] but these results do not establish whether thioacylating metabolites arise from thioketenes or thioacyl halides.

To investigate the chemistry of α-chlorovinyl thiols or thiolates, stable, synthetically accessible α-chlorovinyl 2-nitrophenyl disulfide precursors were prepared (Scheme II). Reaction of *tert*-butyl 1,2-dichloro-3,3,3-trifluoro-1-propenyl sulfide (**5a**) with 2-nitrobenzenesulfenyl chloride[4] gave 1,2-dichloro-3,3,3-trifluoro-1-propenyl 2-nitrophenyl disulfide (**6a**) in good yield.

Thioketenes were identified by cycloaddition reactions with dienes.[5] Disulfide **6a** was reacted for 30 min at room temperature with 1 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) in dry tetrahydrofuran containing 5 equiv of cyclopentadiene. Capillary GC–MS indicated that (*E*)- and (*Z*)-3-(2,2,2-trifluoro-1-chloroethylidene)-2-thiabicyclo[2.2.1]hept-5-ene (**7a**) were formed.[6] Reaction of 1,2,2-trichlorovinyl and 1,2,3,4,4-pentachlorobuta-1,3-dienyl 2-nitrophenyl disulfides (**6b** and **6c**), which were prepared from *tert*-butyl sulfides **5b**[7a] and **5c**,[7b] respectively,

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(2) Reviews: (a) Elfarra, A. A.; Anders, M. W. *Biochem. Pharmacol.* **1984**, *33*, 3729–3732. (b) Anders, M. W.; Lash, L.; Dekant, W.; Elfarra, A. A.; Dohn, D. R. *CRC Crit. Rev. Toxicol.* **1988**, *18*, 311–341. (c) Dekant, W.; Lash, L. H.; Anders, M. W. In *Glutathione Conjugation: Its Mechanism and Biological Significance*; Sies, H., Ketterer, B., Eds.; Academic Press: Orlando; pp 415–447.

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(6) 3-(2,2,2-Trifluoro-1-chloroethylidene)-2-thiabicyclo[2.2.1]hept-5-ene (**7a**) was formed in 35% yield and was purified by preparative TLC (*n*-hexane/chloroform, 70:30): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (AB, tt, J = 12.5 Hz, 2 H, H_7), 4.5 (q, 2 H, H_1–H_4), 6.2 (m, 1 H, H_5), 6.5 (m, 1 H, H_6); ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ 54.4 (C_7), 54.5 (C_1), 56.4 (C_4), 105.0 (q, $^2J_{CF}$ = 40 Hz, F_3CC), 125.0 (q, $^1J_{CF}$ = 272 Hz, CF_3), 139.9 (C_5, C_6), 152.1 (C_3); MS (EI), *m/z* (relative intensity) 226 (M^+, 55), 191 (5), 157 (6), 160 (4), 109 (23), 69 (12), 66 (100), 39 (16); exact mass calcd for $C_8H_6ClF_3S$ *m/z* 225.9828, found 225.9830. The ^{1}H and ^{13}C NMR assignments agree with values reported for analogous compounds; see refs 5a and 5c and the following: Hesse, M.; Meier, H; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 3rd ed.; Thieme-Verlag: Stuttgart, 1987.

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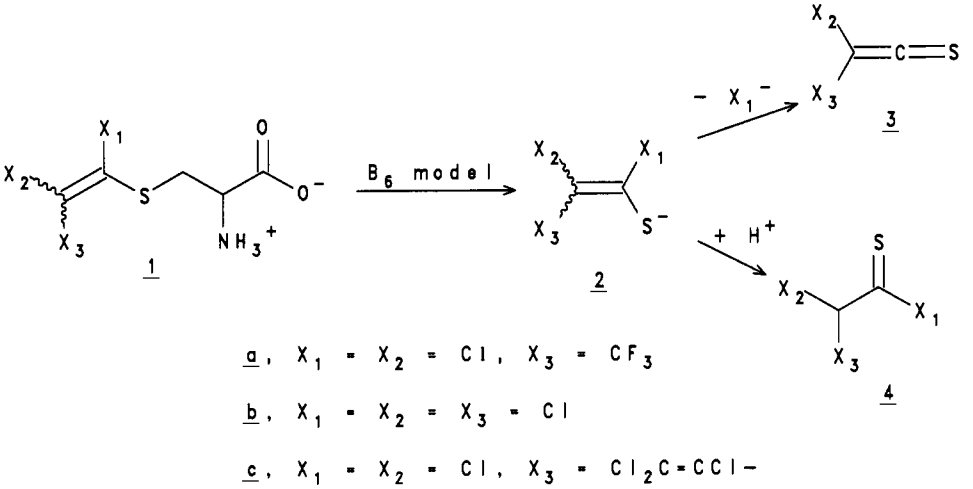
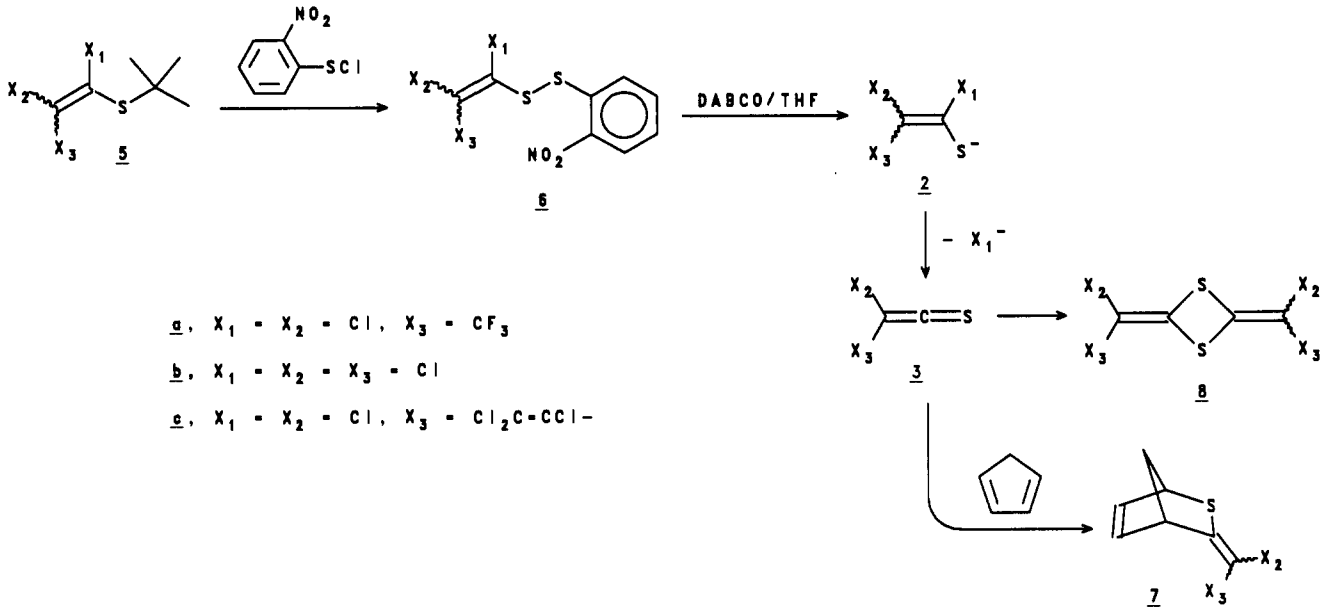
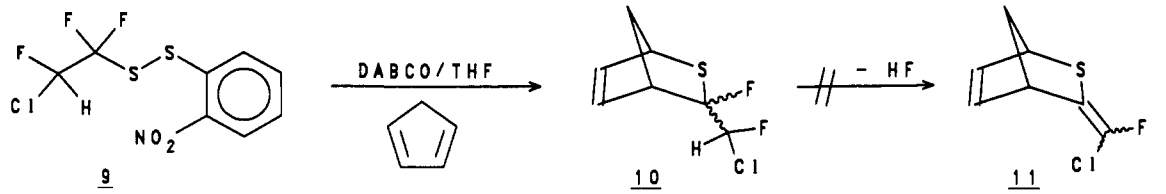
Scheme I



Scheme II



Scheme III



in the presence of cyclopentadiene gave thianorbornenes **7b** and **7c**.

Thianorbornenes formed by reaction of thioacyl chloride tautomer **4a** with cyclopentadiene were not detected. Tautomerization of thiolate **2a** to 2-chloro-3,3,3-trifluorothiopropionyl chloride (**4a**) is not expected in the aprotic medium used. When **6a** was reacted with DABCO in the presence of a proton source (1 equiv of phenol or 2,6-bis(1,1-dimethylethyl)-4-methylphenol) and cyclopentadiene, no evidence for tautomerization to the thioacyl chloride **4a** was obtained, as indicated by GC–MS analysis.

Some cyclopentadiene adducts of thioacyl chlorides eliminate HCl.[8] Reaction of 2-chloro-1,1,2-trifluoroethyl 2-nitrophenyl disulfide (**9**), prepared analogously to disulfide **6a** from *tert*-butyl 2-chloro-1,1,2-trifluoroethyl sulfide,[7b] with DABCO in THF in the presence of cyclopentadiene and analysis by GC–MS showed the formation of (±)-*endo*- and (±)-*exo*-3-fluoro-3-(chlorofluoromethyl)-2-thiabicyclo[2.2.1]hept-5-ene (**10**) (Scheme III). Elimination of HF to give 3-(chlorofluoromethylene)-2-thiabicyclo[2.2.1]hept-5-ene (**11**) was not detected by GC–MS analysis.

Thioketenes dimerize to give 1,3-dithietanes.[5d,9] This reaction was exploited to provide independent confirmation of thiokentene formation from α-chlorovinyl thiolates. When disulfide **6a** was reacted with DABCO in the absence of cyclopentadiene, GC–MS analysis indicated the formation of *syn*- and *anti*-2,4-bis(2,2,2-trifluoro-1-chloroethylidene)-1,3-dithietane (**8a**).[10] Formation

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(10) Dithietane **8a** was formed in 22% yield: MS (EI), *m/z* (relative intensity) 320 (100, M^+, ^{35}Cl), 301 (15), 285 (38, ^{35}Cl), 160 (47), 69 (31). After purification by TLC (hexanes): exact mass calcd for $C_6Cl_2F_6S_2$ 319.8720, found 319.8720.

of 1,3-dithietanes **8b** and **8c** from 1,2,2-trichlorovinyl and 1,2,3,4,4-pentachlorobuta-1,3-dienyl 2-nitrophenyl disulfides (**6b** and **6c**) was also observed.

N-Dodecylpyridoxal in cetyltrimethylammonium micelles, an enzyme model that mimics β-lyase activity,[3a,11] was used to investigate potential biological thioketene formation from cysteine S-conjugates. With this system, S-conjugate **1a** gave thianorbornene **7a**, as demonstrated by GC-MS analysis. In the absence of cyclopentadiene, dithietane **8a** was formed in low yield, by could be detected by GC-MS with selected ion monitoring.

This is the first report of thioketene formation from α-chloroalkenyl thiolates. Because thioketene formation from cysteine *S*-conjugates was also detected with a biologically relevant enzyme model, these results indicate that thioketenes are potential biological reactive intermediates. α-Chloroalkenyl 2-nitrophenyl disulfides should find utility in exploring the reactions of thioketenes with cellular macromolecules, which may contribute to the observed toxicity of cysteine S-conjugates.

Supplementary Material Available: Physical, spectral, and analytical data for compounds **5a**, **6a-c**, **7b,c**, **8b,c**, **9**, and **10** (3 pages). Ordering information is given on any current masthead page.

(11) (a) Kondo, H.; Kikuchi, J.; Uchida, S.; Kitamikado, T.; Koyanagi, E.; Sunamoto, J. *Bull. Chem. Soc. Jpn.* **1985**, 675-681. (b) Incubation mixtures contained 10 mM phosphate buffer, pH 8.0, 0.25 mM *N*-dodecylpyridoxal bromide, 5 mM *S*-(1,2-dichloro-3,3,3-trifluoro-1-propenyl)-L-cysteine,[11c] 3 mM cetyltrimethylammonium chloride, and 1 mM tetrasodium ethylenediaminetetraacetate in a final volume of 1.0 mL and were incubated for 30 min at 37 °C. The incubation mixtures were extracted once with 1 mL of $CHCl_3$, and 1 μL of the extract was injected into the GC-MS apparatus. (c) Vamvakas, S.; Kremling, E.; Dekant, W. *Biochem. Pharmacol.* **1989**, *38*, 2297-2304.

Transition Metal Template Controlled Cycloaddition Reactions. An Efficient Chromium(0)-Mediated [6π + 2π] Cycloaddition

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The photochemically "allowed" interaction of a 6π addend with a 2π partner to produce the important bicyclo[4.2.1]nonane carbon skeleton has received relatively little attention to date due, in large measure, to expected low periselectivity levels during the cycloaddition event. In most instances, multiple, competitive pathways afford complex product mixtures in which the [6 + 2] species is only a minor component.[1] Recent variations on this theme have met with greater success. Feldman and co-workers have demonstrated that an intramolecular version of this photocycloaddition can be achieved under acidic conditions in the tropone series.[2]

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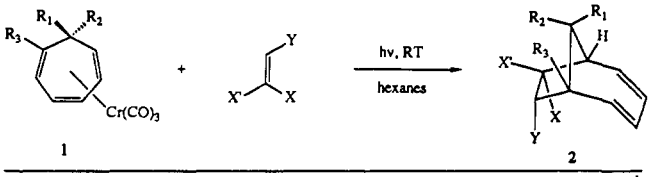
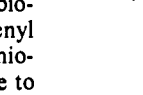
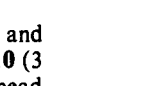
(2) (a) Feldman, K. S.; Come, J. H.; Freyer, A. J.; Kosmider, B. J.; Smith, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 1327. (b) Feldman, K. S.; Come, J. H.; Fegley, G. J.; Smith, B. D.; Parvez, M. *Tetrahedron Lett.* **1987**, *28*, 607. (c) Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M.-J. *J. Org. Chem.* **1989**, *54*, 592. (d) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490.

Table I. Metal-Mediated [6π + 2π] Cycloaddition Reactions



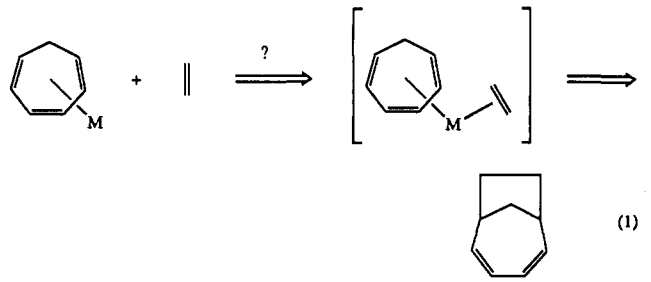
1 2

entry	triene complex	alkene	time,[a] min	yield,[b] %
1	R_1, R_2, R_3 = H	Y = CO_2Et; X, X' = H	15	92
2	R_1, R_2, R_3 = H	Y = COMe; X', X = H	15	97
3	R_1, R_2, R_3 = H	Y, X = CO_2Et; X' = H	17	80
4	R_1, R_2, R_3 = H	Y = CO_2Me; X' = H; X = 	30	91[c]
5	R_1, R_2, R_3 = H	Y = CO_2Me; X = H; X' = 	20	93[d]
6	R_1, R_3 = H; R_2 = OMe	Y = CO_2Et; X, X' = H	10	68
7	R_1 = Me; R_2, R_3 = H	Y = CO_2Et; X, X' = H	12	83
8	R_1, R_2 = H; R_3 = OMe	Y = CO_2Et; X, X' = H	90[e]	81
9	R_1, R_2, R_3 = H	Y = CO_2Et; X' = Me, X = H	90[e]	58
10	R_1, R_2, R_3 = H	Y = CN; X, X' = H	90[e]	36
11	R_1, R_2, R_3 = H	Y = OBu; X, X' = H	90	0
12	R_1, R_2, R_3 = H	maleic anhydride	90[e]	0

[a] All reactions performed by using a Pyrex filter unless otherwise indicated. [b] All products described in the table are purified and exhibit spectral (^1H NMR, ^{13}C NMR, IR) and analytical (HRMS or combustion analysis) data consistent with the assigned structures. [c] A 91% de was obtained based on ^1H NMR integration. [d] A 90% de was obtained based on ^1H NMR integration. [e] Irradiated through a quartz filter.

Sporadic reports of metal-facilitated [6 + 2] reactions have also appeared; however, these have generally been of limited scope.[3]

We have previously reported that transition-metal centers can serve as powerful templates capable of transforming normally inefficient higher order cycloaddition reactions into high-yielding, synthetically useful processes (eq 1).[4] We now disclose that



(1)

chromium(0) complexes of cycloheptatriene undergo an unprecedented photoinduced [6π + 2π] cycloaddition with electron deficient alkene partners. These results serve to further illustrate the potentially general nature of transition metal template control in cycloaddition chemistry.

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(4) Rigby, J. H.; Ateeq, H. S. *J. Am. Chem. Soc.* **1990**, *112*, 6442 and references cited therein.

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