In summary, we report a synthetic route to the biologically active β-anomer of AZT that utilizes inexpensive, non-carbohydrate starting materials.[13] Further studies have shown that this route is not limited only to the formation of AZT. Similar coupling of uracil with acetal **13** yields a substrate that cyclizes to AzddU. In addition, this synthetic protocol should be amenable to the preparation of other 3′ analogues of nucleosides by changing the nucleophile employed in the opening of epoxide **11**. Therefore, this approach should also prove useful in syntheses of other nucleosides with biological significance.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (AI-28731). D.C.L. also acknowledges stimulating discussions with Yvan Guindon, Grace Jung, and Christiane Yoakim (BioMega, Inc.) in which they suggested the possibility that the observed stereoselectivity was a consequence of the "gauche effect".

Supplementary Material Available: Full experimental details for the procedures described herein (9 pages). Ordering information is given on any current masthead page.

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Microscopic Observation of a Polyaphron Transforming into a Microemulsion

F. M. Menger,* N. Balachander, and E. van der Linden

Department of Chemistry, Emory University
Atlanta, Georgia 30322

G. S. Hammond

Department of Chemistry, Bowling Green University
Bowling Green, Ohio 43403

Received March 14, 1991

Organic reactions are usually conceptualized in terms of single molecules or pairs of molecules. However, many reacting systems, and virtually all physical properties, require consideration of multimolecular assemblages in order to model their behavior.[1] A living cell is a wondrous example of a system that operates via a molecular cooperation that cannot be understood by extrapolating the properties of individual species. Indeed, there is a growing suspicion that the collective and holistic features of complex systems can display new and unforseen modes of behavior that are not captured by the Newtonian and thermodynamic approaches.[2] Widespread interest in self-assembling systems illustrates the desire to explore multimolecular phenomena at a relatively simple level. We ourselves have in the past studied molecular communities such as micelles,[3a] vesicles,[3b] films,[3c] pools,[3d] and laminates.[3e] This work led us to examine, by optical microscopy, the transformation of one molecular assemblage, a polyaphron, into another, a microemulsion.

A polyaphron (also called a high internal phase ratio emulsion) has been likened to a gas-in-liquid foam in which the gas has been replaced by a second liquid.[4] In fact, polyaphrons are commonly obtained by first making a foam and then exchanging the gas for a liquid. In a typical preparation, 1 mL of water containing 25–150 mg of surfactant is foamed with a stream of nitrogen. Dodecane (25 mL) is then added slowly with continuous shaking to produce a viscous and opaque "oil-in-water" polyaphron. The photomicrograph in Figure 1A shows densely packed oil globules separated by a thin film of water.[5]

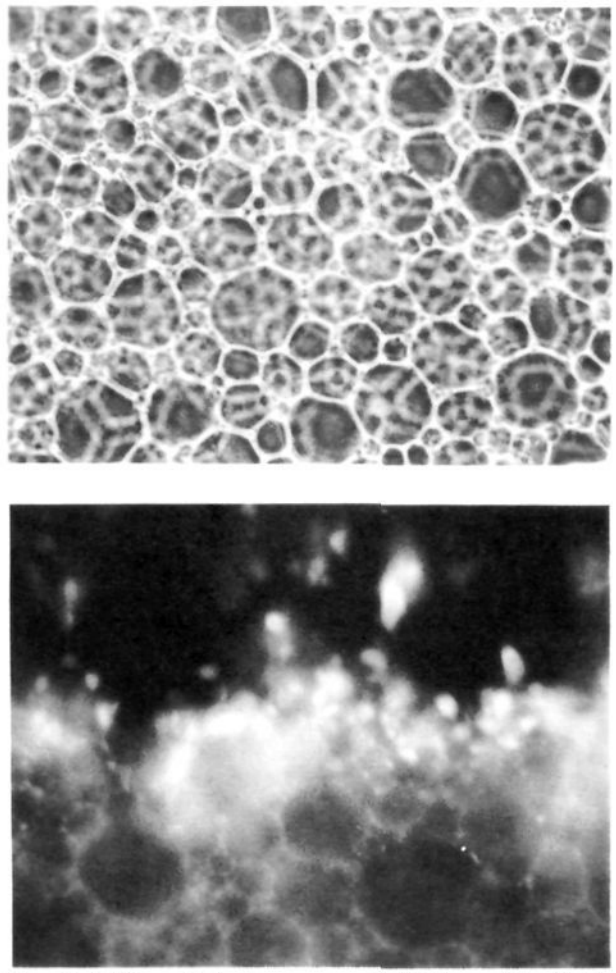

Figure 1. (A) Top: Polyaphron composed of dodecane (25 mL) dispersed in water (1 mL) with 25 mg of cetyltrimethylammonium bromide. The water film contains pyranine, a fluorescent dye. 290× magnification. (B) Bottom: Polyaphron exposed to *n*-hexanol. Within 1 min, water droplets are ejected (fluorescent spots). These gradually disappear as the isotropic microemulsion is formed.

A water-in-oil microemulsion is a fluid, optically transparent dispersion of water in hydrocarbon.[6] Such systems form spontaneously when water is added, for example, to a large excess of *n*-dodecane containing a surfactant and *n*-hexanol (a "cosurfactant"). Note that the water-in-oil microemulsion differs in gross composition from the oil-in-water polyaphron in that only the former possesses *n*-hexanol. Thus, a polyaphron should transform into the thermodynamically stable microemulsion upon exposure of the polyaphron to the alcohol. It was this phase-inversion process that we observed by optical microscopy.

A polyaphron (30–50 mg consisting of water, dodecane, and cetyltrimethylammonium bromide along with 1 mM pyranine, a fluorescent dye, in the water) was placed in the center of a hanging-drop slide resting on the stage of a Leitz Labrolux-S microscope equipped with a UKL condenser and an epifluorescence attachment. With the aid of a Narishige micromanipulator, we placed 5 μL of *n*-hexanol about 5 μm from the edge of the

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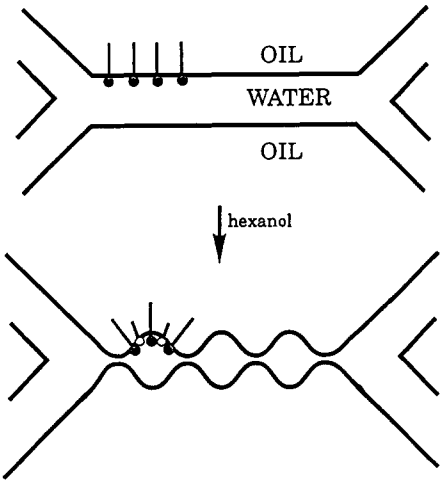

Figure 2. Proposed mechanism for water droplet formation from a polyaphron. Undulation is induced by the presence of *n*-hexanol (represented by the open circles attached to short tails).

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.

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

Wolfgang Dekant,[†] Gudrun Urban,[†] Claus Görsmann,[†] and M. W. Anders*[,‡]

Institut für Toxikologie, Universität Würzburg 8700 Würzburg, FRG
Department of Pharmacology, University of Rochester Rochester, New York 14642

Received October 4, 1990

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,

[†] Universität Würzburg.
[‡] University of Rochester.

(1) This research was supported by National Institutes of Environmental Health Sciences Grant ES03127 (M.W.A.) and by Deutsche Forschungsgemeinschaft Grant SFB172 (W.D., G.U., C.G.).

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