microscopy of the vesicles showed no distortion. An overt diene-yne–butatriene transition might explain the data,[21,29] but it thus would be coincidental that an electronic isomerization would be thermally induced near a temperature where the bilayer structure is known to change, according to DSC.[8] Evidently, these models fit the data poorly.

The data above, along with the known temperature-dependent changes in structure of other phosphatidylcholines,[23,24] suggest that thermally induced changes in bilayer structure alter the polymer conformation, which controls the thermochromism. More precisely, the increased motional freedom of the acyl side chains caused by raising the temperature might allow a more disordered (and less coplanar[25]) polymer with a lower characteristic conjugation length and thus a blue-shifted absorbance spectrum. Reversible thermochromism is observed because the bilayer morphological changes are thermally reversible.

Our proposal is consistent with other observations of thermochromism in polydiacetylenes,[6,7,30] particularly given the similarity of the absorbance and/or fluorescence spectra of the polymer in crystals,[26] in solution[27] and as mono- and multilayers on substrates,[7,17] to those in an aqueous bilayer dispersion.[6,8,16,28,30] Moreover, the greatest effect occurs (Figure 1) near the principal phase transition temperature of the polymerized phospholipid[8] (64.3 °C), suggesting that the electronic change is correlated with the structural change. The fact that reversible thermochromism is much less apparent or absent in other polymerized diacetylenic phosphatidylcholines,[6,30] even those with the same chain length fatty acid (but with differing placement of the diacetylene moiety), suggests the influence subtle changes in the bilayer structure can have on the polymer conformation. Efforts are under way to understand the influence of structure on this phenomenon in greater detail.

Acknowledgment. We are grateful to the Defense Advanced Research Projects Agency for support, Barbara Herendeen for aid in the syntheses, Mark Ross for the mass spectra, and J. Sheridan, P. Yager, M. Nagumo, and A. Snow for helpful discussions. R.B.T. is the recipient of a National Research Council Associateship.

Free Radical Macrocyclization

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Received February 20, 1986

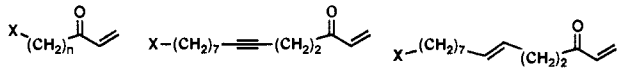
Free radical reactions have been used increasingly in recent years for the synthesis of organic molecules.[1-4] The development of radical synthetic methodology is primarily the result of mechanistic studies of the past 40 years that have identified the important pathways available and have provided detailed reactivity guidelines[5-7] for free radical reactions. Mechanistic studies provided a framework for understanding free radical cyclization,[7-9] for example; and this approach has been extensively utilized for the construction of natural products in subsequent elegant investigations.[10,11] The use of radical cyclization has been limited primarily to the construction of five- and six-membered rings and has not been used for larger ring systems. In fact, the rate of cyclization decreases from 2×10^5 s^{-1} for 5-exo cyclization (5-hexenyl at 25 °C) to <70 s^{-1} for the corresponding 7-exo reaction.[6] It occurred to us that radical cyclization might prove to be possible for larger rings if substrates were chosen that gave consideration to steric and polar effects in the cyclization reaction.[5,13,14] Carbon radicals are nucleophilic and electron-withdrawing substituents activate alkenes toward addition of such radicals. Furthermore, substrates chosen that minimize steric effects in the cyclization transition state are preferred, since this can be a dominant factor in addition reactions. We report here the results of our studies with several substrates for radical macrocyclization. The reaction proves to be a useful one, with yields as high as 75–80% being possible for some substrates.

Table I. Formation of Macrocyclic Ketones via Radical Cyclization

substrate, mM	Bu_3SnH, mM	products (% yield)[a] cyclic	acyclic
1c, 3.3	3.6	**7** (63)	**1f** (22)
1b, 14	26[b]	**7** (30)	**1f** (37)
1d, 6.7	7.4	**9**[c] (54)	**1g** (16)
1a, 3.0	4.0	**8** (15)	**1c** (27)
2a, 5.0	5.5	**11** (76)	**2b** (6)
3a, 5.0	5.5	**10** (78)	**3b** (8)

[a] Yields based on GC. GC yields were confirmed by HPLC isolation on silica gel (94:4, hexane/ethyl acetate). [b] Syringe addition of alkyl halide and tin hydride over 3 h. [c] Reference 22.

The acyclic substrates **1–3** were available by straightforward procedures from readily available starting materials. The compounds **1b** and **1c**, for example, were prepared from 12-bromo-1-dodecanol[15] by pyridinium chlorochromate[16] oxidation to the aldehyde (74%) followed by addition of vinylmagnesium bromide affording an allylic alcohol **4**, $Br(CH_2)_{11}CHOHCH{=}CH_2$ (76%). Oxidation of **4** with Jones reagent[17] gave the ketone **1b** (93%) which was converted to the iodide **1c** by reaction with NaI in methyl ethyl ketone (96%).[18] In a similar manner, **2** was prepared from the bromo alcohol **5**, $Br(CH_2)_7C{\equiv}C(CH_2)_3OH$, and **3** from



1 a; X=I, n=7
b; X=Br, n=11
c; X=I, n=11
d; X=I, n=15
e; X=H, n=7
f; X=H, n=11
g; X=H, n=15

2 a; X=I
b; X=H

3 a; X=I
b; X=H

the bromo aldehyde **6**, $Br(CH_2)_7CH{=}CH(CH_2)_2CHO$. Compound **5** was synthesized by acetylenic coupling of 1,7-dibromoheptane and pent-4-yn-1-ol ($LiNH_2$, 30%) and **6** was constructed by a Claisen rearrangement (120 °C, 24 h, 90%) of the vinyl ether prepared from the alcohol $Br(CH_2)_7CHOHCH{=}CH_2$ by reaction with ethyl vinyl ether and mercuric trifluoroacetate (75%).[18]

Several attempts were made to cyclize the bromide precursor **1b**, utilizing tributyltin, triphenyltin, or tributylgermanium hydrides. Reactions were carried out at concentrations ranging from 1 to 100 mM of bromide and with equivalent or excess hydride

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(15) The bromo alcohol was prepared by CBr_4/PPh_3 on the corresponding diol (50%).
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(18) Analytical data (^1H and ^{13}C NMR, mass spectra, IR, for all intermediates) and combustion analysis for selected intermediates in the synthetic sequences were obtained.

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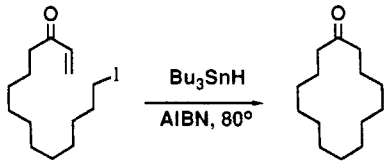
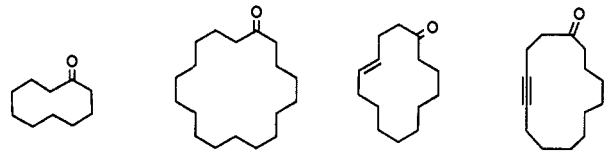
reagents. With the bromide **1b**, the best yields of cyclotetradecanone[19] we could achieve under any conditions tried was 35% and yields in the 20–30% range were typical. The simple expedient of working with the iodide rather than the bromide raised the yields to 60–65% for **1c**, presumably because of better



1c 7, 65%

propagation at the alkyl iodide–stannyl radical step.[20] The conditions which we have found to be most convenient for radical macrocyclization are as follows: The iodide (3–6 mM) in dry benzene, along with 1.1 equiv of tributyltin hydride and 0.1 equiv of the initiator AIBN is refluxed for 3 h under argon. Solvent removal and chromatography on silica eliminate tin products providing the cycloalkanone and acyclic reduction product (**1e–g**) mixture.[21] The cycloalkanones **7–11**[18] could be prepared by this



8 9 10 11

procedure, and the yields of macrocyclization along with reduction are presented in Table I.

Reactions carried out at higher concentrations of substrate and tin hydride gave considerably more acyclic products and generally lower overall product yield than reactions carried out at 3–6 mM substrate. The increase in acyclic to cyclic products at higher concentrations results from more favorable competitive H-atom transfer to the acyclic radical and the decrease in recovery under these conditions probably results from competitive addition of the acyclic radical in an intermolecular event. We note that such intermolecular reactions have a kinetic advantage at substrate concentrations greater than 10 mM in S_N2 macrolactonization systems.[12,24]

A series of quantitative experiments for the substrate **1c** was carried out at 80 °C in benzene and a rate ratio of cyclization to H-atom transfer for the acyclic radical was determined, $k_c/k_H = 2 \times 10^{-3}$ M^{-1}. On the basis of the known k_H for H-atom transfer from tributyltin hydride to primary alkyl radicals of 6.2×10^6 M^{-1} s^{-1},[25] the rate constant k_c for the radical derived from **1c** is 1.2×10^4 s^{-1}.

Particular comment should be made about the substrates **2a** and **3a**. These systems lead to higher yields of macrocycles than the fully saturated substrates, in some cases the product accountability being nearly quantitative. For both of these substrates, the possibility of serial cyclization is an issue, since the radical generated by addition to the α,β-unsaturated ketone has the possibility of a second transannular 5-exo cyclization. We have been unable to detect such serial cyclization products (**3a** would give a [9.3.0] system, for example), but we are continuing to examine this possibility for other substrates.

The construction of macrocyclic systems is a long-standing problem in synthetic organic chemistry.[26] Substituted macrocyclic ketones and lactones would appear to be available without elaborate protection–deprotection schemes by the method described here. In this regard, we have carried out preliminary experiments that confirm that the method can be extended to macrolide systems, intramolecular radical addition to acrylate esters providing the lactone by C–C bond formation.

Acknowledgment. NAP gratefully acknowledges support of this research from NIH (HL-17921).

(19) We thank Professor J. Marshall and V. Audia of the University of South Carolina for an authentic sample of cyclotetradecanone.

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(22) We thank Drs. H. Bost and J. Byers of Bartelsville, OK, for an authentic sample of cycloocatadecanone.

(23) A complete kinetics study of the systems reported here will be subsequently published.

(24) We have isolated two products from **1a**–tin hydride reactions which preliminary data suggest are dimer-type products.

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Dimethylenecyclobutadiene

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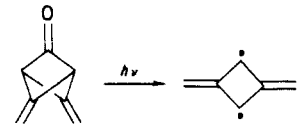
Received September 25, 1985

Dimethylenecyclobutadiene (I) may be considered to be an

I

edge-to-edge, double trimethylenemethane[1,2] or a cyclobutadienyl dicarbinyl diradical. From a broader perspective, the diradical I is a new member of the non-Kekulé class of molecules;[3] it is also a new six-π-electron isomer of benzene. Dimethylenecyclobutadiene (I) is predicted to be a ground-state triplet.[4] For these reasons, there is substantial incentive to synthesize I, to explore its spectroscopic properties,[5] and to examine its chemical reactivity.

Our approach to I was predicated upon low-temperature photolytic excision of carbon monoxide from the ketone dimethylenebicyclo[1.1.1]pentanone (II).[6]



II I

Direct irradiation of the ketone II at 260 nm in the cavity of a Varian E-4 ESR spectrometer at 10 K yielded the triplet spectrum shown in Figure 1.[7] The spectrum is characterized by

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(3) The non-Kekulé appelation is due to: Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969; pp 232–234. The first non-Kekulé compound to be observed by ESR was trimethylenemethane.[1]

(4) Borden, W. T.; Davidson, E. R. *J. Am. Chem. Soc.* **1977**, *99*, 4587. Davidson, E. R.; Borden, W. T.; Smith, J. *Ibid.* **1978**, *100*, 3299, and references therein.

(5) See the recent observation of 1 by: Snyder, G. J.; Dougherty, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 1774. Snyder, G. J.; Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 299.

(6) The ketone II was synthesized from 3,4-diazatetracyclo-[4.3.0.0^{1,7}.0^{6,9}]nonan-8-one by oxidative extrusion of nitrogen.

(7) There appears to be no dependence on the matrix; the same spectrum was observed in methyltetrahydrofuran, isopentane, methylcyclohexane, perfluorobutyltetrahydrofuran (PFBTHF), 1:1 PFBTHF/perfluoroheptane, and 1:1 PFBTHF/perfluorotributylamine.

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