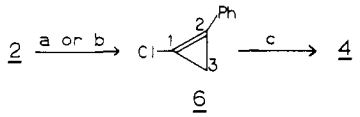
Scheme II[a]



6

[a] Reagents: (a) NaOH-H_2O (50:50)/THF/Bu_4NHSO_4. (b) KOBu-*t*/THF/12 °C. (c) Fp_2/NaOH-H_2O (50:50)/THF/Bu_4NHSO_4.

analysis[9] (see Scheme I). Initial difficulty in assigning the correct structure for **3c** was attributed to the unusual opening of the cyclopropane ring (vide infra) and the ^1H NMR spectrum which exhibited significantly different η^5-C_5H_5 (Cp) resonances. Also, an AB pattern would be predicted for the benzylic hydrogens, while a singlet was observed. Knowing the correct structure, one can attribute the large Cp chemical-shift difference to the anisotropic nature of the central phenyl group which shields the *cis*-Cp and the 2 H singlet to accidental equivalence of the benzylic hydrogens.

The initial purple compound (isolated in 17% yield) was assigned structured **3t** on the basis of its spectral[8] properties and thermal conversion to **3c** ($K_{eq} \sim 20{:}1$, cis–trans; $t_{1/2} \simeq 5$ h at 80 °C). The anticipated AB pattern for the benzylic hydrogens was indeed observed ($J = 16$ Hz).

Information related to a possible mechanism for the formation of **3** deserves attention at this time. First, the reaction is general for dichlorocyclopropanes possessing an aryl group in the 2 position.[10] However, a hydrogen must also be present on carbon 2, since 1,1-dichloro-2-methyl-2-phenylcyclopropane fails to yield a vinylidene dimer. Second, 1,1-dichloro-2-phenylcyclopropane (**2**) yields **4**[11] in 28% yield and none of the isomeric **5**. Third, when **1** was reacted in NaOD/D_2O, one deuterium was incorporated into the benzylic position of **3t**. All of these facts are consistent with a base promoted elimination of HCl from the dichlorocyclopropanes to produce chlorocyclopropanes as key intermediates in the reaction.[12] In fact, **2** was found to rapidly produce the known[13] 1-chloro-2-phenylcyclopropene (**6**) under the phase-transfer conditions but in the absence of Fp_2. When all of **2** was consumed under these conditions and then Fp_2 added, comparable yields of **4** were obtained. Production of **6** from **2** by using potassium *tert*-butoxide[13a] and subsequent phase-transfer reaction as above gave **4** (see Scheme II). Therefore, the chlorocyclopropenes are strongly implicated as the key intermediates.

Cleavage of the cyclopropene ring must occur at the C_1–C_3 bond in **6** to produce **4**. The mechanism for such a cleavage may involve a cyclopropene to vinylcarbene rearrangement[14] or a transition-metal insertion into that bond.[17] Studies are in progress to differentiate between these two processes and further define the mechanism.[18] A detailed examination of a variety of bridging vinylidene complexes and their chemistries is also under way.

Acknowledgment. Partial support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation is gratefully acknowledged. E.V.D. acknowledges support from the University of Oklahoma/Technical University of Berlin Chemistry Exchange Program and technical assistance by J. Soufi.

(9) Crystal data at −135 °C: $C_{28}H_{22}O_3Fe_2 \cdot C_4H_{10}O$; M_r 592.3; triclinic, $P\bar{1}$; $a = 12.792$ (7), $b = 15.514$ (5), $c = 7.021$ (16) Å; $\alpha = 93.37$ (6), $\beta = 80.93$ (9)°, $\gamma = 96.12$ (3)°; $V = 1366.8$ Å^3; $Z = 2$; $D_c = 1.439$ g cm^{-3}; μ (Mo $K\alpha$) = 11.1 cm^{-1}. $R = 0.072$ for all 5613 reflections ($2\theta \leq 53°$, Mo $K\alpha$ radiation). Full details of the structural analysis will be submitted elsewhere.

(10) Other cyclopropanes found to give similar adducts: 1,1-dichloro-2-phenylcyclopropane; *trans*-1,1-dichloro-2-methyl-3-*p*-tolylcyclopropane; *trans*-1,1-dichloro-2-methyl-3-*p*-anisylcyclopropane; 1,1-dichloro-2,2-dimethyl-3-phenylcyclopropane; 1,1-dichloro-2,2-dimethyl-3-*p*-tolylcyclopropane.

(11) **4c**: IR (heptane) 2000 s, 1969 m, 1808 s cm^{-1}; ^1H NMR (CS_2, 100 MHz) δ 2.82 (s, 3 H, CH_3), 4.40 (s, 5 H, Cp_a), 4.88 (s, 5 H, Cp_b), 7.1–7.6 (m, 5 H, Ph). **4t**: IR (heptane) 1971 sh, 1960 s, 1808 m cm^{-1}; ^1H NMR (CS_2, 100 MHz) δ 2.92 (s, 3 H, CH_3), 4.25 (s, 5 H, Cp_a), 4.79 (s, 5 H, Cp_b), 7.1–7.6 (m, 5 H, Ph).

(12) The reaction of **1** with NaOD/D_2O confirms that one hydrogen is replaced with solvent deuterium. This labeling experiment is consistent with the proposed base promoted elimination of HCl from **1** to form the cyclopropene. The external deuterium found in the product is introduced at a later, yet undefined, step in the mechanism.

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(14) Previous kinetic studies on the cyclopropene to vinylcarbene rearrangement have shown activation energies in the 30–40 kcal/mol region.[15] The high activation energy would seem to rule out this possibility for the current reaction which proceeds readily at room temperature. However, the compounds that were studied in the thermal reactions were mainly hydrocarbons, and no systemic examination of substituent effects, especially with heteroatoms, has been reported.[16] A cyclopropene to vinylcarbene rearrangement was used to explain ring-opened products in the reaction of 1-chlorocyclopropenes with methoxide ion in methanol at room temperature.[13b] Appropriately substituted cyclopropenes, such as those encountered in the current work, may indeed rearrange to vinylcarbenes at or near room temperature. Therefore, vinylcarbenes cannot be ruled out as possible intermediates at this time.

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(18) It is interesting that we have been unable to carry out the above transformation, even from pregenerated cyclopropenes, by using conditions other than phase transfer. Efforts to define the reactive iron species under these conditions are under way.

End-to-End Cyclization of Hydrocarbon Chains. Photochemical and Computer Simulation Studies

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Hydrocarbon chains are essential components of a multitude of systems including micelles, microemulsions, and biological membranes which depend upon chain flexibility for their unique properties.[1] As a consequence, the factors which influence hydrocarbon chain conformation have been the topic of current concern, both among theoretical chemists and experimentalists.[2] Of particular importance to the development of this field are instances where conformationally dependent experimental phenomena can be simulated by means of theoretical models, since this not only provides a test of the model and its parameters but permits new insights into the experimental results themselves.[3]

Since the classic paper by Kuhn[4] in 1934, models of increasing sophistication have been used to examine the factors which influence the shape of polymethylene chains in solution. The most successful of these are various forms of the rotational isomeric state (RIS) model, whose development was pioneered largely by Flory and his co-workers.[2] The model is "realistic" in that it treats the chains as a sequence of CH_2 groups in the geometries of gauche and trans rotational states at each bond. While many chain

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(2) P. J. Flory, "Statistical Mechanics of Chain Molecules", Wiley Interscience, New York, 1969.

(3) (a) M. A. Winnik, *Acc. Chem. Res.*, **10**, 173 (1977); (b) M. A. Winnik, R. E. Trueman, G. Jackowski, D. S. Saunders, and S. G. Whittington, *J. Am. Chem. Soc.*, **96**, 4843 (1974); (c) M. Dettenmaier, *J. Chem. Phys.*, **68**, 2319 (1978).

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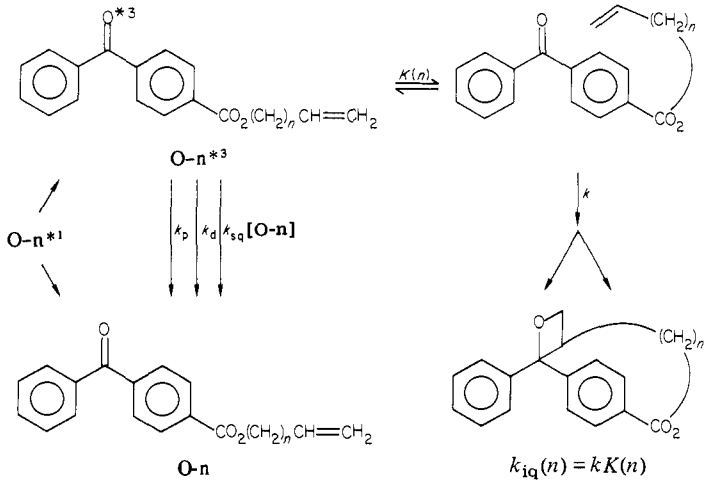
Scheme I



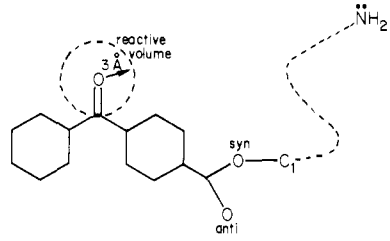
properties have successfully been simulated with this model, end-to-end cyclization remains a critical test for the RIS model, since the details of the cyclization reaction may affect the validity of some of its simplifying assumptions.

Kuhn examined end-to-end cyclization for the infinitely flexible Gaussian chain and found that the cyclization probability $W(0)$ decreased with chain length n as $W(0) \sim n^{-3/2}$. This behavior has been observed for long polymers in a Θ solvent (an appropriately poor solvent for long polymer chains in which the chain dimensions are compressed to match those predicted by simple theories): polymers behave "ideally". Cyclization of finite chains and oligomers are not described so simply. Theoretical approaches by Fluendy,[5] Flory,[6] and Sisido[7] have explored how one might examine end-to-end cyclization in terms of the RIS model. Attempts to apply these models to cyclization of hydrocarbon chains have been largely frustrated by complications in medium ring formation in these systems.

For example Stoll and Rouvé[8] measured the equilibrium constant for lactone formation for $HO(CH_2)_nC(=O)OH$, and Mandolini and Illuminati[9] examined the kinetics of their formation from $Br(CH_2)_nC(=O)O^-$. In both sets of data, cyclization is suppressed for rings of 7–12 atoms due to steric interactions which distort bond and rotational angles. These factors prevent the RIS model from accommodating the geometric details of the chain. The same comment applies as well to experiments on intramolecular fluorescence quenching in $Me_2N-(CH_2)_n-NMe_2$ by Halpern[10] and on the chain length dependence of the activation energy for cyclization in ω-bromoalkylcatechol monoethers.[11]

In order to circumvent the distortions caused by ring strain in hydrocarbon chain cyclization, one must choose a system in which the steric effects that cause the ring strain are suppressed. One set of molecules satisfying these requirements is benzophenone-4-$CO_2(CH_2)_nQ$ (**O-n**). In this system, one can excite the benzophenone chromophore with UV light and study the kinetics of intramolecular phosphorescence quenching. For Q which are electron donors, this quenching involves an exciplex in which Q is spatially proximate to the ketone carbonyl oxygen. Intramolecular quenching thus requires end-to-end cyclization of the molecule. The aromatic ring contained within the cycle should minimize transannular steric repulsions caused by ring closure.

Since our interest is in the *cyclization probability* of the chain, Q must be chosen with care. It must be a sufficiently active quencher to make hydrogen abstraction from the chain an unimportant contributor to luminescence quenching; yet its reaction must be inefficient enough for the chain to reach conformational equilibrium before reaction. All these requirements are met by the groups Q = —CH=CH_2 and —NH_2. Both are electron-donor quenchers which react 10^3 times slower, in bimolecular reactions with typical triplet state benzophenones, than the diffusion controlled rate. In our experimental work, the former proved easier to synthesize and study, whereas in our theoretical simulations, it was necessary to choose the molecules with Q = $-NH_2$.



The theoretical simulation involved a diamond lattice version of the rotational isomeric state model. The steric requirements of the benzophenone were accommodated by designating as occupied those lattice sites which best represented its shape. Both the syn and anti rotational states of the ester group were considered. Chains were grown stepwise by using a modified form of the Rosenbluth algorithm previously described.[12] In these polymethylene chains, the pentane effect (g±g∓ sequences) were suppressed by the second-neighbor avoiding character of the random walk. After each step in the walk, an $-NH_2$ group was temporarily added to the chain end and tested for ring closure. The NH_2 was removed, and an additional CH_2 was added to the chain end. This process was then repeated. Cyclization was counted if the N was within 3.1 Å (3 tiers of lattice sites) from the carbonyl oxygen *and* with its lone pair pointing toward that oxygen. Monte Carlo methods[12,13] were used to estimate partition functions for cyclized $Z_{cy}(n)$ and all $Z_{total}(n)$ chains by using a gauche–trans energy difference of 600 cal/mol. Cyclization probabilities [$W(O)$] were calculated at each chain length from $W_n(O) = Z_{cy}(n)/Z_{total}(n)$. The conformational contribution to the cyclization entropy was estimated from $\Delta S_{cy} = R \ln W_n(O)$.

Values of $W_n(O)$ from these simulations are shown in the top half of Figure 1. Short chains are unreactive; they cannot react with the ketone oxygen. Cyclization has an onset, a maximum at $n = 12$, and a decrease for longer chains. The oscillations in $W_n(O)$ derive from chain stiffness—the chains are not permitted

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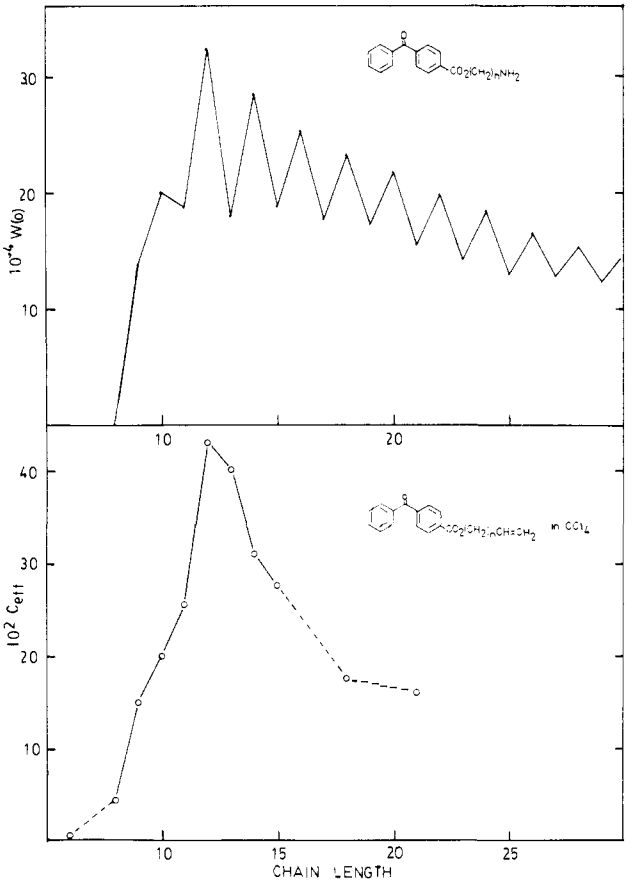

Figure 1. The upper part is a plot of the simulated cyclization probability $W(O)$ vs. chain length n for the molecules shown. Cyclization is detected by the presence of the nitrogen of the NH_2 group within 3.1 Å of the ketone carbonyl oxygen with its nonbonded electron pair directed toward that oxygen. Monte Carlo methods are used to estimate partition functions; see text. The lower part is a plot of $C_{eff} = k_0(n)/k_q^{(2)}$ for the quenching of aromatic ketone phosphorescence in CCl_4 solution at 25 °C.

to deviate from the gauche and trans rotational angles—and from the odd–even parity of diamonds lattice sites within the reactive volume. The model overestimates these oscillations. Real chains are able to undergo small torsional twists about each of its C–C bonds (Scheme I). The corresponding ΔS_{cy} values vary from −16 cal mol^{-1} K^{-1} for $n = 12$ to −18 cal mol^{-1} K^{-1} for $n = 30$.

Experimental results were obtained from flash photolysis experiments on **O-n** (Q = —CH=CH_2) at 10^{-3}–10^{-4} M in CCl_4 solution.[14,15] Exponential lifetimes τ_n were measured, and $1/\tau$ values were extrapolated to infinite dilution ($1/\tau_n^0$). Under these conditions

$$1/\tau_n^0 = 1/\tau_{Me} + k_{iq}(n)$$

where $\tau_{Me} = (k_p + k_d)^{-1}$ is the lifetime of the corresponding methyl ester **O-**(Me), and k_p and k_d are, respectively, the rate constants for radiative and radiationless decay of the chromophore. The term $k_{iq}(n)$ represents the chain length dependent rate constant for intramolecular phosphorescence quenching. A small fraction of $k_{iq}(n)$ is due to intramolecular hydrogen abstraction. Its contribution is known from our previous studies of molecules with Q = CH_3. We refer to the corrected values as $k_0(n)$. These describe quenching by Q and are proportional to the chain end-to-end cyclization probability. These values are plotted in the bottom half of Figure 1. What is particularly important about our results is that studies at various temperatures(from −20 to 100 °C) show that the *activation energy for intramolecular quenching is independent of chain length* (E_a = 2.6 kcal/mol) for $n > 8$. Hence the plot in the lower half of Figure 1 reflects only changes in cyclization entropy.

A more meaningful way of treating the experimental data is to normalize $k_0(n)$ values to remove the contribution of ketone excited-state reactivity.[3a] This can be done by dividing $k_0(n)$ by the second-order rate constant $k_q^{(2)}$ for the reaction of **O-**Me with an appropriate model alkene. For this purpose we have chosen 1-pentene. The $k_q^{(2)}$ value of 1.6×10^7 M^{-1} s^{-1} for this reaction is 1000 times smaller than that for a diffusion controlled reaction and emphasizes that a conformational equilibrium is reached in the excited state of **O-n** before reaction. The ratio [$C_{eff} = k_0(n)/k^{(2)}$] has units of mol/L. It represents the effective concentration of the quencher Q in the reactive volume about the C=O group. While this volume is not known, one can calculate that a C_{eff} value of 1×10^{-2} M corresponds to a P_n value of 1×10^{-4} in a reactive volume of 17 Å^3. This value for the size of the reactive volume is not unreasonable and emphasizes that in spite of the simplifying assumptions, the lattice-based rotational isomeric state model is able to simulate effectively both qualitative and quantitative features of end-to-end cyclization in molecules like **O-n**.

Acknowledgment. We thank NSERC Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

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(15) Since solvent effects can affect molecular conformation, the choice of solvents for comparing experiments with theory is somewhat delicate. In RIS model calculations in which steric repulsions between groups far removed along the chain contour are treated as hard sphere repulsions, the proper reference state for experiments is the athermal solution.[16] CCl_4 approximates an athermal solvent for alkane chains.

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^{197}Au Mössbauer Spectroscopic Data for Antiarthritic Drugs and Related Gold(I) Thiol Derivatives

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Gold(I) thiolates (AuSR) have been used for many years in the production of decorative finishes to ceramics, etc. More recently, compounds of this type in which SR is, for example, a thiomalate or a substituted thioglucose group have attracted considerable attention for the treatment of rheumatoid arthritis and inflammatory disorders.[1-6] Despite this importance, very little is known of the structures of any of these thiolates. X-ray crystallography has shown that an analogous silver compound, $AgSC_6H_{11}$, has a polymeric structure involving both two- and three-coordinate silver,[7] but the gold thiolates have not been crystallized. However, Mössbauer spectroscopy with ^{197}Au has been shown to be well suited to the determination of structures of gold compounds,[8] and we now present data for a variety of gold(I) thiolates, including some of the drugs in current use. The data establish polymeric structures with linear coordination at gold.

Previous studies have shown that, in combination, the isomer shift (IS) and quadrupole splitting (QS) are diagnostic of the number and type of ligands bound to gold (ref 8 and references

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