measuring the relative stabilities of the hydrogen-bonded complexes.[5] This empirical relationship (called the linear SEE equation) has been observed for a variety of kinds of chemical change in which the reaction centers are tagged by a p-FC_6H_4 group.[2] The relationship is interpreted as involving approximately linear relationships between the relative electron density changes at the reaction center and the corresponding changes in potential energy.[2]

To the extent that aqueous pK_A values may be taken as measures of the relative potential energies for nearly complete proton transfer to base in polar aprotic solvent,[6] the shifts for ion-pair formation with p-$FC_6H_4SO_3H$ may be anticipated (and are observed) to be parallel to pK_A values. Another estimator of the relative potential energy for nearly complete proton transfer is provided by the $\overline{\Delta H^\circ}$ value of the following reaction carried out in CH_2Cl_2 solution (the use of the ethyl acetate complex is needed to obtain solubility of the acid).

$$p\text{-}FC_6H_4SO_3H\cdots EtOAc + B \rightleftharpoons p\text{-}FC_6H_4SO_3^-\cdots HB^+ + EtOAc$$

We have measured $\overline{\Delta H^\circ}$ values utilizing the method of Arnett,[7] in which dilute base solution is injected into a solution with approximately a 20-fold excess of acid. The $\overline{\Delta H^\circ}$ value obtained does depend upon the acid–base ratio since this influences the solvation of the ion pair (by hydrogen bonding and other solvation interactions).[8] However, relative values of $\overline{\Delta H^\circ}$ obtained under essentially identical conditions may be accepted as approximately quantitative measures of the relative potential energy changes. Table I shows that $\overline{\Delta H^\circ}$, pK_A, and ion-pair Δ values are all three quite parallel.

We believe the results of Table I support strongly the premise[5] that the markedly different extents of apparent proton transfer[9] in the hydrogen-bonded complexes ($<\sim30\%$) and the hydrogen-bonded ion pairs ($>\sim65\%$) are predominantly responsible for different base scales against proton donors (*i.e.*, the different extents of proton transfer introduce important differences in the effective nuclear charges acting on the bonding electrons). This interpretation is indicated by the fact that the close parallelism between pK_A, $\overline{\Delta H^\circ}$, and Δ values for our hydrogen-bonded ion-pair systems is not upset by the presence of hydration effects in pK_A values. It therefore is unlikely that the hydration effects on pK_A are the predominant cause for the lack of any single generalized correlation of Δ and pK_{AB} values for the corresponding p-$FC_6H_4OH\cdots B$ complexes with pK_A values.[10] Studies on the role of solvation on the mobile equilibria between hydrogen-bonded complexes and hydrogen-bonded ion pairs are in progress, as well as applications of these equilibria to proton-transfer kinetics.[11]

(5) R. W. Taft, D. Gurka, L. Joris, P. von R. Schleyer, and J. W. Rakshys, *J. Amer. Chem. Soc.*, **91**, 4801 (1969).

(6) This is suggested by the work of Arnett on linear free energy–enthalpy relationships for proton-transfer equilibria; *cf.* E. M. Arnett, R. P. Quirk, and J. J. Burke, *ibid.*, **92**, 1260 (1970).

(7) E. M. Arnett, W. G. Bentrude, and P. McDuggleby, *ibid.*, **87**, 1541 (1965).

(8) (a) H. C. Brown and R. R. Holmes, *ibid.*, 77, 1727 (1955); (b) H. Van Looy and L. P. Hammett, *ibid.*, **81**, 3872 (1959); (c) E. J. Forman and D. N. Hume, *ibid.*, **83**, 1564 (1961); (d) M. M. Davis, *Nat. Bur. Stand. U. S. Monogr.*, No. **105** (1968).

(9) D. Gurka, R. W. Taft, L. Joris, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 5557 (1967).

(10) The alternate interpretation is also inconsistent with the observation that the F nmr shifts of 0.01 M p-FC_6H_4OH in binary H_2O mixtures of either 0.70- or 0.50-mol fractions of H_2O are in the same unique (non-pK_A) order as the Δ values in CCl_4 solution,[2] *i.e.*, pyridine < DMA < HMPA (unpublished results of Dr. L. Joris. We are indebted to Professor V. Gold for suggesting this experiment).

(11) (a) P. W. Arana, C. W. Su, and J. W. Watson, *Chem. Commun.*, 363 (1970); (b) J. E. Crooks and B. H. Robinson, Abstracts, International Conference on Mechanisms of Reactions in Solution, University of Kent at Canterbury, July 20, 1970, D1.

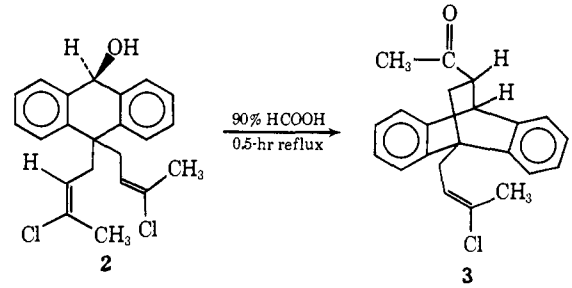
H. B. Yang, R. W. Taft*
Department of Chemistry, University of California
Irvine, California 92664
Received November 9, 1970

Intramolecular Alkylation of Internal Chloro Olefins. A Facile Route to the D Ring in 20-Keto Steroids

Sir:

We recently demonstrated that intramolecular electrophilic attack upon 2-chloro-1-ene side chains constitutes a general method for cycloalkanone synthesis[1] and also noted that internal chloro olefins provide entry to cycloalkyl ketones.[1] This report illustrates how acetylcycloalkanes can be quickly assembled from 1,3-dichloro-2-butene and the homologous 2,5-dichloro-2-pentenes.[2] A particularly relevant illustration of the power of this approach in organic synthesis is the direct assembly of the trans-fused 1-acetyl-8-methylhydrindan system, exemplified in the transformation **11** → **12** below, which promises to have broad utility in construction of the C/D hydrindan system of steroids.[3]

Typical of the value of 1,3-dichloro-2-butene (**1**) as an annelating agent is the efficient cyclization of **2**,[4,5] mp 104–106°, prepared by alkylation of anthrone with excess **1** and subsequent lithium aluminum hydride reduction, to **3**[4] in 92% yield. A noteworthy feature of this reaction[6] is retention in **3** of an *un-*



2 **3**

(1) P. T. Lansbury, E. J. Nienhouse, D. J. Scharf, and F. R. Hilfiker, *J. Amer. Chem. Soc.*, **92**, 5649 (1970).

(2) M. S. Newman and G. Kaugars, *J. Org. Chem.*, **31**, 1379 (1966).

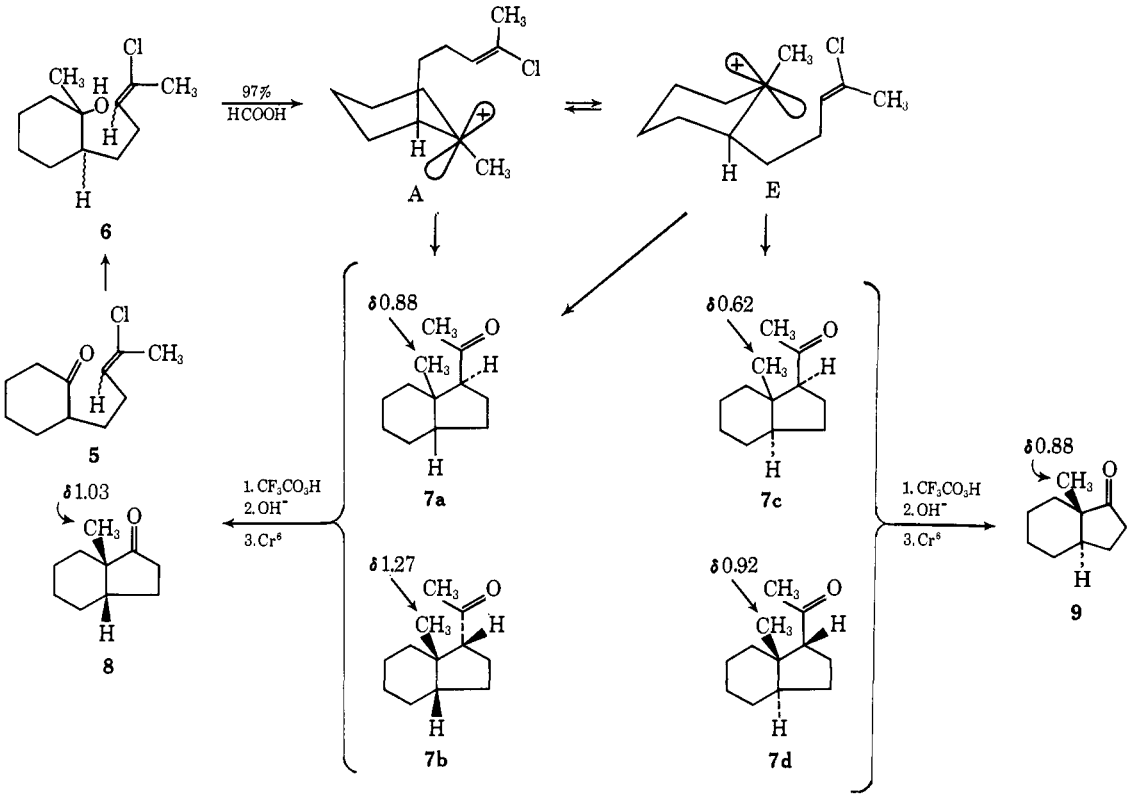
(3) For recent discussions of this problem and some solutions, see: (a) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965); (b) G. Stork and P. L. Stotter, *J. Amer. Chem. Soc.*, **91**, 7780 (1969); (c) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. French, D. G. Marten, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, 541 (1966).

(4) Characterized fully by (a) satisfactory nmr, ir, uv, and mass spectral analyses where appropriate and (b) elemental analysis.

(5) Most vinyl chlorides used in this work are a cis–trans mixture, which can be used without separation since neither geometric isomer derived therefrom offers any substantial advantages in the ring-forming step.

(6) Vicinal coupling of the bridgehead proton (δ 4.6 ppm, J = 2.5 Hz) in **3**, which disappears upon deuteration with base, confirms that a transannular allylic shift (from C_9 to C_{10}) did *not* preceed cyclization. Had this been the case (interchange bridgehead groups in structure **3**), the bridgehead proton would be split at least into a triplet, with no

Scheme I



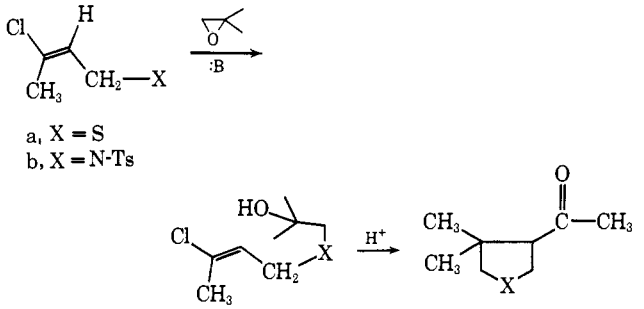
changed chlorocrotyl substituent, which further supports our previous contention[1] that enols are *not* involved in formolytic cyclizations.[7]

For initial exploitation of 2,5-dichloro-2-pentene[5] (**4**) we alkylated cyclohexanone[8] to produce **5**,[5] which was in turn treated with ethereal methylmagnesium iodide. The resuling carbinol **6**[4a] formolyzed almost quantitatively to an oily mixture of four 1-acetyl-8-methylhydrindans (**7**)[4a] characterizable by their individual 8-CH_3 nmr signals, as noted in Scheme I, and in part by alternate synthesis.[9] Degradation of the ketone mixture (**7a–d**), using Baeyer–Villiger oxidation, ester saponification, and chromic acid oxidation,[10] afforded *cis*-8-methyl-1-hydrindanone (**8**)[11] from **7a** and **7b** and *trans*-8-methyl-1-hydrindanone (**9**)[10] from **7c** and **7d**. The ratio of **8** to **9** was *ca.* 3.1 (vpc on Carbowax 20M column, 150°) from a number of runs, indicating that while the cyclization was quite efficient,[12] the stereochemical outcome was not, insofar as applying the method to steroid synthesis.

Since cyclization of the conformationally mobile *tert*-cyclohexyl cations (see Scheme I) may proceed more rapidly from ion A, thus enriching the product mixture only in **7a** and **7b**, we felt that a decisive experiment should utilize a rigid bicyclic carbonium ion with a relatively nonepimerizable side chain as well. Accordingly, monoalkylation[13] of $\Delta^{1,9}$-octalone[14] with **4** (first converted to the iodide[4a]) afforded **10**[4a] (ir_{film} 6.02 μ carbonyl; uv λ_{max}^{EtOH} 205, 249 mμ; M^+ at 252), which was selectively reduced with lithium in ammonia[15a] by inverse addition[15b] at −75° to provide **11**[4a] (carbonyl band at 5.86 μ, M^+ 254) in 65% yield;

change upon H–D exchange adjacent to the ketone. Such a rearrangement did occur in 9,9-diallyl-10-anthrol during acetolysis (A. L. J. Beckwith, W. B. Renfrow, A. Renfrow, and J. K. Tuebner, *Tetrahedron Lett.*, 3463 (1968)).

(7) Additional applications of **1** involved assembly of heterocycles a and b, following principles e‹pounded earlier;[1] P. C. Briggs, Ph.D. Thesis, State University of New York at Buffalo, 1970.



(8) *Via* the imine salt method (G. Stork and S. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963)).

(9) An independent synthesis of **7a** and **b** involved conjugate addition of lithium dimethylcuprate to 1-acetyl-$\Delta^{1,8}$-hydrindene (W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, **27**, 3263 (1962)) followed by equilibration; the epimeric pair was degraded to pure **8**.

(10) *Cf.* C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, p 409. These small-scale degradations gave *ca.* 50% overall yields but individual steps were found to proceed to completion by infrared monitoring.

(11) W. S. Johnson, *J. Amer. Chem. Soc.*, **66**, 215 (1944). We thank Professor Johnson for samples of semicarbazones of **8** and **9**.

(12) Analogous results were obtained from ethyl- and vinylmagnesium bromide adducts derived from **5**, giving the corresponding 8-ethyl- and 8-vinyl-1-acetylhydrindan mixtures (P. T. Lansbury and T. R. Demmin, unpublished results).

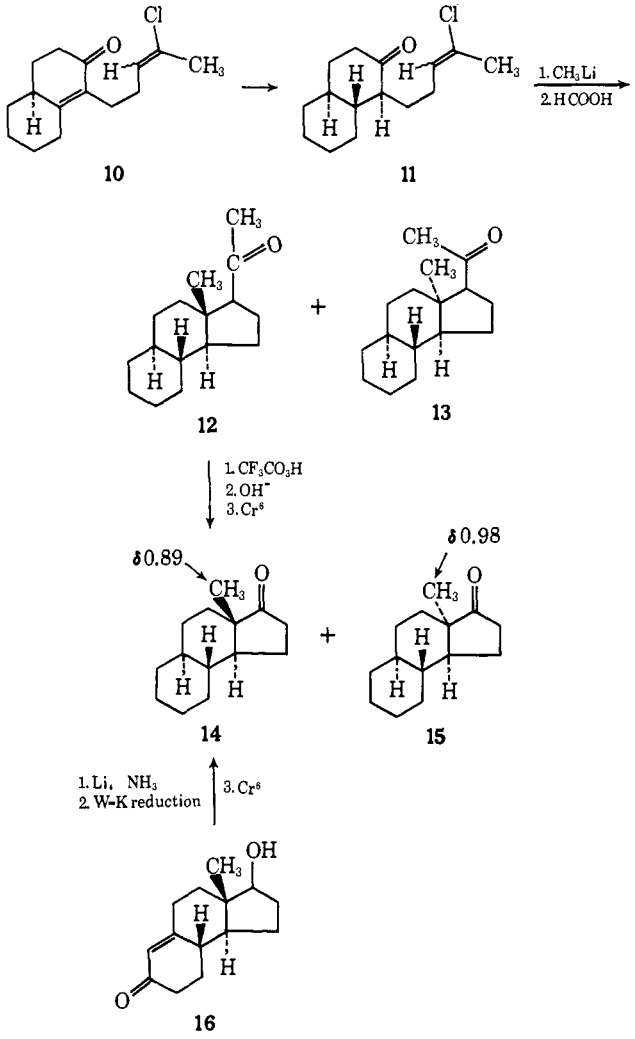
(13) N. W. Atwater, *J. Amer. Chem. Soc.*, **82**, 2847 (1960).

(14) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(15) (a) Reductive alkylation of the octalone (G. Stork, N. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965)) with **4** produces the *trans*-2-decalone with an axial side chain that cannot be fully epimerized without extensive dehydrochlorination. (b) *Ca.* 4 mmol of lithium in 50 cm^3 of liquid ammonia in a jacketed, *cooled* addition funnel was added slowly to 2 mmol of **10** in 25 cm^3 of ammonia and 15 cm^3 of ether which was stirred, also at −75°. After the addition, work-up was performed as usual.[15a]

conventional Birch reduction resulted in reduction of the vinyl chloride as well as the enone. Conversion

Scheme II



of **11** to the carbinol with methyllithium proceeded in 85% yield; subsequent formolysis produced a 2:1 mixture of tricyclic ketones[4a] **12** and **13** (*ca.* 90%, based on the carbinol; see Scheme II). Degradation of this mixture[10] gave trans-fused **14**[4a] and its cis epimer **15** in a ratio of *ca.* 65:35 (vpc on SE-30 column, 190°). Presumably this observed ratio closely reflects the relative amounts of **12** and **13** present before the degradation sequence.[10] Both **14** and **15** showed infrared carbonyl bands at 5.75 μ (neat) and the expected M^+ at *m/e* 206. Full confirmation of the stereostructure of **14** was obtained by an alternate, three-step conversion of tricyclic ketone **16**[16] which produced material identical with that from **12**.

It is now clear that the D ring in 20-keto-steroid synthesis can be successfully trans fused onto ABC or BC precursors without subsequent epimerization, when the chloro-olefin side chain, which can be modified in useful ways, is kept equatorial. In closing, we wish to emphasize that these results, taken with earlier ones,[1] broaden the options available for direct construction of functionalized five-membered rings.

(16) Kindly furnished by Dr. G. Nomine of Roussel-Uclaf.

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P. T. Lansbury,* P. C. Briggs
T. R. Demmin, G. E. DuBois
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214
Received November 30, 1970

Nuclear Magnetic Resonance Studies of Poly-DL-alanine and Poly-L-alanine in Solvents with Strong Acids

Sir:

Many polypeptides undergo conformational transitions when solvent composition, or temperature, is varied.[1] In mixed solvents containing strong organic acids, the driving force for the transition may arise from preferential interactions of the peptide residues with the hydrogen-bonding solvent,[2a-c] or from electrostatic repulsions developed from protonation of the amide groups by the strong acid.[3,4]

Many physicochemical techniques have been used to obtain some insight into the molecular basis of these transitions in acid solvents.[4] In recent years nmr investigations have been particularly prevalent.[5] Of

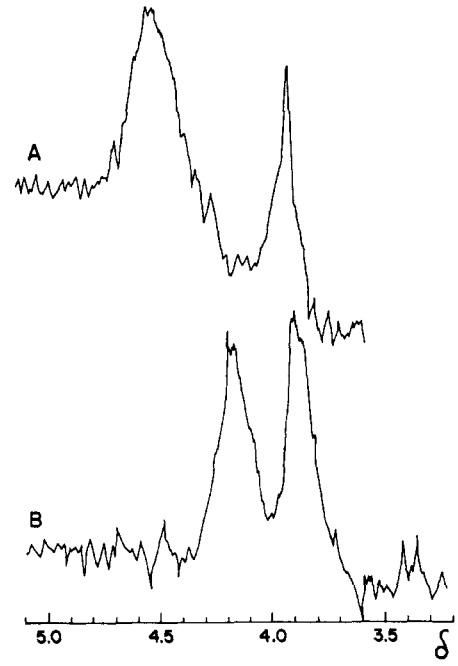

Figure 1. Nuclear magnetic resonance spectra of: A, 0.1% poly-DL-alanine in 12% CF_3COOH–88% $CDCl_3$; B, 0.1% poly-L-alanine in 1% CF_3COOH–99% $CDCl_3$. Chemical shift, δ, in parts per million, downfield from tetramethylsilane reference.

(1) G. D. Fasman, Ed., "Poly-α-amino Acids," Marcel Dekker, New York, N. Y., 1967, and references cited therein.
(2) (a) W. E. Stewart, L. Mandelkern, and R. E. Glick, *Biochemistry*, **6**, 143 (1967); (b) F. A. Bovey, *Pure Appl. Chem.*, **16**, 417 (1968); (c) J. A. Ferretti and B. W. Ninham, *Macromolecules*, **3**, 30 (1970), and references cited therein.
(3) S. Hanlon and I. M. Klotz, *Biochemistry*, **4**, 37 (1965).
(4) J. H. Bradbury and M. D. Fenn, *Aust. J. Chem.*, **22**, 357 (1969), and references cited therein.
(5) G. C. K. Roberts and O. Jardetzky, *Advan. Protein Chem.*, **24**, 447 (1970).