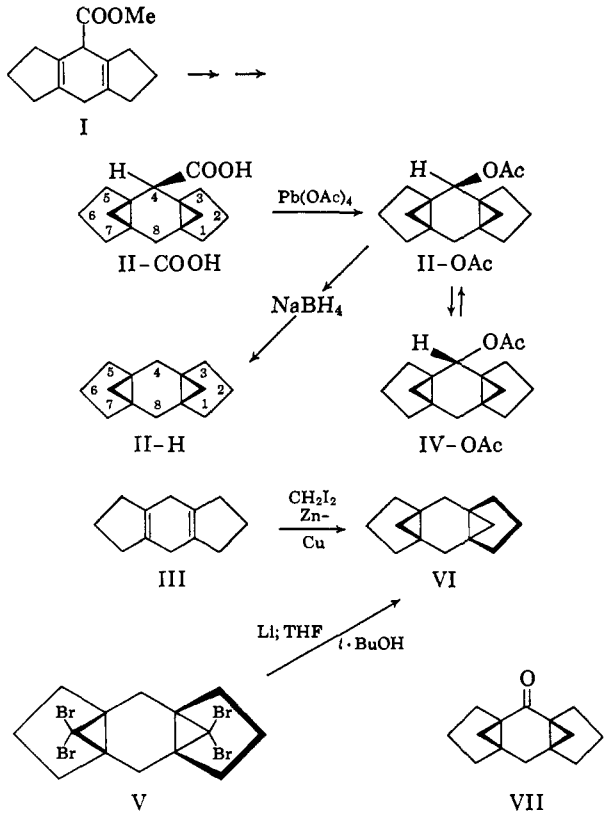

at τ 7.51 for four bisallylic protons and no vinyl proton signal. One route from III to VI is by way of the bisdibromocarbene adduct[4] V, mp 260–263°, obtained along with monodibromocarbene adduct,[4] mp 30–32°, from treatment of III with $CHBr_3$ and KOBu-*t*. The *trans* relationship of the cyclopropane groups in V is indicated by a zero dipole moment[7a] as well as by the nmr spectrum (CCl_4) which shows a sharp singlet for four protons at τ 8.33 corresponding to only one variety of C_4 and C_8 proton. Debromination of V with Li and *t*-BuOH in THF leads to the parent *trans* hydrocarbon[4] VI, mp 49–50°, whose nmr spectrum (CCl_4), with a sharp singlet at τ 8.22 for the four equivalent C_4 and C_8 protons,[7b] and an AB quartet with J_{AB} = 5 cps, τ_A 9.59 and τ_B 10.07 for the four cyclopropane protons, is consistent with the *trans* designation.[7b] The parent *trans* hydrocarbon VI (>99.5% *trans*) is also obtained from the Simmons–Smith reaction on the dihydrohydrindacene III. This result is thus in striking contrast with the one observed from the Simmons–Smith reaction on the dihydrohydrindacenecarboxylic ester I, emphasizing the directing effect of the COOMe group.[2c]

On the basis of the available evidence it is thus clear that the compounds designated by II have the *cis* relationship of the cyclopropane groups. The arguments for an all-*cis* configuration of II-COOH with the carboxyl group also *cis* have been given previously.[2c] That acetate II-OAc is also the *cis* epimer is clear from additional evidence. Thus, treatment of II-OAc with $LiAlH_4$ in ether gives rise to the corresponding alcohol[4] II-OH, mp 90–91°, whose nmr spectrum (CCl_4) shows a singlet at τ 5.83 for the α-proton. This alcohol is converted readily by active MnO_2 to the corresponding ketone[4] VII, mp 123–124°, carbonyl stretching frequency 1655 cm^{-1}, whose nmr spectrum (CCl_4) shows an AB quartet with J_{AB} = 6 cps, τ_A 9.16 and τ_B 9.60 for four cyclopropane protons. Reduction of this ketone gives rise to mixtures of alcohol II-OH and its epimer IV-OH, containing *ca.* 50% of the epimer when $LiAlH_4$ is employed in ether and *ca.* 80% of the epimer when 0.25 *M* $NaBH_4$ is used in refluxing *i*-PrOH (22 hr). Twice recrystallized IV-OH,[4] mp 102–104°, shows in its nmr spectrum (CCl_4) a singlet at τ 6.52 for the α-proton. By holding reaction times to a minimum, this alcohol may be acetylated with Ac_2O in pyridine at room temperature to yield the corresponding acetate[4] IV-OAc, mp 58–61°, whose nmr spectrum shows a singlet at τ 5.46 for the α-proton and an AB quartet with J_{AB} = 5 cps, τ_A 9.43 and τ_B 9.93 for the cyclopropane protons.

Attempts to equilibrate the epimeric alcohols II-OH and IV-OH by conventional means, using $Al(OPr\text{-}i)_3$ in *i*-PrOH, were unsuccessful because of the great tendency toward ionization displayed by these systems. Thus, ether formation competes too well with equilibration. However, it is possible to equilibrate the acetates smoothly in Ac_2O. In this solvent at room temperature, acetate IV-OAc undergoes very clean epimeric equilibration with a half-life of *ca.* 1 hr (k = *ca.* 2×10^{-4} sec^{-1}). At equilibrium the epimeric ratio, II-OAc:IV-OAc, is 98.97:1.03 as analyzed by nmr using a Varian C-1024 time-averaging computer (CAT) on 100 scans of the α-proton region of the spectrum.

That the *cis* epimeric assignment should be given to II-OAc and II-OH and the *trans* assignment to IV-OAc and IV-OH is clear on the basis of two criteria. One is the considerably higher nmr chemical shift for the α-proton in the IV-OH and IV-OAc relative to II-OH and II-OAc due to the shielding effect of the cyclopropane rings *cis* to the α-proton in the IV derivatives.[7b] The other is the greater thermodynamic stability of the II-OAc relative to IV-OAc, models predicting greater opposition to an acetoxy group from the cyclopentano groups in IV-OAc than from the cyclopropano groups in II-OAc. On the basis of the nmr evidence, the II-OMe is also *cis*, the solvolysis of II-OAc being highly stereospecific.[2a] The same kind of stereospecificity is obviously associated with the II-COOH–$Pb(OAc)_4$ reaction, product formation probably occurring here from a carbonium ion.[3]

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(7) (a) W. D. Kumler, private communication. For a related case, see W. D. Kumler, R. Boikess, P. Bruck, and S. Winstein, *J. Am. Chem. Soc.*, **86**, 3126 (1964); (b) see R. S. Boikess and S. Winstein, *ibid.*, **85**, 343 (1963), for analogous nmr examples.

Rate and Stereochemistry of Solvolysis of a Biscyclopropylcarbinyl System[1]

Sir:

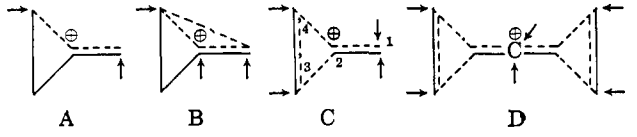
We have previously discussed[2b] the possible multiplicity of nonclassical structures for ions related to

(1) (a) Research supported in part by the National Science Foundation; (b) reported in part at the Annual Meeting of the Japanese Chemical Society, Osaka, Japan, April 4, 1965, and the Japanese–American Seminar in Physical Organic Chemistry, Kyoto, Japan, April 6–10, 1965.

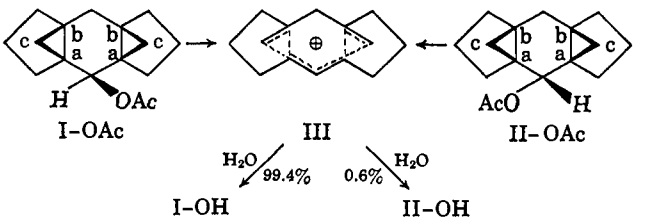
(2) (a) See P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc.,

allylcarbinyl, cyclopropylcarbinyl, and cyclobutyl derivatives, homoallyl[2b] (A), bicyclobutonium[2c] (B), and "symmetrical homoallyl" [2b] (C) types being considered.[2] In formulas A, B, and C are indicated the patterns of electron delocalization, together with the presumed points of attack by nucleophiles if one species is to be the sole product-forming one.[2b] In the "symmetrical homoallyl" structure, the visualized geometry was one with the plane of the trigonally hybridized C_1 carbon atom perpendicular to the plane of the "cyclopropane" ring.[2b] This conformation was suggested by wave mechanical considerations to be most favorable for interaction of the cyclopropyl group with the C_1 cationic center.[2b] The effects of two or three cyclopropyl groups on the same cationic center tend to be additive,[3] and this fact may be accommodated on the basis of any of the three modes of interaction (A, B, or C). D represents a biscyclopropylcarbinyl cation based on the "symmetrical homoallyl" or C style of interaction.

The nmr spectra of several cyclopropyldialkylcarbinyl and cyclopropylphenylcarbinyl cations in FSO_3H–SO_2–SbF_5 or FSO_3H at low temperatures have been observed recently,[4] and these have supported the "symmetrical homoallyl" or C type of structure. Deno[4b] refers to the latter as the "bisected" structure. Products and stereochemistry of solvolysis of related secondary systems, methylcyclopropylcarbinyl[5a,b] and 2-bicyclo[4.1.0]heptyl,[5b] also support the C type of structure for the intermediate cation.



In the case of biscyclopropylcarbinyl cations, the nmr spectra[4] of several of them are in accord with structure D, but we know of no solvolytic stereochemical work on related systems. The present communication reports the reactivity and stereochemical behavior in solvolysis of the epimeric biscyclopropylcarbinyl systems I and II which have the two cyclopropane groups in a *cis* relationship.[6a] Epimer I is the all-*cis* one, while II has the leaving group *trans* to the cyclopropane methylene groups. Therefore, configurations are more favorable[2b] toward participation of the a–b cyclopropane bonding electrons during ionization of I-OAc and the a–c cyclopropane bonding electrons in ionization of II-OAc. The results are of interest in connection with nonclassical ions as regards structure and possible relationships between ground-state and transition-state free energies.[2b]



As already evident from qualitative observations,[6a] the I and II esters are very reactive in solvolysis. First-order solvolysis rate constants for I-*p*-nitrobenzoate, I-OPNB, mp 121–122°, and I-OAc and II-OAc in 80 and 90% aqueous acetone are given in Table I.

Table I. Solvolysis of Esters

Solvent	Temp, °C	10^5k, sec^{-1} I-OPNB	I-OAc	II-OAc
90% Me_2CO	25.0	70		
80% Me_2CO	25.0	770	15.0[a]	7.83
Product from 80% Me_2CO + $NaHCO_3$	25.0	% I-OH	99.4[b]	99.5[b]
		% II-OH	0.6[b]	0.5[b,c]

[a] 24.5°. [b] Accuracy, 0.1%. [c] After correction for a small amount of *trans*-II-OH in the starting *trans*-II-OAc analyzed with the CAT. No II-OH or II-OAc was detected in the starting I-OAc.

As regards solvolysis products, essentially quantitative yields of alcohol, very nearly pure I-OH, were obtained from hydrolysis of I-OPNB, I-OAc, and II-OAc in 80% acetone containing $NaHCO_3$. This same kind of stereochemical result is observed in methanolysis[6a] of I-OAc. Examination of the nmr spectra of the products from I-OAc and II-OAc using a Varian C-1024 time-averaging computer (CAT) showed both alcohol products to be identical, 99.5% *cis*-I-OH and 0.5% *trans*-II-OH. No other product (<0.1%) could be detected by way of any extraneous peak due to a new product[7] (*e.g.*, signals for a new α-proton or a vinyl proton).

The quantitative identity of products from both I-OAc and II-OAc shows that the identical intermediate ion or spectrum of ions is involved for both epimeric esters. While the available evidence does not preclude the participation of more than one variety of nonclassical species, none of it requires such multiplicity. The evidence is consistent with one species having both cyclopropyl groups in the "symmetrical homoallyl" or "bisected" arrangement. This species is represented by III. We should note that the "symmetrical homoallyl" designation is strictly applicable only to symmetrically substituted systems. With unsymmetrical substitution of the cyclopropane rings, as in the present case, the a–b and a–c bonds are inevitably involved at least somewhat unequally.

Both electron delocalization and steric effects are involved in the control of rate and stereochemistry of solvolysis of the I and II derivatives. The rate of ionization of I-OPNB is nearly as high as that of the spirodienyl ester[8] IV-OPNB which leads to a benzen-

Publishers, New York, N. Y., 1965, for an excellent reprint collection and commentary; (b) S. Winstein and E. M. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959), and previous papers; (c) J. D. Roberts, *et al.*, *ibid.*, **81**, 4390 (1959).

(3) (a) H. Hart and J. M. Sandri, *ibid.*, **81**, 320 (1959); (b) H. Hart and P. A. Law, *ibid.*, **84**, 2462 (1962).

(4) (a) C. V. Pittman, Jr., and G. Olah, *ibid.*, **87**, 2998 (1965); (b) N. Deno, *et al.*, *ibid.*, **87**, 3000 (1965).

(5) (a) J. D. Roberts, Abstracts, 16th National Organic Chemistry Symposium of the American Chemical Society, Seattle, Wash., June 15–17, 1959, p 9; (b) H. L. Goering and K. E. Rubenstein, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 28–31, 1966, p 5K.

(6) (a) L. Birladeanu, T. Hanafusa, and S. Winstein, *J. Am. Chem. Soc.*, **88**, 2315 (1966); (b) T. Hanafusa, L. Birladeanu, and B. Johnson, unpublished work.

(7) Only under very vigorous conditions, permitting many repeated ionizations of I derivatives, are any cyclopropane ring-opened products observed. These are still being investigated.

(8) E. C. Friedrich and S. Winstein, *Tetrahedron Letters*, **No. 11**, 475 (1962); (b) E. C. Friedrich, unpublished work.

ium-type ion. The enormous accelerating effect of α-cyclopropyl groups is clearly evident. Comparing further, the rate of ionization of I-OPNB is 32 times that of the simpler analog without the cyclopentano rings,[6b] V-OPNB, or the value estimated for the dicyclopropylcarbinyl analog[3a] VI-OPNB, 7.5×10^5 times that of the bicyclic analog[8b] VII-OPNB containing only one cyclopropane ring, and 3×10^7 times that of the allylic cyclohexenyl ester[8b] VIII-OPNB. The relative rates of solvolysis in 80% acetone at 25°, estimated from available rate data, are listed with the structural formulas.

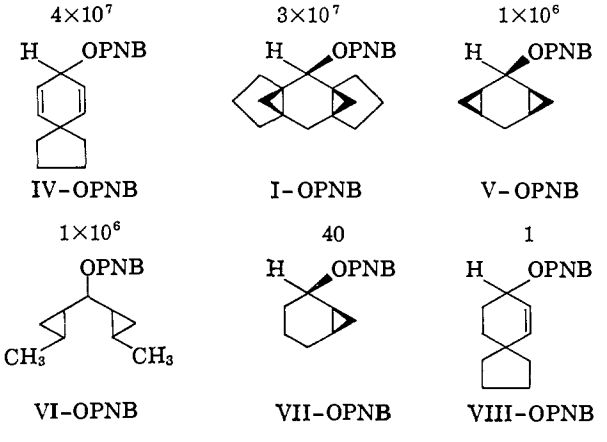
As regards relative ionization rates of the *cis* and *trans* epimers, that of the *cis*-I-OAc is *ca.* twice as high as that of the *trans*-II-OAc. The free-energy difference between the *trans* transition state and the *cis*, RT ln 200, is in the same direction and slightly greater than the ground-state free energy difference, *RT* ln 100, which we know from actual equilibration.[6a] The stereospecificity in alcohol product formation shows that the free-energy difference between *trans* and *cis* transition states in alcohol formation is also *RT* ln 200, the same as the difference between *trans* and *cis* acetate transition states.

Kinetic and thermodynamic control of products are, of course, correlated with reactivity[2b] by means of eq 1 and 2, where K measures thermodynamic control, (k_{II}/k_I) is a reactivity ratio R, and (k_{-I}/k_{-II}) is a partition factor P representing kinetic control or stereospecificity. Applying eq 2 to alcohol equilibration, we know exactly only the value of P, 200, from the solvolysis results. However, we can approximate R as *ca.* 1/2, the value from solvolysis of the acetates, and K as *ca.* 100 from equilibration of the acetates.

$$\text{II-X} \underset{k_{-II}}{\overset{k_{II}}{\rightleftharpoons}} \text{R}^+ \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} \text{I-X} \qquad (1)$$

$$K = \frac{(\text{I-X})}{(\text{II-X})} = \left(\frac{k_{II}}{k_I}\right)\left(\frac{k_{-I}}{k_{-II}}\right) = RP \qquad (2)$$

It is interesting to compare the situation with the I and II epimers with that pertaining to the *i*- and epi-*i*-cholesteryl epimers.[2b] With I and II, the more stable epimer is slightly more reactive and is highly favored in kinetic product control. On the other hand, with the *i*- and epi-*i* derivatives, the less stable *i* epimer is more reactive and highly favored by kinetic product control. This illustrates the different possible blends of steric factors connected with the leaving (or incoming) group in ground and transition states and stereoelectronic factors connected with participation of the a–b and a–c cyclopropane bonding electrons in electron delocalization of the transition state.



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A Pictorial Description of the "Lock and Key" Theory[1]

Sir:

We wish to report a striking model for enzymatic specificity, the cycloamylose-catalyzed reactions of substituted phenyl esters. The cycloamyloses (cyclodextrins) approximate a torus and are capable of forming inclusion compounds in solution[2] with a variety of organic and inorganic substances. Furthermore, the cycloamyloses have been shown to impose both rate accelerations and decelerations on organic reactions, such as the acceleration of the cleavage of diphenyl pyrophosphate (with concomitant phosphorylation of the cyclodextrin)[3] and the deceleration of the hydrolysis of ethyl *p*-aminobenzoate.[4] We have investigated the effect of cycloamyloses on the rate of reaction of substituted phenyl acetates in order to determine the stereochemical requirements of the interaction in these systems.

The alkaline hydrolysis of a series of substituted phenyl acetates was followed spectrophotometrically by observing the liberation of the phenol at pH 10.6. The accelerating effects of cyclohexaamylose and cycloheptaamylose on the rates of some of these reactions are shown in Table I. The accelerations are dependent on the concentration of cycloamylose, approaching a maximum (saturation) value at high concentration, as has been noted before.[3,4] The data were treated by a variation of Michaelis–Menten kinetics[5] to determine the rate constant of the bound species, k_c, and the (dissociation) constant of binding, K_d, in Table I. We have also observed competitive inhibition of the cycloamylose rate accelerations[6] by addition of molecules such as *m*-chlorobenzoate ion[7] to the reaction mixture. The observations of saturation and competitive inhibition suggest that the reaction proceeds through a cycloamylose–ester complex.

The cycloamylose accelerations (k_c/k_u) are often large and are markedly substituent dependent. In contrast, the accelerations of these hydrolyses by 0.06 *M* α-methyl glucoside are small (10–20%) and are independent of substituent. Although the alkaline hydrolysis of substituted phenyl acetates follows a Hammett relationship with $\rho = 1.07$ (correlation coefficient

(1) This research was supported by the National Science Foundation.
(2) F. Cramer, "Einschlussverbindungen," Springer-Verlag, Berlin, 1954; D. French, *Advan. Carbohydrate Chem.*, **12**, 189 (1957); J. A. Thoma and L. Stewart in "Starch: Chemistry and Technology," Vol. I, R. L. Whistler and E. F. Paschall, Ed., Academic Press Inc., New York, N. Y., 1965, p 209.
(3) N. Hennrich and F. Cramer, *J. Am. Chem. Soc.*, **87**, 1121 (1965).
(4) J. L. Lach and T. F. Chin, *J. Pharm. Sci.*, **53**, 924 (1964).
(5) A. K. Colter, S. S. Wang, G. H. Megerle, and P. Ossip, *J. Am. Chem. Soc.*, **86**, 3106 (1964).
(6) See also N. Hennrich and F. Cramer, *ibid.*, **87**, 1121 (1965).
(7) *m*-Chlorobenzoic acid is known to form relatively stable complexes with cycloamyloses: J. L. Lach and T. F. Chin, *J. Pharm. Sci.*, **53**, 69 (1964).