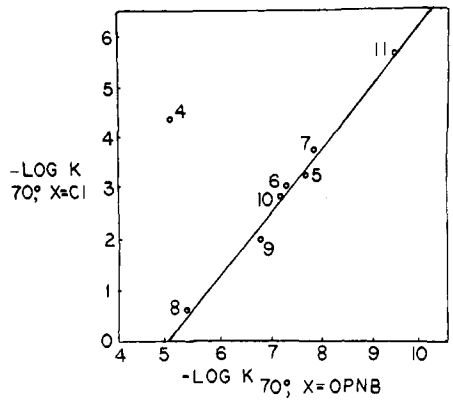
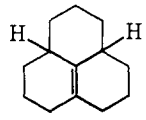


Figure 1. Correlation of the solvolysis rates of tertiary chlorides in 80% ethanol with the corresponding *p*-nitrobenzoates in 80% acetone at 70° (correlation coefficient = 0.994 omitting **4**). The data are summarized in Table I.

only olefin **12** on treatment with KO-*t*-C_4H_9 in $(CH_3)_2SO$



12

at 55° for 2 hr or as solvolysis product in 80% ethanol.[11]

The conductometric rate constants for solvolysis of **4**-Cl in 80% EtOH were 5.30×10^{-6} sec^{-1} at 49.85° and 7.31×10^{-5} sec^{-1} at 75.3 ($\Delta H^{\pm}$ = 22.4 kcal/mol; $\Delta S^{\pm} = -13.6$ eu). Interpolation gave a rate constant of 4.36×10^{-5} sec^{-1} at 70°, a value in excellent agreement with that predicted by eq 1. This confirms the existence of the very large *p*-nitrobenzoate leaving group effect in **4**-OPNB.

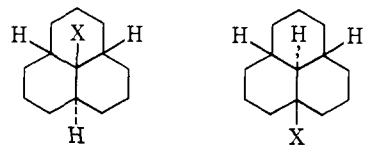
Figure 1 expresses this leaving group effect graphically. In most systems where 1,5- and 1,6-type nonbonded interactions are absent, *p*-nitrobenzoate rate data are correlated well by eq 2. On the basis of eq 2, **4**-OPNB, which deviates markedly, is 2960 times faster than expected. We ascribe this acceleration (amounting to 5.4 kcal/mol in free energy) to relief of *p*-nitrobenzoate strain.

$$-\log k_{\mathrm{Cl,80\%EtOH,70^\circ}} = -1.24 \log k_{\mathrm{OPNB,80\%acetone,70\%}} - 6.25 \quad (2)$$

This conclusion has important implications for the interpretation of the solvolytic data of highly branched tertiary *p*-nitrobenzoates. As seen in **1**-OPNB, $(t\text{-Bu})_3$COPNB suffers from the same kind of 1,5- and 1,6-interactions as does **4**-OPNB. Relief of *p*-nitrobenzoate strain (F strain) should be a significant factor in the acceleration observed (at 70° in 60% (weight) dioxane, **1**-OPNB/*t*-Bu-OPNB = 5100).[12] A computer quantitative analysis[13] of such highly congested systems will be presented separately. This analysis shows that little strain is actually relieved during ionization of many but not all highly branched chlorides[14] and alcohols.[3] Whenever possible, solvolytic reactivity studies should employ chloride or similar leaving groups as opposed to esters in order to minimize F-strain effects.

(11) The preparation of the four isomeric perhydro-9*b*-phenalenols, the chemistry of the perhydrophenalene system, and the solvolytic reactivity of the isomeric *p*-nitrobenzoates will be presented separately.
(12) Calculated from values in ref 9.
(13) Unpublished calculations of D. Khoury, Princeton, University.
(14) For example, V. J. Shiner, Jr., and G. F. Meier, *J. Org. Chem.*, 31, 137 (1966), showed that the more reactive chloride obtained from di-*tert*-butylmethylcarbinol (P. D. Bartlett and M. S. Swain, *J. Amer. Chem. Soc.*, 77, 2801 (1955)) was not di-*tert*-butylmethylcarbinyl chloride (18.4 times more reactive than *tert*-butyl chloride) but rather was triptyldimethylcarbinyl chloride (89,000 times more reactive than *tert*-butyl chloride). Our calculations[13] are in agreement with these results.

Table I. Comparison of Solvolysis Rates of Chlorides in 80% Ethanol with the Corresponding *p*-Nitrobenzoates in 80% Acetone at 70°



6 **7**

Compound	$k_{(Cl)}$, sec^{-1} (80% ethanol, 70°)	$k_{(OPNB)}$, sec^{-1} (80% acetone, 70°)
4	4.36×10^{-5} [a]	8.35×10^{-8} [a]
2-Methyl-2-*exo*-norbornyl (**8**)	2.42×10^{-1} [b]	3.75×10^{-6} [c]
2-Methyl-2-adamantyl (**9**)	1.05×10^{-2} [d]	1.32×10^{-7} [e]
tert-Butyl (**10**)	1.51×10^{-3} [f]	5.47×10^{-8} [g]
6	7.63×10^{-4} [h]	3.99×10^{-8} [g]
5	5.68×10^{-4} [i]	1.79×10^{-8} [g]
7	1.95×10^{-4} [h]	1.18×10^{-8} [a]
1-Adamantyl (**11**)	2.45×10^{-6} [j]	3.05×10^{-10} [a]

[a] This work. [b] K. L. Servis, S. Borcic, and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968). [c] S. Ikegami, D. L. Vander-Jagt, and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 7124 (1968). [d] J. M. Harris, unpublished results, $\Delta H^{\pm}$ = 22.3 kcal/mol and $\Delta S^{\pm} = -2.9$ eu. [e] Reference 10. [f] A. H. Farnberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2770 (1956). [g] H. C. Brown and W. C. Dickason, *ibid.*, **91**, 1226 (1969). [h] Reference 5. [i] A. F. Boschung, M. Geisel, and C. A. Grob, *Tetrahedron Lett.*, 5169 (1968); K. B. Becker, A. F. Boschung, M. Geisel, and C. A. Grob, *Helv. Chim. Acta*, **56**, 2747 (1973). [j] P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961).

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Evidence against Appreciable Hidden Return in Solvolyses of Simple Secondary Substrates

Sir:

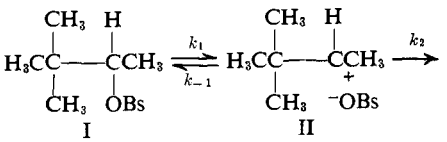
A new mechanism for anchimeric assistance has been postulated recently;[1-3] acceleration due to neighboring

(1) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 6031 (1969).
(2) (a) V. J. Shiner, Jr., and W. Dowd, *J. Amer. Chem. Soc.*, **91**, 6528 (1969); (b) V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *ibid.*, 7748 (1969).
(3) (a) W. M. Schubert and P. H. LeFevre, *J. Amer. Chem. Soc.*, **91**, 7746 (1969); **94**, 1639 (1972); (b) W. M. Schubert and W. L. Henson, *ibid.*, **93**, 6299 (1971).

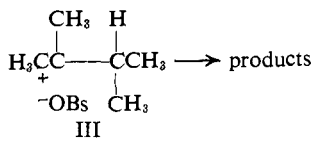
group participation may occur *after* and not *during* intimate ion pair formation.[4,5a] Shiner, Fisher, and Dowd[2b] reported that in trifluoroacetic acid (TFA) 3,3-dimethyl-2-butyl (pinacolyl) brosylate (I) solvolyzed 2800 times faster than 2-propyl brosylate at 12°. This acceleration was attributed not to methyl participation in the pinacolyl ionization step, k_1, but to differences in ion pair partitioning (k_{-1} *vs.* k_2) between the two substrates (eq 1).[4,5a] 2-Propyl brosylate was postulated to

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+X^- \xrightarrow{k_2} \text{products} \qquad (1)$$

exhibit "hidden return" ($k_{-1} \gg k_2$), which was alleged to retard severely (many hundred fold) the observed rate of solvolysis.[6-8] Rapid methyl rearrangement in the pinacolyl ion pair II was suggested to prevent such hidden return ($k_2 \gg k_{-1}$). We believe that these interpretations are incorrect.



I II



III

There is negligible evidence that solvolyses of pinacolyl arenesulfonates are anchimerically assisted.[3a,9-14]

(4) For recent reviews of the mechanism of solvolysis and ion pair formation see (a) D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972); (b) J. M. Harris, *Progr. Phys. Org. Chem.*, in press; (c) D. J. Raber, J. M. Harris, and P. v. R. Schleyer in "Ions and Ion Pairs in Organic Reactions," Vol. 2, M. Szwarc, Ed., Wiley, New York, N. Y., in press; (d) P. v. R. Schleyer in "Reaction Transition States," J. E. Dubois, Ed., Gordon and Breach, New York, N. Y., 1972, pp 197–210.

(5) V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, New York, N. Y., 1970, (a) pp 91–159; (b) pp 100–101; (c) pp 129–130; (d) p 125.

(6) This interpretation implies that the rates of solvolyses of many substrates which do not rearrange are *anomalously slow* (due to internal return); an extreme for mof this mechanism is represented by Sneen's speculative proposal that all SN2 reactions may proceed *via* nucleophilic attack on a rapidly and reversibly formed intimate ion pair.[7] For criticisms, see ref 4 and 8.

(7) (a) R. A. Sneen, *Accounts Chem. Res.*, **6**, 46 (1973); (b) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362 (1969); (c) H. Weiner and R. A. Sneen, *ibid.*, **87**, 292 (1965); (d) J. M. W. Scott, *Can. J. Chem.*, **48**, 3807 (1970); (e) J. Koskikallio, *Acta Chem. Scand.*, **26**, 1201 (1972).

(8) B. J. Gregory, G. Kohnstam, M. Paddon-Row, and A. Queen, *Chem. Commun.*, 1032 (1970); D. J. McLennan, *J. Chem. Soc., Perkin Trans. 2*, 1577 (1972); D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 4821 (1971); M. H. Abraham, *J. Chem. Soc., Chem. Commun.*, 51 (1973); J. F. Bunnett and D. L. Eck, *J. Amer. Chem, Soc.*, **95**, 1900 (1973).

(9) (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952); S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952); (b) G. C. Calhoun and R. L. Burwell, Jr., *ibid.*, **77**, 6441 (1955); (c) P. v. R. Schleyer, *ibid.*, **86**, 1854, 1856 (1964); (d) D. Bethell and V. Gold, "Carbonium Ions," Academic Press, New York, N. Y., 1967, p 263 ff.

(10) Acetolysis of pinacolyl tosylate is *slower* than expected from a σ^* treatment[11] due to the greater nucleophilic solvent assistance in less-hindered substrates; trifluoroacetolysis of even 2-propyl tosylate is believed to be limiting or nearly so: P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **92**, 2542 (1970).

(11) (a) A. Streitwieser, Jr., *J. Amer. Chem. Soc.*, **78**, 4935 (1956); (b) "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 122–126; (c) J. J. Harper, Ph.D. Thesis, Princeton University, 1968.

(12) Neighboring methyl in I appears to be less effective toward participation than the tertiary β-hydrogen in 3-methyl-2-butyl tosylate or the β-phenyl in 3-phenyl-3-methyl-2-butyl tosylate.[9a,c,d]

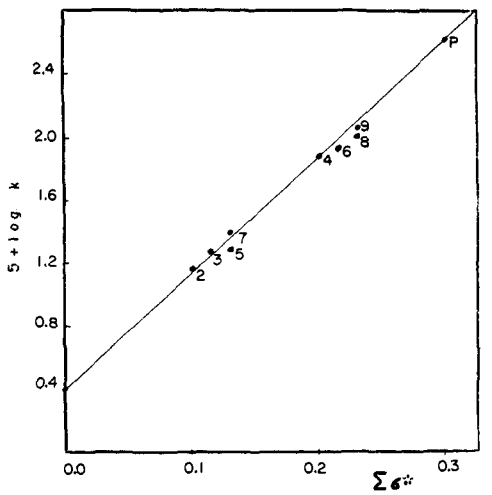


Figure 1. Rates of solvolysis of simple secondary tosylates in trifluoroacetic acid *vs.* $\Sigma\sigma^*$ (ref 19); $\rho^* = -7.21$, correlation coefficient = 0.998. Identification: 1, 2-propyl; 2, 2-butyl; 3, 2-pentyl; 4, 3-pentyl; 5, 2-hexyl; 6, 3-hexyl; 7, 2-heptyl; 8, 3-heptyl; 9, 4-heptyl; P = pinacolyl.

Actually, pinacolyl tosylate solvolyzes less than 200 times faster than 2-propyl tosylate at 25° in TFA (280 times at 12°?).[15-18] This acceleration is indicated to be entirely or almost entirely due to inductive–hyperconjugative effects by the linear $\Sigma\sigma^*$ plot, Figure 1.[19,20] The extent of deviations from such $\Sigma\sigma^*$ plots[11,16] are known to provide reliable and quantitative measures of anchimeric assistance.[11,21] Figure 1 shows that there is no kinetic evidence for abnormal behavior of either 2-propyl or pinacolyl in TFA and no basis for expecting mechanistic differences, such as hidden return in 2-propyl or anchimeric assistance in pinacolyl.

In order to test these conclusions, we have studied the analogous 1-adamantylmethylcarbinyl system IV. Because of the extra strain in the homoadamantyl skeleton, VII, rearrangement of IV is unfavorable;[22] buffered

(13) See G. Biale, D. Cook, D. J. Lloyd, A. J. Parker, I. D. R. Stevens, J. Takahashi, and S. Winstein, *J. Amer. Chem. Soc.*, **93**, 4735 (1971).

(14) For rates and products of closely related secondary neopentyl-type solvolyses, see A. P. Krapcho, J. E. McCullough, and K. V. Nahabedian, *J. Org. Chem.*, **30**, 139 (1965); A. P. Krapcho, B. S. Bak, R. G. Johnson, and N. Rabjohn, *ibid.*, **35**, 3722 (1970), and ref 11c. Also see B. Stephenson, G. Solladié, and H. S. Mosher, *J. Amer. Chem. Soc.*, **94**, 4184 (1972).

(15) In TFA at 25° (sec^{-1}), k(2-propyl tosylate) = 2.49×10^{-5} (ref 16), 2.27×10^{-5} (ref 17), and 2.14×10^{-5} (ref 18a) and k(pinacolyl tosylate) = 4.09×10^{-3} (ref 18b) and 3.79×10^{-3} (at 24.1°, ref 11c).

(16) P. E. Peterson, R. E. Kelley, Jr., R. Belloli, and K. A. Sipp, *J. Amer. Chem. Soc.*, **87**, 5169 (1965).

(17) A. Streitwieser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

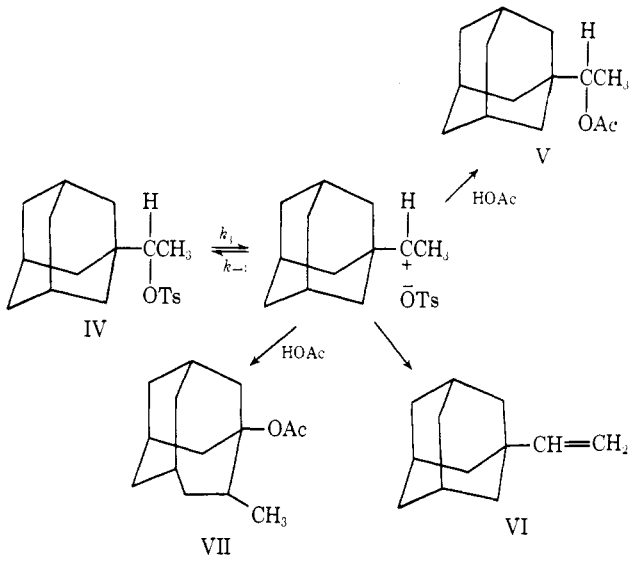
(18) (a) J. E. Nordlander and W. J. Kelly, *J. Amer. Chem. Soc.*, **91**, 996 (1969); (b) J. E. Nordlander, R. E. Gruetzmacher, and F. Miller, *Tetrahedron Lett.*, 927 (1973).

(19) Solvolytic data from ref 16, σ^* values taken from R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 591.

(20) Using Peterson's ρ value for TFA,[16] pinacolyl is calculated to solvolyze 130 times faster than 2-propyl tosylate.

(21) (a) C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4294 (1969); (b) P. v. R. Schleyer and C. J. Lancelot, *ibid.*, **91**, 4297 (1969); (c) C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N. Y., 1972, pp 1347–1483; (d) L. Stêhelin, J. Lhomme, and G. Ourisson, *J. Amer. Chem. Soc.*, **93**, 1650 (1971); (e) L. Stêhelin, L. Kanellias, and G. Ourisson *J. Org. Chem.*, **38**, 847 (1973).

(22) (a) J. E. Nordlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966). See also (b) S. H. Liggero, S. Sustmann, and P. v. R. Schleyer, *ibid.*, **91**, 4571 (1969); (c) E. M. Engler, J. E. Andose, and P. v. R. Schleyer, *ibid.*, **95**, 8005 (1973).



acetolysis at 100° gives mainly (60%) the unrearranged acetate V and olefin VI.[23] According to Shiner's proposal, this lack of rearrangement and incomplete retention of stereochemistry indicates that "hidden return" in IV should be sharply increased in magnitude and Shiner's mechanism predicts that the solvolysis of IV should be significantly slower than I.

The experimental results do not confirm this prediction. The two compounds (I and IV) solvolyze at almost equal rates. The relative rates, corrected for differing sulfonate leaving groups vary from 3.6 to 0.6 (Table I), indicating that hidden return cannot be a major factor in these solvolyses.[24,25] Conventional carbonium ion theory predicts a rate enhancement factor of 2–3 in the adamantyl compound due to the inductive effects of the extra γ and δ carbon atoms,[26] and this is observed in the weakly nucleophilic solvents (97% trifluoroethanol and HCO_2H). Slightly lower ratios in other solvents may be due to small differences in the substrates' sensitivities to solvent ionizing power and/or nucleophilicity.[24]

Table I. Solvolysis Rate Constants[a] for 1-Adamantylmethylcarbinyl Tosylate(k_{IV}) and 3,3-Dimethyl-2-butyl Brosylate (k_I)

Solvent[b]	k_{IV}	k_I	(k_{IV}/k_I)	Corrected ratio[c]
97T	9.65 (30.2)[d]	7.98[f]	1.21	3.6
HCO_2H	75[k]	85.8[g]	0.87	2.6
CH_3CO_2H	0.014[i]	0.07[g] (0.019)[e,h]	0.20	0.6
	(7.5)[l]	(27)[l]	(0.28)[l]	(0.83)[l]
50E	1.8[i]	10.11[f]	0.18	0.89
80E	0.079	0.636[f]	0.124	0.62

[a] 10^{-5} sec^{-1} at 25° determined conductometrically, except where stated otherwise—OTs mp 117–118°. [b] 97T = 97% w/w trifluoroethanol–water; 80E = 80% v/v ethanol–water. [c] For tosylates assuming OBs/OTs = 3.0 in 97T, HCO_2H, and CH_3CO_2H and OBs/OTs = 5.0 in ethanol–water. See D. D. Roberts, *J. Org. Chem.*, **37**, 1510 (1972). [d] Brosylate mp 108.5–109.5°. [e] Tosylate. [f] Reference 2b. [g] Reference 9. [h] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2780 (1956). [i] Rates from conductivity measurements checked by titration. [j] Calculated from data in 80E, 70E, and 60E using log (k/k_0) = 0.8Y. [k] Conductivity measurements less reliable in this solvent. [l] At 70°.

It is now necessary to question seriously *all* the arguments on which Shiner's conclusions are based. Shiner's evidence[2] from additions to double bonds is indirect and ambiguous.[27–29] At best, it is supplementary to the main arguments based on α-deuterium isotope effects (α-*d*).[5,30] The α-*d* of 1.15–1.16 for pinacolyl brosylate,[2b] not strongly solvent dependent and smaller than the "limiting" value of 1.22–1.25 (*e.g.*, 2-adamantyl,[31] propargyl-type sulfonates,[32b] cyclopentyl brosylate in 70% and 97.5% trifluoroethanol,[32b] and 2-propyl tosylate in TFA[17]), indicated to Shiner that a different rate limiting step was involved, *formation* of intimate ion pair (k_1) for pinacolyl, but *dissociation* of intimate ion pair for isopropyl in trifluoroacetic acid.[2b,5d] In contrast, the linear free-energy plot, Figure 1, implies that all the compounds on the line have the same rate determining step.

Although the magnitude of α-*d* is known also to depend on the leaving group and on the degree of nucleophilic solvation, it has been assumed that α-*d* is independent of the structure of the alkyl part of the substrate.[5,30b] We now propose that bulky substituents, such as the *tert*-butyl group in I, influence the α-C–H bending mode and reduce the magnitude of the α-secondary isotope effect. Supporting experimental evidence comes from the even lower α-*d* of 1.107 ± 0.01 for 1-adamantylmethylcarbinyl brosylate (IV-OBs) in 97% trifluoroethanol at 25°.[33] β-Methyl substitution does have a significant effect on fractionation factors, in contrast to Shiner's conclusion.[5b,34]

(23) The olefin VI did not react with acetic acid under these conditions; the nmr spectrum of the solvolysis product after partial reaction (about one half-life) indicated the possibility that a small amount (~20%) of rearranged acetate VII was formed but little of this product remained at the end of the reaction. Acetolysis of optically active tosylate showed that the acetate V was about 75% racemized, the remainder being acetate of retained configuration. Trifluoroacetolysis with $NaOOCCF_3$ buffer of IV yielded only the unrearranged trifluoroacetate.

(24) Minor ion pair effects (*e.g.*, as might be revealed by ^{18}O labeling)[25] or anchimeric assistance in IV of small magnitude (<10) cannot be excluded.

(25) A. F. Diaz, I. Lazdins, and S. Winstein, *J. Amer. Chem. Soc.*, **90**, 1904 (1968).

(26) (a) k(2-PentOTs in TFA)/k(2-BuOTs in TFA) = 1.3.[16] Rate enhancement of three γ-carbon atoms = $(1.3)^3$ = 2.2; (b) I. B. Mazheika, I. S. Yankovskaya, and Ya. Yu. Polis, *Zh. Obshch. Khim.*, **41**, 1633 (1971); (c) D. J. Raber (unpublished results) showed that 1-adamantyldimethylcarbinyl bromide solvolyzes six times faster than *tert*-butyldimethylcarbinyl bromide.

(27) The literature indicates that olefin additions exhibit significant mechanistic differences from solvolysis.[4c,28,29]

(28) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 3901 (1967), and references cited therein.

(29) See also G. G. Ecke, N. C. Cook, and F. C. Whitmore, *J. Amer. Chem. Soc.*, 72, 1511 (1950).

(30) (a) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, 90, 418 (1968); (b) V. J. Shiner, Jr., M. W, Rapp, E. A. Halevi, and M. Wolfsberg, *ibid.*, 90, 7171 (1968); (c) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *ibid.*, **91**, 4838 (1969); (d) V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *ibid.*, **92**, 232 (1970).

(31) (a) J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 2551 (1971); (b) V. J. Shiner, Jr., and R. D. Fisher, *ibid.*, **93**, 2553 (1971).

(32) (a) V. J. Shiner, Jr., and W. Dowd, *J. Amer. Chem. Soc.*, **93**, 1029 (1971); (b) K. Humski, V. Sendijarvić, and V. J. Shiner, Jr., *ibid.*, **95**, 7722 (1973).

(33) Three independent conductometric measurements gave α-*d*'s of 1.111, 1.108, and 1.103.

(34) The dependence of α-*d* isotope effects on *substrate structure* is also indicated by the remarkably low values of k_H/k_D = 0.99 found for hydrolysis of the *cis*- and *trans*-2-vinylcyclopropyl bromides (J. H. Ong and R. E. Robertson, *Can. J. Chem.*, in press and private communication).

At present, we are not aware of any evidence in solvolyses of simple secondary substrates that requires postulating hidden return of large magnitude.[35-37] All kinetic data for nonanchimerically assisted substrates can be quantitatively explained, within a small rate factor, by varying degrees of nucleophilic solvent assistance. Such nucleophilic assistance is reduced in weakly nucleophilic solvents and sterically hindered substrates;[38] in these situations, the carbonium ion character of the transition state is greater and inductive/hyperconjugative effects are larger in magnitude.[12,16]

Acknowledgments. This work was supported by grants from the National Science Foundation, the National Institutes of Health (AI-07766 and GM-19134), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Hoffmann-La Roche, Nutley, N. J. S. H. L. and M. A. I. were recipients of National Institutes of Health Postdoctoral Fellowships. We thank J. M. Harris and V. J. Shiner, Jr., for critical comments.

(35) This comment applies to k_s solvolyses of unactivated secondary substrates. There are good indications that solvolysis of *tert*-butyl chloride in trifluoroethanol involves some hidden return.[30e,36,37]

(36) J. M. Harris, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 5729 (1970).

(37) T. W. Bentley, unpublished results.

(38) T. W. Bentley, F. L. Schadt, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94**, 992 (1972).

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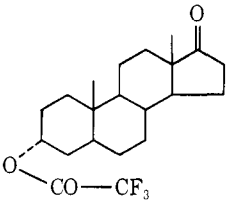
Selective Steroid Halogenations Directed by Proximity and Substituent Effects

Sir:

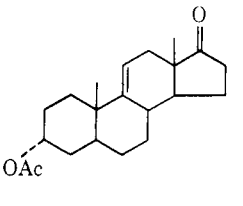
We have reported[1] that certain free radical halogenating reagents, and in particular phenyliodine dichloride, are sufficiently selective that in a random attack on a steroid nucleus halogenation occurs to an appreciable extent only at carbons 5, 9, and 14. Furthermore, our previous work indicated that the proportion of attack among these three positions could be influenced by substituents on the steroid skeleton. Halogenation at C-9 allows easy introduction of the 9(11) double bond which permits entry into the corticosteroids; our procedure has also been utilized by Djerassi[2] in the synthesis of a starfish sterol. Halogenation at C-14, and subsequent introduction of the Δ14 double bond in a steroid, is of interest with respect to the synthesis of cardiac-active steroids.

Although in the previously described procedure appropriate substituents could suppress attack at C-5 and allow the production of various proportions of Δ9(11) and Δ14 steroids, it would clearly be desirable to be able to direct exclusively the introduction of one or the other of these functionalities. We now wish to report that with appropriate substituent effects we can direct the halogenation to the introduction of a 9(11) double bond in an attractive corticosteroid precursor.[3] Alternatively, by the application of intramolecular orientation procedures to this halogenation, we have been able to direct it to the selective introduction of the Δ14 double bond or the 9(11) double bond.

Although bulky substituents at C-17 have some effect in suppressing the halogenation at C-14, the most convenient and effective group is simply the C-17 carbonyl, which deactivates C-14 to halogenation presumably by a combination of polar and conformational effects. As we have indicated earlier, C-5 halogenation can be diminished by attachment of an electron-withdrawing group at C-3, and particularly effective is a 3α substituent which is thus 1,3-diaxial with the C-5 hydrogen. Commercially available androsterone was converted to its trifluoroacetate (I), mp 123.5–124°,[4]



I



II

and 1.0 g was halogenated with 1 equiv of $C_6H_5ICl_2$ in benzene at 10^{-2} *M* by irradiation with a sun lamp for 10–15 min. The product was then dehydrochlorinated and saponified with methanolic KOH, acetylated, and chromatographed. Unfunctionalized androsterone acetate (25%) was separated from 3α-acetoxy-5α-androst-9(11)-en-17-one (II), mp 187.5–189°.[4] (41%) and *ca.* 5% of the corresponding Δ5 isomer. The remaining 25% of more polar material, containing chlorine, was formed by further halogenation.[5] With 2 equiv of $C_6H_5ICl_2$ conversion was 95%, with 49% of II being isolated. Again the only other products detected are a trace of the Δ5 isomer, and 34% of polar products of further reaction.

Selective functionalization at C-14 was obtained by applying our principle of remote oxidation to this halogenation process. We have described selective functionalization of steroids by attached benzophenone[6,7] or nitrite ester derivatives,[7] but it was problematical whether internal attack by a rigid attached reagent far from the attachment point could also be applied in a radical chain reaction. In a chain process there must be both an intramolecular hydrogen transfer in the attack on the substrate and an intermolecular halogen transfer to carry the chain. For the former, low concentrations are required to suppress competing intermolecular hydrogen abstractions, and under these conditions it is not necessarily clear that the chain transfer steps would be possible. However, it turns out that halogenation by $C_6H_5ICl_2$ can indeed be turned into a

(1) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972).

(2) J. E. Gurst, Y. M. Sheikh, and C. Djerassi, *J. Amer. Chem. Soc.*, **95**, 628 (1973).

(3) Introduction of the appropriate side chain, conversion of a Δ9(11) double bond to an 11-oxy substituent, and modification of ring A to a Δ4-3-one system are all well-known processes.

(4) Characterized by mass and pmr spectra.

(5) Apparently some of the olefin is formed directly and reacts further during halogenation. Treatment of II with $C_6H_5ICl_2$ in the *dark*, followed by our standard work-up, afforded similar polar material.

(6) R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Amer. Chem. Soc.*, **95**, 3251 (1973), and references therein.

(7) R. Breslow, *Chem. Soc. Rev.*, **1**, 553 (1972).