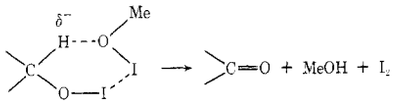
$[MeONa]_a)[MeOI] + [I_2]_a[MeONa]_a \doteq 0$. Since K_4 is considerably larger than unity, [MeOI] is equal to $[MeONa]_a$ (if $[MeONa]_a < [I_2]_a$) or $[I_2]_a$ (if $[MeONa]_a > [I_2]_a$).

(10) (a) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, **79**, 1897 (1957); (b) Y. Okamoto and H. C. Brown, *ibid.*, **79**, 1903 (1957); (c) *ibid.*, **79**, 1909 (1957).
(11) (a) P. S. Fredricks and J. M. Tedder, *J. Chem. Soc.*, 3520 (1961); (b) *ibid.*, 144 (1960).
(12) (a) D. S. Ashton, J. M. Tedder, M. D. Walker, and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1346 (1973); (b) W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1973).
(13) The reviewer suggested an alternative scheme in which hydride is abstracted by an oxygen atom of methyl hypoiodite.



However, since the electrophilicity of oxygen of methyl hypoiodite should be less than that of iodine, this scheme is less probable.

(14) (a) S. R. Hooley and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1053 (1973); (b) P. M. Henrichs and P. E. Peterson, *J. Amer. Chem. Soc.*, **95**, 7449 (1973).
(15) F. Y. Wiselogle and Sonneborn, III, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1944, p 90.

Solvents of Low Nucleophilicity. XV. Effects of Substituents at C-17 upon the Rates of Solvolysis of 3-Tosyloxy Steroids[1]

Paul E. Peterson* and Dhansukh M. Chevli

Department of Chemistry, St. Louis University, St. Louis, Missouri 63156, and Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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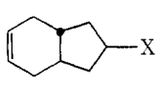
Rates of solvolysis of 3α- and 3β-tosyloxy androstanes having substituents at C-17 were determined in the solvents acetic acid, formic acid, and trifluoroacetic acid. Electronegative substituents at C-17 cause decreased solvolysis rates by factors up to sixfold. Simple electrostatic calculations show that dipole–dipole interactions are almost certainly too small and dipole–charge interactions are probably too small to account for the effects. Partial removal or delocalization of both negative poles of the dipoles *via* hydrogen bonding interactions with solvent, especially in trifluoroacetic acid, can account for the results. A larger effective dielectric constant for the interactions involving negative charges may be a contributing factor.

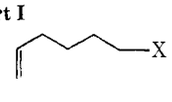
It has been generally believed that in unhindered saturated systems the effect exerted by electronegative substituents upon rates and equilibria[2] is small for substituents separated from a reaction center by several carbon atoms. However, it is now known that remote substituents may exert substantial effects particularly in various carbonium ion reactions. Typical values of k_H/k_X, the ratios of rate constants for reactions of compounds bearing the substituents H and X, respectively, are shown in Chart I for addition of trifluoroacetic acid to comparable bicyclic and acyclic alkenes.[3] The similar magnitude of effects in additions to alkenes and in tosylate solvolyses is illustrated by the data given in Chart II.[4] Based on these comparisons and on the data given in Chart III for the reaction of a 10-substituted 1-undecene, substituent effects exerted across the entire steroid polycyclic skeleton would be expected to be observable in the solvolysis of steroidal tosylates of general formula **6** (Chart III). In the present paper we report the observation of substituent effects in the acetolysis, formolysis, and trifluoroacetolysis of the steroidal tosylates, **6**. The known geometry of the steroid skeleton allows us to draw important conclusions regarding the origin and solvent dependence of the substituent effects.

Chart I



1

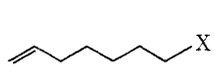
X = CN; k_H/k_X = 152



2

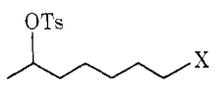
X = CN; k_H/k_X = 61.8

Chart II



3

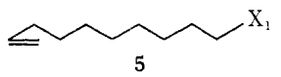
X = Cl; k_H/k_X = 5.00



4

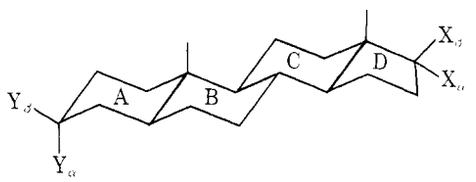
X = Cl; k_H/k_X = 3.88

Chart III



5

X = CN, k_H/k_X = 2.10



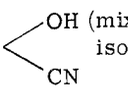
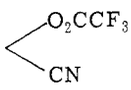
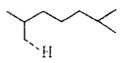
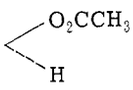
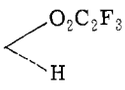
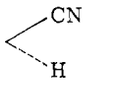
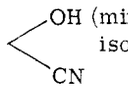
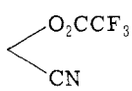
6

Y_β = OTs Y_α = H or

Y_β = H Y_α = OTs

Description and Results. The steroidal tosylates **6**, whose structures are indicated in Table I were synthesized. Rates of solvolysis were determined, and the results are given as k_H/k_X values in Table I. Values of k_X may be calculated from data in the footnotes of Table I. The key to the preparation of the 17-cyanohydrins proved to be prior introduction of the tosylate group, followed by the reaction of the 17-ketone group with liquid hydrogen cyanide for a prolonged time. Several C-17 steroid cyanohydrins which are analogous in structure to ours are reported to be mixtures, with one isomer predominating to the extent of 85–90%.[5] In a 1946 paper,[5c] the predominant isomer was said to be the β-hydroxy compound (formerly called α). Rereading the earlier papers did not lead us to the source of this assignment, although there is a hint[5c] that optical rotations may have been used as indicators of stereochemistry. Nevertheless, subsequent workers in the steroid field have accepted the β-hydroxy configuration of the predominant isomer. This isomer, somewhat surprisingly, is said[5c] to undergo acylation (possibly because the hydroxyl is pseudoequatorial) considerably more rapidly than the α-hydroxy

Table I
Values of k_H/k_X for Steroidal Tosylate Solvolyses

Registry no.	17-Substituent	k_H/k_X Trifluoroacetic acid[a]	Formic acid[b]	Acetic acid[c]
	3α Series			
52522-73-3	H_2	1[d]	1[e]	1[f]
10429-00-2	=O	4.66	2.68	1.44
52522-74-4 52555-20-1		4.68	2.10	
52522-75-5		6.07	3.25	
	3β Series			
1254-34-8	H_2	1[g]		1[h]
3381-52-0		1.13, 1.23[i]		1.04
52522-76-6		2.55		
52522-77-7		2.62, 2.39[i]		
52522-78-8		3.33		
10429-07-9	=O	3.55		1.31
52522-79-9 52522-80-2		4.72		
52522-81-3		6.02		

[a] For solvolysis at 25.0° of solutions 0.05 *M* in tosylate and 0.125 *M* in sodium trifluoroacetate. [b] For solvolysis at 25.0° of solutions 0.05 *M* in tosylate. [c] For solvolysis at 70.0° of solutions 0.1 *M* in tosylate and 0.11 *M* in sodium acetate. [d] 10^5k = 352 sec^{-1}. [e] 10^5k = 26.8 sec^{-1}. [f] 10^5k = 16.0 sec^{-1}. [g] 10^5k = 16.6 sec^{-1}. [h] 10^5k = 262 sec^{-1}. [i] Duplicate values are given to indicate the precision obtained.

isomer, with precipitation of β-acylated product. These observations suggest that the crystalline cyanohydrin trifluoroacetates which we prepared are the β-trifluoroacetoxy compounds. In the study reported here, the cyanohydrins and their trifluoroacetates were included only as convenient illustrations of the maximum substituent effect which can be obtained by placing electronegative groups at C-17 and at a comparable position in an acyclic system. Inclusion of results for these compounds, even in the case of the presumed epimeric mixtures of cyanohydrins, tends to confirm the consistent picture of substituent and solvent effects which we found, but our discussion of geometrically defined substituents will be based on those compounds where the geometry is unambiguous.

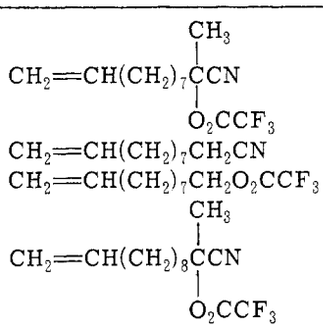
In our preparation of 3α-tosyloxy-17β-trifluoroacetate the 3α-tosyloxy group was introduced prior to sodium borohydride reduction of the 17-ketone function, to give the 17β-alcohol which, upon trifluoroacetylation, yielded the 17β-trifluoroacetate. Here the β configuration seems assured from the many analogous cases of α attack upon C-17 carbonyl groups reported in the steroid literature.[6a] The same comment applies to the 17β-cyano compound which we obtained by catalytic hydrogenation of the α,β-unsaturated nitrile.[6b] In contrast with the cases mentioned above, several of our preparations (*cf.* Experimental Section) utilized the more obvious route involving introduction of the sensitive tosylate group in the last reaction step.

Table II
Products from Trifluoroacetolysis of 3α- and 3β-Tosyloxy-5α-androstane

Isomer	Olefin, %	Alcohols, rel % 3α	3β
3α-Tosyloxy	90.8[a]	79[d]	21[d]
	89.5[a]		
3β-Tosyloxy	61.5[a]	54[c]	46[c]
	56.1[b]	55[d]	45[d]

[a] From hydrogen uptake. [b] From column chromatography on alumina. [c] Quantitative tlc. [d] Quantitative ir.

Table III
Relative Rate of Addition of Trifluoroacetic Acid to Alkenes, 60.0°

Compounds	k_H/k_X
	3.22[a]
$CH_2{=}CH(CH_2)_7CH_2CN$	2.10[b]
$CH_2{=}CH(CH_2)_7CH_2O_2CCF_3$	1.79[b]
	2.14[c]

[a] Calculated by dividing log k_H/k_X for 2-cyano-2-trifluoroacetoxy-11-dodecene by the attenuation factor 0.65 to get the estimated value of log k_H/k_X for the undecene derivative. [b] From ref 3. [c] Measured in this study.

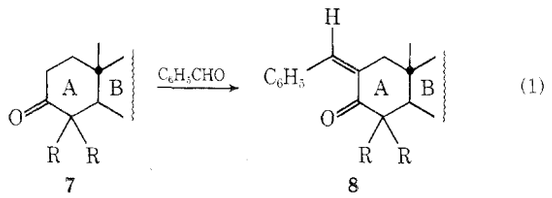
The products of trifluoroacetolysis of 3α- and 3β-tosyloxyandrostane were studied by a combination of techniques with the results given in Table II.

Finally, the cyanohydrin trifluoroacetate of 11-dodecen-2-one was prepared,[7] and the rate of addition of trifluoroacetic acid to the double bond was measured in order to assess the inductive effect of the cyanohydrin trifluoroacetate substituent. The result is given in Table III, along with previously determined data for comparison. In Table III, we also give the estimated k_H/k_X value for the addition of trifluoroacetic acid to the cyanohydrin trifluoroacetate of 11-undecen-2-one, whose substituent is at the correct distance for comparison with our steroids (*cf.* formula **5**).

Discussion

Absence of Conformational Transmission. Inspection of Table I reveals that substituents at the C-17 position lead to rate depressions for solvolysis at C-3 by factors up to sixfold (for the cyanohydrin trifluoroacetate substituent). All rates are qualitatively in accord with the operation of inductive substituent effects (polar effects; *cf.* footnote 2) of the approximate magnitude anticipated from the comparison made in the introduction. However, we must also consider the possible role of another type of substituent effect, Barton's well-publicized "conformational trans-

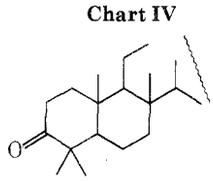
mission" effect.[8] This effect was discovered in the base-catalyzed condensation of benzaldehyde with triterpenoid and steroidal ketones which reacted according to eq 1.[8] Struc-



7 8 (1)

tural modifications, including introduction of double bonds in ring B or substituents at C-11, led to rate variations, typically by factors of less than five. The authors state that "the differences in rate from the standard probably arise, in main part, from conformational distortion produced by unsaturated substituents (and to a small extent by saturated ones)." We imagine that this distortion is transmitted through the saturated molecules by a slight flexing of valency angles and alteration of atomic coordinates.[8] It was concluded from the study of triterpenoids that in the absence of some disturbing unsaturation, the partial system **9**, (Chart IV) has an essentially constant reaction rate.

Chart IV



9

It may be seen from inspection of the C-17 substituents of our own study (*cf.* Table I) that they are "saturated" at the bond attaching them to the ring (except for the ketone) and that they, furthermore, fall outside the "active region" (formula **9**), suggesting that "conformation transmission" is not an important source of our substituent effects. This tentative conclusion is strengthened by the absence of an appreciable effect (k_H/k_X = 1.1–1.2) of the C_8H_{17} side chain at C-17 in the 3β-tosylate trifluoroacetolysis. The alkyl substituent should be larger than the trifluoroacetoxy substituent (for which k_H/k_X = 2.4–2.6) and should presumably give a larger "conformational substituent effect," quite in contrast with our observations.

Recently a study of the quantitation of long-range effects in steroids by molecular orbital calculations appeared.[9] Although the authors concluded that two types of conformational transmission were the source of long-range effects, we believe their molecular orbital model, involving interaction of CH_3F (taken as a model electronegative substituent) with an ethylene molecule, does not adequately represent effects in reactions having ionic (charged) transition states (the usual case). Accordingly, the conclusion[9] that electrostatic effects are negligible is inapplicable to a cited paper[10] and to our study.

Evidence for Inductive Effects. Inductive effects (that is, polar effects which may be field effects[2]) of substituents at C-3 and at C-17 upon rates of addition of bromine to Δ-5,6-steroids have been reported.[11] The inductive origin of the effects was inferred from the parallelism which was observed upon substitution at the two sites.[11] Similarly, an electrostatic origin of effect of C-17 substituents upon the relative rates of α and β epoxidation of Δ-4,5-3-keto steroids has been postulated.[12] The unavailability of one of the epimers in the case of the parent compound (having hydrogens at C-17) hinders the interpretation of the results, as does the observation of some further oxidation of the epoxides to acidic products under the reaction conditions. In other published work rate variations by factors of 1.2 or less were observed when the effect of substituents at C-17 upon the rate of substitution activated vinyl chloride by methoxide at C-4 was investigated.[13] Rate effects of four- to sevenfold upon reactivity at C-6 attended the introduction of electronegative substituents at C-3 in the acetolysis of 6α-tosyloxy-3α- and -3β-chloro-5α-cholestane.[14] The 1.8-fold slower rate for the 3β compound at 75° was ascribed to the smaller attractive interaction between the cationic reaction center and the negative end of the C-3 dipole in this isomer. Repulsive interactions dominated more strongly in this circumstance. Finally, yield increases in acetylation of 3-substituted 12α-hydroxy-5β-cholanates have been observed when the 3-substituent is electronegative.[15]

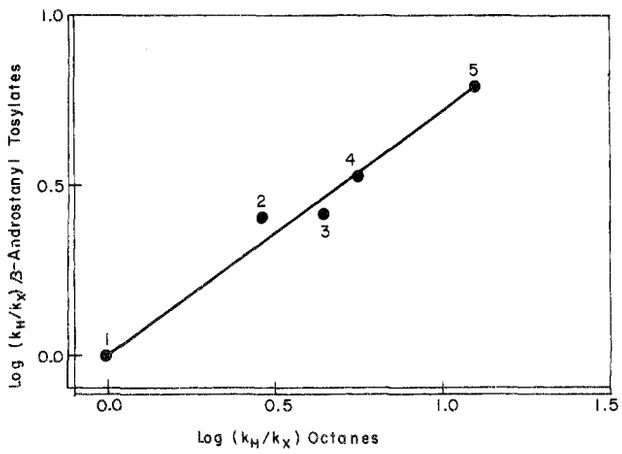


Figure 1. Plot of substituent effects in C-17 substituted steroidal tosylate trifluoroacetolyses *vs.* substituent effects in the addition of trifluoroacetic acid to ω-substituted 1-octenes. Substituents: 1, H; 2, $OCOCH_3$; 3, $OCOCF_3$; 4, CN; 5, CN and $OCOCF_3$. For substituent 5 the octene value was estimated using an attentuation factor (*cf.* Table III).

In Figure 1 is shown a plot of log k_H/k_X for the rates of trifluoroacetolysis of our 3α-steroid tosylates *vs.* log k_H/k_X for the addition of trifluoroacetic acid to ω-substituted 1-octenes. The alkene data are chosen as a source of substituent effects instead of the standard σ_I or σ^* values of the Hammett–Taft equation, log $k_X/k_H = \rho\sigma_I$, because trifluoroacetic acid is known to increase the σ_I value of oxygen- and nitrogen-containing substituents by hydrogen bonding to the substituents.[16] The approximate linear free energy relationship of Figure 1 provides solid support for an inductive origin of our substituent effects, although the range of substituents is more limited than would be desirable. The absence of an effect of the alkyl side chain ($\sigma_I \simeq 0$) is again particularly impressive.

In previously studied aliphatic tosylate solvolyses,[4] successively decreasing ρ_I values (−5.36, −4.49, and −2.71, respectively, based on 4-chloro-2-butyl tosylate solvolysis) were obtained as the solvent was varied in the order trifluoroacetic acid, formic acid, acetic acid. The similarity of these effects to those observed in the present study (Table I) provides a second line of evidence for an inductive origin of our steroid substituent effects.

A possible source of effects of remote substituents is substituent influence upon micelle formation, which has not been ruled out as the source of an unusual effect of the C-17 C_8H_{17} side chain upon C-3 ketone homologation.[17] A substituent effect upon the formation of aggregates, including dimers, arising from the previously understimated[18] attractive forces in σ-bonded systems, is also a conceivable factor in our studies as are effects (*e.g.*, conformational

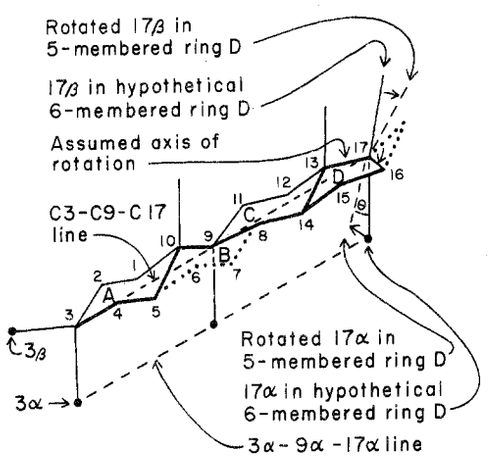


Figure 2. Illustration of geometric relationships which characterize C3–C17 interactions.

changes or modification of dielectric properties) arising from clustering of solvent molecules around the substituent. However, none of these factors presently appears to offer the demonstrated predictive capacity of the hypothesized inductive (polar) origin of our substituent effects.

Calculation of Maximum Expected Electrostatic Interactions. Considerable success has been attained in the estimation of the magnitude of substituent effects by calculation of the electrostatic interaction of charged and dipolar substituents with the reaction site.[19] Stock and coworkers have provided new evidence for the nature of electrostatic effects in the form of reversed substituent effects,[19b,c] in addition to supplying recent examples of calculations involving the Westheimer–Kirkwood cavity model.

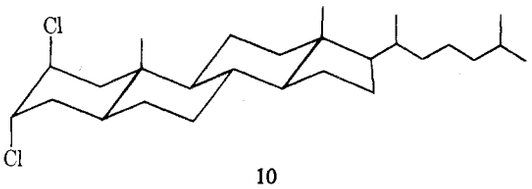
In our study, it was of particular interest to see if the effects of truly remote substituents, reported in the present study, are of the general magnitude expected of electrostatic interactions. Accordingly, we calculated the effect of an array of electronic charges located at C-3 (positive), at the 3α or 3β position (negative), at C-17 (positive), and at the 17α or 17β position (negative) (*cf.* Figure 2). Only the four r_i values (distances) between the substituent and the reaction site are counted in eq 2, which gives the desired electrostatic energy. In eq 2, the r values are in ångstroms, q is

$$E = \sum_i qq'/r_i D_E = \sum_i (3.32 \times 10^5)(qq'/r_i D_E) \quad (2)$$

in units of electronic charge, D_E is the effective dielectric constant, taken to be 2 in order to obtain a maximum interaction, and E is in calories per mole.[20] The results of our calculations for steroids of hypothesized geometry to be mentioned, along with results for steroids **10**, **11**, and **12** (Chart V) whose coordinates were available from X-ray crystal structures,[21] are given in Table IV. The use of charges at the atomic coordinates to represent dipoles finds precedent in recent work of Golden and Stock,[19b] and Dewar, Golden, and Harris.[22]

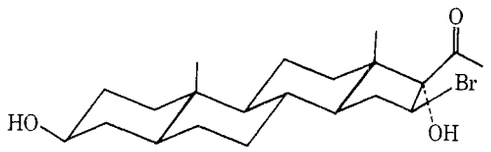
For the calculations reported in Table IV (except those based on X-ray data), the C-3–O-3 bond and C-17–X bonds were assumed to be 1.54 Å in length except as noted later for C=O and C—C≡N substituents. In Figure 2, the geometry associated with the five-membered ring D which we used is compared with that of a hypothetical homosteroid (dotted lines) in which ring D is a chair cyclohexane unit. The 17α bond is rotated by the angle θ, compared to the bond in the homosteroids, and 17β is similarly rotated. (We assumed a rotation of 30° about the 17–13 bond, based on inspection of Dreiding models.) When a C-17 ketone substituent was present, it was assumed to be half-way between C-17 α and β substituents. That is, the assumed oxygen-17-13-12 dihedral angle was +30°. In this instance the assumed C-17–O bond distance was 1.23 Å and the C-13 to C-17 bond distance was 1.516. Not surprisingly, the calculated (Table IV) ketone dipole interaction with an axial C-3 substituent, 79 cal/mol, lies between the values 453 and −178 for α and β C-17 dipoles. For 17α-CN and 17β-CN substituents the C-17–C and C≡N bond lengths were taken to be 1.46 and 1.16 Å, respectively.

Chart V



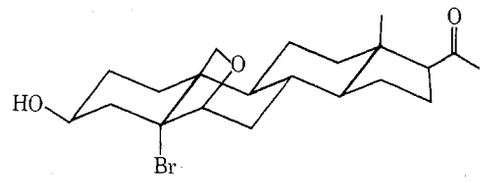
10

2β,3α-Dichloro-5α-cholestane



11

16β-Bromopregnane-17α,3β-diol-20-one



12

5α-Bromo-6,19-oxidopregnan-3β-ol-20-one

Included in Table IV are energies for various combinations of interaction in which the substituent or reaction site is considered to be positively charged, instead of dipolar. Those dipoles having both ends at similar distances from the charge give relatively small interactions, which may be negative (attractive) as illustrated for α-C≡N with the charge considered to be on carbon. The larger charge–dipole interactions are approximately 2 kcal/mol, whereas the calculated charge–charge interaction is 19 kcal/mol.

The negative values for some of the calculated interactions (Table IV) appear at first to be surprising. However, careful examination shows that these values arise from geometries in which the dipoles have an attractive orientation, the negative end of one being near the positive end of the other. Although the calculations are suggestive of opportunities for the observation of reversed substituent effects, which have been found in a dihydroanthracene system,[19b] we shall see that our experimental results suggest that dipole–dipole interactions are an unrealistic model for interactions in solvolysis transition states.

Comparison of Calculated and Measured Substituent Effects. In Table V selected observed substituent effects from Table I are tabulated in units of kcal/mol in $\Delta\Delta G^*$. For comparison, calculated values from Table IV are listed, scaled to represent the actual substituents C–O and C≡N by multiplying values from Table IV by 0.049 and 0.074, respectively. These scale factors represent the fractions of an electronic charge, which, when separated by the C–O and C≡N bond distances, d, reproduce the dipole moments of these groups.[23]

Table IV
Energies of Interaction (Calories per Mole), C-3 to C-17, for Model Steroid (Selected Actual Steroid Values in Parentheses)

Type of C-3 group	Interaction type	17α-C^+X^-	17α-$C^+=O^-$	17β-C^+X^-	17α-C^+N^-	17β-C^+N^-
3α, axial	3-Dipole, 17-dipole	453	79	−178 (−223[a])	314	−56
3β, equatorial	3-Dipole, 17-dipole,	28 (−19[b])	240	507 (676)[b] (570)[c]	138	344
3 positively charged	3-Charge, 17-dipole	390	964	1837	626	1363
3α, axial	3-Dipole, 17- or 20-charged	256[d]			−197[e]	434[f]
3β, equatorial	3-Dipole, 17- or 20-charged	2525[d]			2499[e]	2020[f]
3,positively charged	3-Charge, 17-charge	19,067				

[a] Value for the steroid **10** (Chart V). [b] Value for **11** (Chart V). [c] Value for **12** (Chart V). [d] For C-17 positively charged. [e] For 17α-$C^+\equiv$ (17α-$C^+\equiv N^-$ with negative charge absent. The positive carbon is numbered C-20.). [f] For 17β-$C^+\equiv$17β-C^+X^-.

Table V
Comparison of Selected Observed Substituent Effects and Calculated Maximum Effects

C-3 orientation	C-17 substituent	$2.303RT$ log k_H/k_X, kcal/mol	Energy,[a] dipole-dipole	Energy,[a] C-3 charged	Energy,[a] C-17 charged
α, OTs	O_2CCF_3	1.0			
	CN				
α, OTs	=O	0.58	0.039	0.472	0.125
β, TsO	=O	0.65	0.117	0.472	1.240
β, TsO	β, CN	0.71	0.255	1.006	1.495
β, TsO	β, O_2CCF_3	0.55			
β, TsO	O_2CCF_3	1.06			
	CN				

[a] kcal/mol.

The data of Table V allow us to state what is possibly the most important result of our study. The observed interactions for the keto steroids are several times larger than the calculated maximum dipole–dipole interactions, and the interaction in the cyano steroid is also significantly larger. These results support the intuitive feeling that substituent effects are larger than expected for solvolyses in trifluoroacetic acid, and, by inspection of Table I, for solvolyses in formic acid. Below we discuss two types of charge delocalization which may lend to large observed interactions.

We first consider the possible effect of delocalization of positive charges by polarization of adjacent carbon atoms, or, particularly for carbonium ions, by a perhaps equivalent partial filling of the vacant orbital by overlap with adjacent C–H or C–C bonds (hyperconjugative delocalization). The effect of such positive charge delocalization is given in Table VI for various "charge ratios," which we define by giving an example. The charge ratio is said to be 0.2 if the ratio of the charge on each carbon atom adjacent to the cationic center to that on the center itself is 0.2, the total charge being one unit. Charges farther than three atoms distant were ignored (assumed to be zero). In the calculations the substituent positive charge was also considered to be delocalized to the same extent as the carbonium ion charge, and all interactions between the substituent and the reaction site were summed. It may be seen in Table VI that substantial increases in dipole–dipole energy are produced by moderate amounts of delocalization. The possible importance of this effect in causing the slow fall-off of the inductive effect with distance for cationic reactions in trifluoroacetic acid has been pointed out.[4] This type of delocalization somewhat resembles the so-called classical or through-bond inductive effect. However, the latter, by tradition, has no geometric dependence and, accordingly, differs from our postulated delocalized charge effect. Extraordinarily, no physical model (in terms of charge distribution) for the through-bond inductive effect has ever been proposed, and it seems somewhat surprising that so much time has been spent disproving the importance of a concept which has no theoretical underpinning.

Table VI
Comparison of C-3–C-17 Electrostatic Interactions for Delocalized *vs.* Localized Positive Charges

Charge ratio	Ratio of energy: delocalized/localized Dipole-dipole	Charge-dipole	Charge-charge
0.0	1	1	1
0.1	1.28	1.10	1.02
0.2	2.01	1.35	1.09
0.3	3.26	2.01	1.19

Although a dominant role for internal charge delocalization previously seemed possible, we note (*cf.* Table VI) that the calculated interaction of such charges for a molecule of known geometry falls short of that found for "charge ratios" up to 0.3. The value of 0.3 is larger than the expected one, based on molecular orbital calculations in the propyl cation which shows a Mulliken population of the empty orbital of only 0.198 for the 2-butyl cation.[24]

Accordingly, in order to explain our results, we turn to what might be termed "negative charge delocalization," namely, delocalization of the negative ends of the dipoles into the solvent. Hydrogen bonding of solvent to the negative atom, or in the extreme, protonation, presumably may partially or completely cancel the negative charge. Indeed, Dewar and Grisdale have implicitly assumed such an effect in their earlier F–M treatment of substituent effects,[25] but have reduced the cancellation due to solvation from 100 to 10% in their more recent correlation.[21] There is no indication that 10% was shown to give optimum results, however.

The results of dropping the tosylate negative charge only, or both negative charges, are shown in Table IV

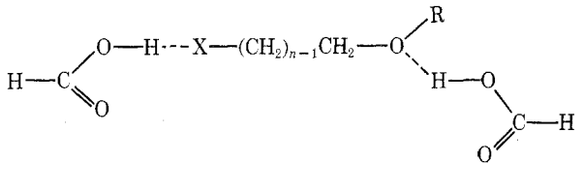
(charge–dipole and charge–charge energies, respectively). [The effect of also considering partial positive charge delocalization for charge–dipole interactions is given (Table VI) for comparison with the dipole–dipole case.] Replacing the C-3 dipole by a positive charge is seen (Table V) to achieve good, presumably fortuitous, agreement beteen calculated and observed values. Placing the charge at C-17 is somewhat less satisfactory in that the calculated difference in interactions of 3α and 3β dipoles is not found experimentally. Actually, there is strong evidence that trifluoroacetic acid does hydrogen bond strongly to oxygen- and nitrogen-containing substituent groups, causing their substituent effects to be enhanced with respect to those of halogen substituents. Accordingly, the observed substituent effects probably reflect substantial negative charge dispersal for both dipoles.[26] The calculated effects in such instances could be substantially larger than the charge–dipole interactions shown in Table V, although not as large as the charge–charge interaction of 19 kcal/mol (Table IV). Substantially increased magnitudes of values calculated according to the assumptions used are presumably necessary for any realistic reconciliation of observed and calculated data, since the effective dielectric constant will presumably[27] be larger than the assumed value, 2, and since the change in charge on C-3 and on the attached tosylate oxygen upon going from reactant to transition state will certainly be less than the assumed one electronic charge unit.

A priori, a *large* effective dielectric constant might have been found in our formolyses. According to the Westheimer–Kirkwood model, the effective dielectric constant for long, thin ellipsoids having interacting charges at the foci (or, alternatively, for molecules having the interacting charges near the surface)[28] approaches that of the solvent. The dielectric constants of acetic, formic, and trifluoroacetic acid are 8.42, 57.9, and 6.15, respectively.[29] Consulting Table I we note that there is no indication that the large dipole moment of formic acid has an appreciable effect on the results. The results suggest that experimentally accessible rigid molecules exhibit little solvent influence upon the Kirkwood–Westheimer effective dielectric constant in solvolysis transition states.

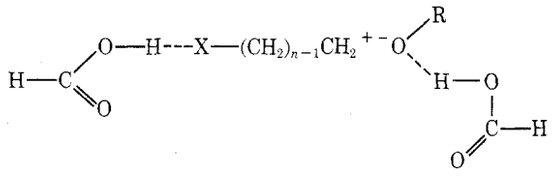
The apparently similar results for formic and trifluoroacetic acid also suggest that the large magnitudes of substituent effects are not primarily a result of the negative ends of the dipoles sensing a higher effective dielectric constant. Golden and Stock[18b] have considered the possibility that such an effect is important in other systems, as have Henbest and Jackson.[12] The small substituent effects observed for reactions in acetic acid (Table I) parallel the results observed for aliphatic systems[4] and may be connected with the occurrence of SN2- or E2-like transition states in this solvent.[30] One additional observation in regard to the influence of solvent is that extremely high ratios (approximately 17) of k for solvolysis of corresponding axial and equatorial tosylates in trifluoroacetic acid are noted (*cf.* values, Table I, footnotes). In the present paper, we refrain from examination of the possible nature of the solvolysis transition states in the light of the axial–equatorial effects, in order to focus on the nature of the substituent effects which we observed.

It seems appropriate here to mention the possible implications of our results for future studies. Our tentative hypothesis that solvation of the negative ends of the dipoles through hydrogen bonding drastically modifies substituent–reaction site interactions in solvolyses in formic and trifluoroacetic acid suggests that attempts to match experiment results with Kirkwood–Westheimer type calculations would suffer from the apparent lack of an *a priori* basis for choosing the type of interactions (charge–dipole, etc.) to be fitted to the model. On the other hand, it would appear promising to apply molecular orbital calculations in which hydrogen bonding solvation is included at the substituent and reaction site, one molecule per site, as illustrated in the example of Chart VI.

Chart VI



reactant



transition state

Ab initio molecular orbital calculations for fluorine substituent effects in carbonium ions in the gas phase showed an attenuation of interactions with distance between the substituent and the reaction site by ~2/3 per CH_2 group[24] similar to the values reported for carbonium ion reactions in trifluoroacetic acid. It is interesting that the calculated interactions were of the charge–dipole type, again suggesting that for the reactions in solution the negative end of the tosylate dipole in the transition state may be partially lost by hydrogen bonding solvation. It is to be noted that the molecular orbital calculations are subject to the same ambiguity mentioned for Kirkwood–Westheimer calculations. That is, one might have presumed that calculations which include a negative counterion weakly bonded to the cationic center would be the appropriate ones for comparison with solvolytic data, and such may prove to be the case for solvolyses in solvents more weakly solvating than formic acid. The alternatives are to determine experimentally which theoretical model matches the data, or, as mentioned above, to include a solvent molecule at the reaction site and make the calculations themselves the basis for deciding whether the solvent hydrogen bond has a major role in determining the substituent effect.

Conclusion. Although it might seem that substituent effects have been explored to the point of exhaustion, our work suggests that an area of study involving strongly solvated substituents exists which has not been extensively explored. Our demonstration and others cited that the remoteness of substituents separated from reaction sites by the entire steroid skeleton does not preclude study of their effects considerably expands the possibilities for additional work.

Experimental Section

General Information. Starting materials (Sigma Chemical Co.) and previously reported compounds showed the melting point reported in the literature. Analyses were performed by Scandanavian Microanalytical Laboratories. The nmr spectra were taken on a Varian A-60 spectrometer.

3α- and 3β-Tosyloxy-5α-androstan-17-one. The reported tosylates[31] were prepared from androsterone and epiandrosterone, respectively.

3α-Tosyloxy-17β-hydroxy-17α-cyano-5α-androstane. 3α-Tosyloxy-5α-androstan-17-one (3.11 g, 7 mmol) was dissolved in

20 ml of tetrahydrofuran and cooled to 5°. To this solution 15 ml of liquid hydrocyanic acid (prepared by a previously described method)[32] and a drop of saturated solution of sodium cyanide were added. After stirring for 45 min at 5°, the mixture was allowed to warm to room temperature and was stirred for an additional 1 hr. It was then neutralized with a few drops of cold 25% aqueous sulfuric acid solution. A semisolid organic material was precipitated on addition of 10 ml of water. The mixture was extracted with ether. The ether solution was washed with water, dried, and concentrated in rotary evaporator. Attempted crystallization from different solvents gave amorphous yellow powder, mp 132–134°, presumed to be too unstable for analysis; yield 2.30 g (70%). The stereochemical assignment and the possibility of the presence of some of the C-17 epimer have been discussed (*cf.* ref 5). The nmr spectrum and the ready conversion into a pure trifluoroacetate provide evidence for the predominance of one C-17 epimer.

The infrared spectrum showed –OH and –CN absorptions at 3400 and 2232 cm^{-1}, respectively. The nmr spectrum showed angular methyl peaks at δ 0.77 and 0.85, singlet for –OH at δ 3.68, and a broad peak of 3β-hydrogen, centered at δ 4.82.

3β-Tosyloxy-17β-hydroxy-17α-cyano-5α-androstane. The compound, possibly containing some C-17 epimer, was prepared from 3β-tosyloxy-5α-androstan-17-one in a manner similar to that described for the 3α epimer, mp 136–142°.

3α-Tosyloxy-17β-trifluoroacetoxy-17α-cyano-5α-androstane. For preparation of the compound whose assignment of stereochemistry at C-17 has been mentioned in the Discussion, a solution of 3α-tosyloxy-17β-hydroxy-17α-cyano-5α-androstane (0.950 g, 2 mmol) in 10 ml of anhydrous ether was cooled to 0° with ice. To this solution 1.0 g (10 mmol) of trifluoroacetic anhydride was added. After 12 hr, white crystals of trifluoroacetate had deposited on the side of the flask. These crystals were collected by suction filtration, washed with a mixture of ether–pentane (1:1) and dried under high vacuum. The mother liquor yielded a second crop. Recrystallization from ether–pentane gave 1.05 g (91%) of trifluoroacetate, mp 104–105°. The infrared spectrum showed a strong carbonyl absorption at 1788 cm^{-1}.

Anal. Calcd for $C_{29}H_{36}F_3NO_5S$; C, 61.36; H, 6.32. Found: C, 61,24; H, 6.33.

3β-Tosyloxy-17β-trifluoroacetoxy-17α-cyano-5α-androstane. The compound presumed to have the designated configuration at C-17 (*cf.* Discussion), mp 111–113°, was prepared from 3β-tosyloxy-17β-hydroxy-17α-cyano-5α-androstane in a manner similar to that described for the 3α epimer.

Anal. Calcd for $C_{29}H_{36}F_3NO_5S$: C, 61.36; H, 6.32. Found: C, 61.41; H, 6.27.

3α-Tosyloxy-5α-androstane. 3α-Hydroxy-5α-androstane was prepared from the C-17 ketone by following the procedure described by Huang-Minlon[33] to give the known 3α-hydroxy-5α-androstane,[34] 4.2 g (95%). The tosylate was prepared, white crystals from ethanol, mp 98–99°, 3.9 g (91%). The nmr spectrum showed angular methyl peaks at δ 0.75 and 0.83, and 3β-hydrogen at δ 4.6–4.8.

3β-Tosyloxy-5α-androstane. The reported[35] compound was prepared from the alcohol in 94% yield.

Dihydrocholestryl Tosylate. This tosylate[36] was prepared from dihydrocholesterol in 92% yield.

3β-Acetoxy-17β-cyano-5α-androstane. 3β-Acetoxy-Δ^{16}-17-cyano-5α-androstane[37] (2 g, 6 mmol) was reduced over palladium catalyst (10% on charcoal, 100 mg) in acetic acid (25 ml) at atmospheric pressure. After the reduction was complete, the solution was poured into 200 ml of water. The precipitates were collected by filtration and washed with water. After crystallization from ethanol it had mp 129–134°.

Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.73; H, 9.73.

3β-Hydroxy-17β-cyano-5α-androstane. The 3β-acetate was hydrolyzed with 2 *N* sodium hydroxide solution in ethanol. The crude alcohol had mp 142–151°.

3β-Tosyloxy-17β-cyano-5α-androstane. The tosylate was prepared in 95% yield; mp 132–134°.

Anal. Calcd for $C_{27}H_{37}NO_3S$: C, 71.17; H, 8.18. Found: C, 70.98; H, 8.26.

3β-Tosyloxy-17β-trifluoroacetoxy-5α-androstane. 3β-Tosyloxy-5α-androstan-17-one was reduced with sodium borohydride in ethanol at 5° by a conventional method. The resulting alcohol obtained had mp 93–94° after crystallization from ether. The infrared spectrum showed hydroxyl absorption at 3400 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.92; H, 8.58. Found: C, 69.89; H, 8.64.

The above alcohol was trifluoroacetylated with trifluoroacetic anhydride in ether. The trifluoroacetate obtained had mp 142–144°, after one crystallization from ether–pentane mixture. The infrared spectrum showed a strong carbonyl absorption at 1755 cm^{-1}.

Anal. Calcd for $C_{28}H_{37}O_5SF_3$: C, 61.98; H, 6.87. Found: C, 61.95; H, 6.76.

10-Undecylenealdehyde. This aldehyde was prepared by passing 10-undecylenyl alcohol (30 g) through a hot column packed with a copper catalyst. A slow stream of dry nitrogen was passed through the column during this operation. The copper catalyst was obtained from cupric oxide wire which was reduced in a slow current (three to four bubbles per second) of hydrogen and nitrogen mixture (1:10) at a temperature of 280 to 300°. Reduction required 4 hr under these conditions. During the preparation of the aldehyde the dropping time was adjusted so that the column temperature was maintained at 325°. The product obtained was a mixture of the alcohol and the aldehyde. Fractional distillation of this mixture afforded 10-undecylenealdehyde (14 g, 43%), bp 67–68° (0.6 mm).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.89.

11-Dodecen-2-ol. Methylmagnesium iodide was prepared from magnesium turnings (2.5 g, 0.105 g-atom) and methyl iodide (15.23 g, 0.105 mol) in anhydrous ether (50 ml) under nitrogen atmosphere. 10-Undecylenealdehyde (16.8 g, 0.1 mol) in anhydrous ether (100 ml) was added slowly over a period of 30 min, and the mixture was stirred for 2 hr at room temperature. It was then cooled in an ice bath to 0°, 3 *N* hydrochloric acid (50 ml) was added cautiously, and the mixture was stirred until all the precipitate dissolved.

The layers were separated, and the organic layer was washed with dilute sodium carbonate solution and water. After drying, the solvent was removed by distillation and the product was distilled under reduced pressure to give 11-dodecen-2-ol (XIX), bp 92–94° (0.4 mm); yield 14.6 g (79%).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.28; H, 13.03.

11-Cyano-11-trifluoroacetoxy-1-dodecene. This cyanohydrin was prepared in 85% yield from 4.55 g (25 mmol) of 11-dodecen-2-one, 4.9 g (0.1 mol) of sodium cyanide in 120 ml of aqueous ethanol (5:1), and 3 ml of sulfuric acid (0.11 mol) in 10 ml of water. Trifluoroacetylation gave the product, bp 92–95° (0.3 mm). The infrared spectrum showed the expected peaks at 1800 (carbonyl) and 910 and 990 cm^{-1} (terminal double bond). The nmr spectrum showed the presence of a CH_3 group, δ 1.89 (3 H), and terminal vinyl group, δ 4.85–6.05 (3 H).

Anal. Calcd for $C_{15}H_{22}NO_2F_3$: C, 59.00; H, 7.26. Found: C, 60.17; H, 7.56.

The cause for the high carbon analysis is unknown.

Rates. Rates of acetolysis and trifluoroacetolysis were followed as described previously.[4] For compounds, which were soluble enough for preparing 0.05 *M* solutions in formic acid, the rates were determined by ultraviolet spectroscopic analysis of quenched solutions, as previously described[4] for trifluoroacetolysis. However, the solubilities of 3α- and 3β-tosyloxy-5α-androstanes were too low for the quenching method. A modified procedure was used for these toluenesulfonates. 3α-Tosyloxy-5α-androstane (23 mg) was placed in 40 ml of formic acid and stirred for 3 min. The turbid solution was filtered quickly through a sintered glass funnel, and the clear solution obtained was placed in 25.0° bath. The whole operation took 8 min. The solution was withdrawn in intervals and pipetted into ultraviolet cells. Spectra were recorded on a Bausch and Lomb Spectronic 505 spectrometer using formic acid as the reference. The time was noted when the maximum at 272 mμ appeared on the chart. The total time taken after the withdrawal of the solution to the appearance of the maximum at 272 mμ was never more than 90 sec. The maximum at 272 mμ was used in measuring rates, as reported[4] for trifluoroacetolysis.

Trifluoroacetolysis of 3β-Tosyloxy-5α-androstane. A solution of 1.2356 g of 3β-tosyloxy-5α-androstane in 75 ml of trifluoroacetic acid, 0.1271 *M* in sodium trifluoroacetate, was kept at 25° for 8.5 hr (7 half-lives) under hydrogenation conditions using 25 mg of 10% palladium on charcoal (presaturated with hydrogen) as catalyst. The volume of the hydrogen uptake under the experimental condition (temp 25.0°, pressure 758 mm) was 41.10 ml corresponding to 61.5% elimination.[38] The solution was filtered through a sintered glass funnel and was diluted with 1 l. of water. The product was extracted six times with 100-ml portions of ether. The ether extract was washed with a saturated solution of sodium car-

bonate and water and was dried over anhydrous magnesium sulfate. Ether was removed by distillation and the residue obtained was chromatographed over 45 g of neutral alumina (Woelm activity I).

Successive elution with the indicated solvents gave the fractions: (1) 200 ml of pentane, 419 mg of liquid hydrocarbon, corresponding to 56.1% elimination; (2) 150 ml of ether–benzene (1:1), 292 mg of the solid alcohol,[38] mp 101–108°, from hydrolysis of the trifluoroacetates on the column. The alcohol yield corresponds to 36.9% substitution. A 1:1 mixture of authentic 3α- and 3β-hydroxy-5α-androstane had mp 104–112°. The total recovery of alcohols and alkane product (possibly partly rearranged) was 93%. Thin layer chromatography of the alcohol fraction on silica gel gave two spots with R_f values 0.473 and 0.327 in benzene, corresponding to the authentic 3α- and 3β-hydroxy-5α-androstane, respectively.

Quantitative Tlc. The plates were prepared by spreading a slurry of 40 g of silica gel GF_{254} (E. Merck) in 80 ml of distilled water on 20 × 20 cm glass plates. The plates were coated to a thickness of 0.25 mm and allowed to dry at room temperature for about 1 hr. They were then placed in an oven at 150° for 20 min and stored in a desiccator until they were used for separation of compounds.

Acknowledgment. We are indebted to D. Warren Vidrine for providing most of the calculated values of Table IV and for the comparison of these results for unit electronic charges at the atomic coordinates with those applicable to actual dipoles. Support of this work by the National Science Foundation (Grant GP 30683 and earlier grants) is gratefully acknowledged.

Registry No.—3β-Acetoxy-17β-cyano-5α-androstane, 52522-82-4; 3β-acetoxy-Δ^{16}-17-cyano-5α-androstane, 52522-83-5; 3β-hydroxy-17β-cyano-5α-androstane, 52522-84-6; 3β-tosyloxy-17β-hydroxy-5α-androstane, 32625-08-4; 10-undecylenealdehyde, 112-45-8; 10-undecylenyl alcohol, 112-43-6; 11-dodecen-2-ol, 21951-49-5; 11-cyano-11-trifluoroacetoxy-1-dodecene, 52555-19-8.

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(1) Based on the Ph.D thesis of D. M. Chevli, St. Louis University, 1968. Additional calculations were done at St. Louis University (see Acknowledgment) and at the University of South Carolina.
(2) The effects are those normally reflected by the magnitude of the inductive substituent constant σ_I, and we shall call them inductive effects, although the term polar effect also is in use. We shall later comment on the inevitable question of the separation of the substituent effects into component field effects and "through-bond" or "classical" inductive effects.
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