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AN ALTERNATIVE CALCULATION AND RECONSIDERATION OF RATES OF BROMINE ADDITION TO 5,6-UNSATURATED STEROIDS

Paul E. Peterson
Saint Louis University, Department of Chemistry
1402 South Grand Blvd., St. Louis 4, Missouri

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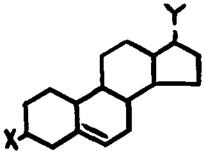
TWO recent communications[1,2] reporting inductive effects of remote substituents in the steroid series were of interest to us because of their relevance to our own studies of the remarkably large inductive effect of certain remote substituents in the addition of trifluoroacetic acid to alkenes.[3] In reference 2 it was reported that rates of bromine addition to 3β-X, 17β-Y-disubstituted androst-5-ene can be correlated by the expression

pk(3β-X, 17β-Y-androst-5-ene) = pk(cholesteryl acetate) • a • b

where



$$\underline{a} = \frac{\text{pk(3β-X-cholest-5-ene)}}{\text{pk(cholesteryl acetate)}}$$

$$\underline{b} = \frac{\text{pk(17β-Y-3β-acetoxyandrost-5-ene)}}{\text{pk(cholesteryl acetate)}}$$

One purpose of the present communication is to point out that a pre-

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[1] V. Schwarz, S. Hermanek, Chem. and Ind. 1212 (1960).

[2] ibid., Tetrahedron Letters 809 (1962).

[3] P. E. Peterson and G. Allen, J. Org. Chem. 27, 2290 (1962).

ferable approach to the calculation of rates for the disubstituted compounds is the use of the difference between pk values in each instance where the quotient of the values was used in reference 2. The pk values for each compound are of course proportional to the free energies of activation; accordingly the difference between the pk values, Δpk_X (or Δpk_Y), corresponding to the presence of two different X (or Y) groups will be proportional to the change in free energy of activation which attends the change from one inductive substituent to another. The pk values for disubstituted compounds are then calculated from the pk value for the reference compound by adding the increments Δpk_X (determined by variation of the X group only) and Δpk_Y (determined by variation of the Y group only). In Table 1, the recalculated pk values are compared with the measured values. The average absolute magnitude of the deviation is shown to be reduced, as expected, compared to the value obtained by the method of reference 2. The recalculation is of course merely a treatment of the data of reference 2 according to the usual assumption that multiple substitution may be viewed in terms of the additivity of substituent effects or, if necessary, in terms of deviations from additivity.

Another purpose of this communication is to show that the apparently surprising magnitudes of the inductive effects reported in references 1 and 2 can be accommodated within the framework of the existing knowledge of the inductive effect of remote substituents.

In one useful approach the effect of a remote substituent is calculated from the effect of a closer substituent by assuming that the effect falls off by a constant factor, here designated by ϵ and frequently found[4] to be approximately 0.5, for each additional bond

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[4] J. C. McGowan, J. App. Chem. 10, 312 (1960) and references given therein

TABLE 1

Calculated and Measured pk Values for Bromine Addition to

3β-X and 17β-Y-Disubstituted Androstenes

X,(Δ pk_X)	Y,(Δpk_Y)	pk Calc'd	pk Measured	Deviation (This paper)	Deviation (Ref.2)
OBz (0.16)	CO_2CH_3 (0.42)	3.13	3.03	+ .10	+ .11
OTs (0.73)	CO_2CH_3 (0.42)	3.70	3.59	+ .11	+ .23
$OCOCCl_3$ (1.06)	CO_2CH_3 (0.42)	4.03	3.91	+ .12	+ .29
OBz (0.16)	OBz (0.42)	3.13	3.10	+ .03	+ .04
$OBzNO_2$(p)(0.51)	OB_2NO_2(p)(0.49)	3.55	3.60	- .05	+ .04
$OCOCCl_3$ (1.06)	$OCOCCl_3$ (0.64)	4.25	4.14	+ .11	+ .39
OBz (0.16)	O (0.46)	3.17	3.23	- .06	- .04
$OCOCCl_3$ (1.06)	O (0.46)	4.07	4.06	+ .01	+ .21
$OCOCCl_3$ (1.06)	OBz (0.42)	4.03	4.10	- .07	+ .10
		Average Absolute Deviation		0.07	0.16

separating the remote substituent from the reaction center. For polycyclic systems an unambiguous calculation is accomplished if it is assumed that all of the σ bond paths between the substituent and the reaction center contribute to the inductive effect. The multiplicity of paths lends a certain air of novelty to the calculations (cf. Fig.1), but a reasonable fall-off factor of 0.51 leads to a ratio of 3.9 for the effect of the same substituent in the X and Y positions, which is the measured value obtained from a plot of pk_X vs. pk_Y for cases where the X and Y substituents are identical. Finally a ρ^* value[5] between 2.7 (based on the substituents OH, OCH_3, OAC and Cl) and 2.0 (based on CH_3O and p-$CH_3C_6H_4SO_3$) can be calculated based on the pk_X values and the σ^* values of the X substituents.

These values are approximately the values expected if it

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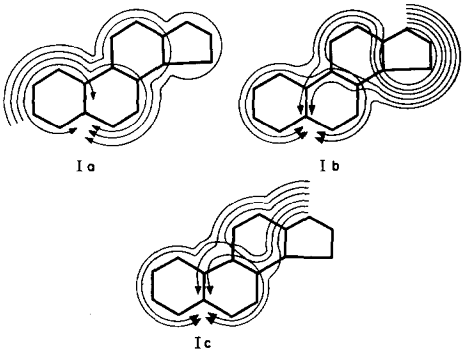
[5] R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", edited by M. S. Newman, John Wiley and Sons, Inc., New York, 1956, p. 556.

is assumed that the bromination reaction[1,2] has a ρ^* value of -3.5 to -4.1 when substituents are present on a neighboring carbon atom. Various carbonium ion reactions have ρ^* values in this range.[5] In the case under discussion the substituent is one carbon atom farther removed from the reaction center. Using $\epsilon \cong 0.5$ and considering the two main paths of transmission of the inductive effects leads to the prediction of an effective ρ^* value of about 0.6 times the value characteristic of neighboring substituents.

Fig. 1

Paths for transmission of the inductive effect between C-3 and C-5 (Ia) or C-17 and C-5 (Ib) and (Ic). The charge in the transition state is considered to be at C-5. Example of calculation:

$$\text{C-3 to C-5} = (.51)^2 + (.51)^4 + (.51)^8 + (.51)^{12} + (.51)^{15}$$



Ia

Ib

Ic