

Addition Reactions of Glycals. VI.¹

Chlorination of D-Glucal Triacetate with Iodobenzene Dichloride

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Chlorination of D-glucal triacetate with iodobenzene dichloride was investigated under several conditions. The free-radical addition gave 3,4,6-tri-O-acetyl-2-chloro-2-deoxy- α -D-mannopyranosyl chloride predominantly, together with $-\alpha$ - and $-\beta$ -D-glucopyranosyl chlorides, but no $-\beta$ -D-mannopyranosyl chloride. In an oxygen atmosphere the free-radical addition was inhibited and an ionic addition of chlorine took place with a slower rate, giving the products produced by the ionic addition of molecular chlorine with the same ratio.

Until recently it has been postulated that three mechanisms, an ionic, a free-radical, and a molecular addition, played an important role in the addition of chlorine to olefins using iodobenzene dichloride (IBD). Bloomfield² studied the chlorination of natural rubber with IBD in refluxing carbon tetrachloride with or without hydroquinone, and concluded that the free-radical chain reaction was involved. Barton and Miller³ studied the stereochemistry of the chlorination of cholesteryl benzoate and found that the chlorination with IBD gave 5 α ,6 α -dichlorocholestan-3 β -yl benzoate and the 5 α ,6 β isomer, while that with molecular chlorine gave the 5 α ,6 β dichloride. In the IBD chlorination they proposed that in the presence of water an ionic addition took place to give the *trans* dichloride and in the absence of water a molecular addition took place to give the *cis* dichloride. Cristol, Stermitz, and Ramey⁴ reported that the chlorination of acenaphthylene with molecular chlorine unexpectedly gave the *cis* dichloride in 27% yield, while that with IBD in the presence of 1,3,5-trinitrobenzene gave the *trans* dichloride in 28% yield. Summerbell and Lunk⁵ reported that the chlorination of *p*-dioxene with IBD gave *cis*- and *trans*-dichloro-*p*-dioxanes in 5 and 95% yields, respectively, while that with molecular chlorine gave 61% *cis* and 39% *trans* dichlorides. Tanner and Gidley⁶ studied the chlorination of norbornene with IBD and found that the reaction proceeded by two distinguishable and controllable mechanistic pathways, an ionic and a free-radical, but not a molecular addition.

In a preceding paper,¹ we studied the solvent effects in the chlorination of D-glucal triacetate (1) with molecular chlorine and found that in nonpolar solvents *cis*-addition products, 3,4,6-tri-O-acetyl-2-chloro-2-deoxy- α -D-glycopyranosyl chloride (2) and $-\beta$ -D-mannopyranosyl chloride (3), were predominantly obtained and in polar solvents *trans*-addition products, 3,4,6-tri-O-acetyl-2-chloro-2-deoxy- β -D-glucopyranosyl chloride (4) and $-\alpha$ -D-mannopyranosyl chloride (5), were predominantly obtained. We wish to report herein the results of the chlorination of 1 with IBD and discuss the stereochemistry of the addition reaction.

Results

The addition of chlorine to 1 using IBD as the chlorinating reagent gave products resulting from an

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(2) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944).

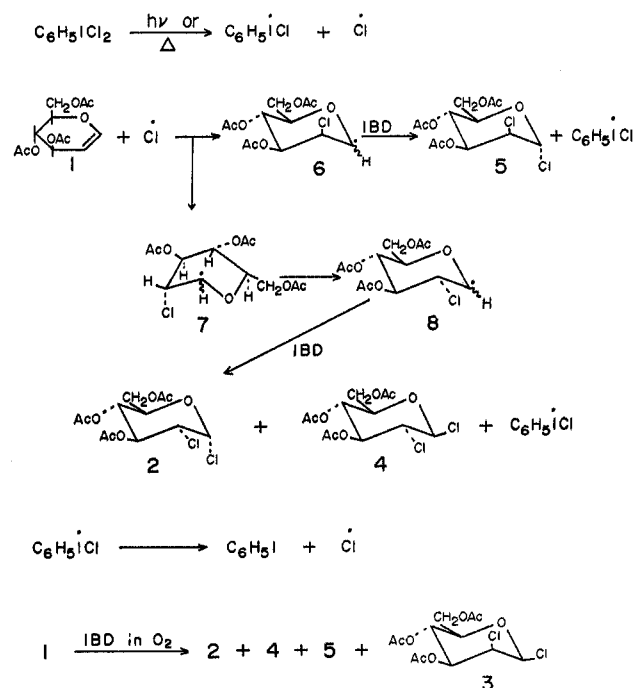
(3) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 370 (1950).

(4) S. J. Cristol, F. R. Stermitz, and P. S. Ramey, *ibid.*, **78**, 4939 (1956).

(5) R. K. Summerbell and L. C. Lunk, *ibid.*, **79**, 4802 (1957).

ionic process or a free-radical chain process, depending upon the condition used. The results are summarized in Table I. The photoinitiated or thermal reaction of IBD with 1 (Scheme I) in carbon tetrachloride in

SCHEME I



nitrogen or argon atmosphere gave 3,4,6-tri-O-acetyl-2-chloro-2-deoxy- α -D-mannopyranosyl chloride (5) and $-\alpha$ -D- and $-\beta$ -D-glucopyranosyl chlorides (2 and 4) in almost quantitative yield in a ratio of 72.8:11.5:15.7, respectively, although the reaction did not proceed in oxygen atmosphere in the dark at temperatures of 0–50°. The addition of a small amount (5%) of *m*-dinitrobenzene⁷ in the photoinitiated reaction in argon atmosphere was found to inhibit the rate of the reaction while the product ratio of 5/2/4 was found to remain constant. The thermal reaction in a flask open to atmospheric oxygen gave a result identical with that of the photoinitiated reaction within experimental error.

The course of the reaction was dramatically changed when the reaction was carried out in oxygen atmosphere. When the reactions were carried out in carbon tetra-

(6) D. D. Tanner and G. C. Gidley, *J. Org. Chem.*, **33**, 38 (1968).

(7) When 1,3,5-trinitrobenzene was used as an inhibitor, retardation of the reaction rate was also observed. However, in this case the product ratio could not be determined owing to the overlapping of the peaks of 5 and 1,3,5-trinitrobenzene.

TABLE I
 CHLORINATION OF D-GLUCAL TRIACETATE WITH IODOBENZENE DICHLORIDE^a

Run	Molar ratio ^b	Temp, °C	Solvent	Time, min	Conditions	Product distribution ^c					
						5	2	4	3	5/ (2 + 4)	4/2
1	1.2	2, 30, or 40	CCl ₄	1200	Dark, O ₂						
2	10	30 ± 0.1	CCl ₄	2	Irradiation, ^d N ₂	69.0	12.8	18.2		2.2	1.4
3	1	30 ± 0.1	CCl ₄	2	Irradiation, N ₂	72.8	11.6	15.6		2.7	1.3
4	0.5	30 ± 0.1	CCl ₄	2	Irradiation, N ₂	72.7	11.5	15.8		2.7	1.4
5	0.3	30 ± 0.1	CCl ₄	2	Irradiation, N ₂	72.9	11.3	15.8		2.7	1.4
6	0.2	30 ± 0.1	CCl ₄	2	Irradiation, N ₂	75.9	8.7	15.4		3.1	1.8
7	0.1	30 ± 0.1	CCl ₄	2	Irradiation, N ₂	76.8	9.6	13.6		3.3	1.4
8		30 ± 0.1	CCl ₄	2	Irradiation, N ₂	68.4	13.7	17.9		2.2	1.3
					<i>m</i> -Dinitrobenzene						
9	1.2	78	CCl ₄	15	Dark, Ar ^e	71.4	12.0	16.6		2.5	1.4
10	1.2	78	CCl ₄	15	Dark, air	70.9	12.1	17.0		2.4	1.4
11	1.2	78	CCl ₄	15	Dark, O ₂ ^e	4.0	82.2	3.8	10.0		
12		2	CCl ₄	3	Dark, O ₂ , Cl ₂	2.5	85.8	3.1	8.6		
13	1.2	2	PC	150	Dark, O ₂	42.0	9.5	44.5	4.0		
14		2	PC	3	Dark, O ₂ , Cl ₂	45.6	8.6	41.7	4.1		

^a Each reaction was carried out twice. ^b IBD/1. ^c Determined by glpc. ^d By 200-W incandescent light bulb. ^e The reactions were carried out in sealed ampoules.

chloride in the dark in oxygen atmosphere at 78° and in polar propylene carbonate at 2°, the four isomeric dichlorides were obtained in the same ratio as in the ionic addition of molecular chlorine to **1** in these solvents, respectively, with retarded rates.

Isolation of the products from the photoinitiated reaction by repeated preparative tlc afforded **2**, **4**, and **5** in 6.3, 11.1, and 43.1% yields, respectively. These dichlorides were proved to be identical with authentic specimens, which were obtained in the ionic addition of chlorine to **1**, by mixture melting point determinations and comparison of their ir and nmr spectra. The analyses of the reaction mixtures were carried out by glpc and the identity of the products was confirmed by comparison of their retention times and by simultaneous injection of the authentic specimens with the mixture to observe peak enhancement.

Discussion

Tanner and Gidley⁶ differentiated the ionic and free-radical mechanisms in the reaction of norbornene with IBD and concluded that the reaction proceeded *via* two mechanisms, an ionic and a free-radical, but not a molecular addition. The present study gave the same conclusion.

In the ionic addition of molecular chlorine to **1**,¹ we found that in nonpolar solvents *cis* dichlorides (**2** and **3**) were predominantly obtained and the amounts of the *cis* dichlorides were decreased with increasing solvent polarity, and conversely, in polar solvents, *trans* dichlorides (**4** and **5**) were predominantly obtained, and the amounts of the *trans* dichlorides were decreased with decreasing solvent polarity. These results would be expected if the chlorination of **1** with IBD proceeds *via* ionic process.

Free-Radical Chain Reactions.—In the thermal and photoinitiated reactions of **1** with IBD in the absence of oxygen, a hydrogen-abstraction reaction, in which PhICl was shown to be the chain-carrying species,^{8,9} could not be observed at all, and addition products **2**, **4**,

and **5** were obtained in good yield but **3** was not detected in any measurable extent in the products. Inhibition of the rate of these reactions with molecular oxygen and a trace amount of *m*-dinitrobenzene confirms the chain nature of the reaction. In the former case, the inhibition of the radical chain addition was so complete at 78° that only the ionic reaction was observed, while in the latter the inhibition was not complete and the free-radical reaction was still dominant. Also, in the thermal reaction in a flask open to the atmosphere, the products from the free-radical addition were obtained. This result may be attributed to the low solubility of oxygen in carbon tetrachloride at this temperature. From these results it is concluded that the products obtained in the additions of IBD to cholesteryl benzoate⁸ in the absence of water, acenaphthylene,⁴ and *p*-dioxene,⁵ as Tanner and Gidley⁶ reported, may be interpreted as those from the free-radical addition but not molecular *cis* addition.

Ionic Addition Reactions.—When the reaction was carried out in a sealed ampoule in carbon tetrachloride in the presence of molecular oxygen at 78° or in polar propylene carbonate at 2°, the proportion of the products was completely different from that in the free-radical addition and **2**–**5** were obtained in the same ratio as in the ionic addition of molecular chlorine in these solvents, respectively. These results would indicate that molecular chlorine, produced from IBD, is the actual chlorinating reagent in these reactions.

Stereochemistry of the Free-Radical Addition.—It has been shown¹⁰ that free-radical additions to cyclohexene derivatives give *trans*-diaxial products predominantly. In the addition of hydrogen bromide,¹¹ *trans*-diaxial product was obtained stereospecifically. From his experimental data in the chlorination of cyclohexene, Poutsma¹² extrapolated that the "pure" free-radical chlorination with chlorine should give 1,2-dichloro-cyclohexane, in which the amount of *trans* isomer was

(10) For a review, see F. R. Mayo and C. Walling, *Chem. Rev.*, **27**, 351 (1940); B. A. Bohm and P. I. Abell, *ibid.*, **62**, 599 (1962).

(11) See, e.g., H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Amer. Chem. Soc.*, **74**, 3588 (1952); P. D. Readie and P. S. Skell, *J. Org. Chem.*, **31**, 753 (1966); ref 10.

(12) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 2161 (1965).

(8) D. F. Banks, E. S. Huyser, and J. Kleinburg, *J. Org. Chem.*, **29**, 3692 (1964).

(9) D. D. Tanner and P. B. Van Bostelen, *ibid.*, **32**, 1517 (1967).

over 95%, and 3- and 4-chlorocyclohexenes in a ratio of 1.95:1.00:0.60.

In the photoinitiated free-radical addition of IBD to **1**, the ratio of **2**, **4**, and **5** was found to be almost constant within experimental error when the initial concentrations of the reactants were changed, and the four isomeric dichlorides (**2**–**5**) were not affected in any measurable extent under the reaction condition. These results clearly indicate that **2**, **4**, and **5** correspond to the kinetically controlled products.

It has been reported⁶ that in the free-radical chain addition of IBD to olefins the chain-propagating radical was shown to be a chlorine atom. It is reasonable to consider that the first attack by the chlorine atom occurs at the C₂ position of **1**, since a chlorine atom has a rather electrophilic character,¹³ and an alkoxy radical is stabilized by resonance in the radical involved ($-\dot{\text{C}}\text{HO}- \leftrightarrow -\text{C}\dot{\text{H}}\text{O}^+-$), which is found to be small.¹⁴ We previously reported¹⁵ that the free-radical addition of thiolacetic acid to **1** gave 3,4,6-tri-*O*-acetyl-2-*S*-acetyl-1,5-anhydro-2-thio-*D*-mannitol (SAC, axial) and *D*-glucitol (SAC, equatorial) in a ratio of 2.6:1 in good yields. In the present study, the result that **5** (C₂Cl, axial) and **2** + **4** (C₂Cl, equatorial) were obtained in a ratio of 2.7:1 was consistent with the above result. Attack of a chlorine atom on the double bond of **1** from directions perpendicular to the π orbitals gives the intermediate radicals, **6** and **7**, in which **6** is more favored than **7**, since **6** has a chair conformation,¹⁶ probably with some flattening of the ring caused by the participation of the lone-pair electrons of the ring oxygen, whereas **7** has an unfavorable twist-boat conformation. Abstraction of a chlorine atom from IBD by the radical **6** should give **3** and **5**. It is interesting to note that any detectable amount of **3** could not be obtained in the reaction. In the case of the radical **7** it would be more likely to consider^{17–19} that the radical **7** has to isomerize to a radical **8**, which has a chair conformation with some flattening of the ring similar to **6**, before abstraction of a chlorine atom from IBD. Abstraction of a chlorine atom from IBD by the radical **8** should give **2** and **4**. Actually, **2** and **4** were obtained but a surprising observation was that the ratio of **2**/**4** was found to be almost constant (1.4–1.8) under the reaction conditions.

It has been postulated that, in the free-radical additions of thiols to cyclohexene derivatives,^{17,20} abstraction of an atom or a radical from reagent by a radical like **8** occurred at an axial position preferentially. However, LeBel and DeBoer¹⁹ found that, in the four isomeric 1:1 adducts obtained from the free-radical addition of thiolacetic acid to 2-chloro-4-*t*-butylcyclohex-

ene, the ratio of *cis*-3-chloro-*trans*-4-thioacetyl-*t*-butylcyclohexane to the *trans*-3-chloro isomer was 1.8–2.6, while in other thiol additions the ratio was less than 1. They proposed a five-membered, bridged, intermediate radical in equilibrium with the open radical for the explanation of the favorable abstraction of a hydrogen atom in an equatorial position.

The present result, in which the formation of less stable **4** was favored over that of more stable **2**, would be explained by an assumption of an equilibrium between open radical and chlorine-bridged radical as postulated by Skell.²¹ Another explanation would be given by the consideration that, if the structure of the transition state in the abstraction of a chlorine atom from IBD by the radical **8** resembled that of the starting radical, the formation of **4** is favored over that of **2**, since the direction to form **4** is more opened than that to form **2** and Dreiding-model inspection shows that the anomeric effect would not play an important role in the transition state.

In the results of LeBel and ours, the fact that the preferable equatorial abstractions of atoms from the radicals like **8** were observed in two different systems would show that the preferable equatorial abstractions were not always exceptional and further fundamental results would be required.

Experimental Section

Melting points were measured on a Monoscope (H. Boch, Frankfurt am Main, Germany) and were uncorrected. Nmr spectra were obtained in deuteriochloroform with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ir spectra were measured using a Koken Model DS-301 ir double-monochromatic spectrophotometer. Rotations were measured using a Perkin-Elmer Model 141 polarimeter in chloroform. Gas-liquid and preparative thin layer chromatography were carried out as described in the preceding paper. Solvents were evaporated below 40° using a rotatory evaporator.

Materials.—*D*-Glucal triacetate (**1**) was prepared by a method of Helferich, Mulcahy, and Ziegler;²² mp 55–55.5°; $[\alpha]_{\text{D}}^{25} -14.1 \pm 0.5$ (c 1.050, EtOH); $[\alpha]_{\text{D}}^{20} -24.9$ ° (c 0.982) [lit.²² mp 54–55°; $[\alpha]_{\text{D}}^{19} -15.7$ ° (EtOH)]. Solvents were purified as shown in the preceding paper.¹ Iodobenzene dichloride (IBD) was prepared by a method of Lucas and Kennedy,²³ and purified by recrystallization from chloroform and air dried just prior to use.

Reactions of *D*-Glucal Triacetate with IBD.—Reactions were carried out in sealed Pyrex ampoules except for reaction in the air. Reactions in the absence of molecular oxygen were carried out by degassing by a freeze-thaw method and introduction of argon or nitrogen gas dried with sulfuric acid. Photoinitiated reactions were carried out using a 200-W incandescent light bulb at 30 ± 0.1 ° in a thermostated bath. After reaction was finished, an appropriate amount of penta-*O*-acetyl- β -*D*-mannose was added as the internal standard, and the solution was washed with 5% sodium thiosulfate solution and water, dried, and evaporated. The residue was dissolved in carbon disulfide containing a small amount of dichloromethane and the solution was analyzed by glpc. In the case of propylene carbonate, the reaction mixture was diluted with carbon disulfide after the standard had been added and the solution was analyzed. The four isomeric dichlorides and the internal standard were not affected to any measurable extent under the reaction conditions and during the extraction.

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(14) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p 117.

(15) K. Igarashi and T. Honma, *Tetrahedron Lett.*, 751 (1968); *J. Org. Chem.*, **35**, 606 (1970).

(16) W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 4850 (1964), reported in the esr study that a radical obtained by a hydrogen-atom abstraction from *p*-dioxane had a chair conformation.

(17) F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965).

(18) E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1963); E. S. Huyser, H. Benson, and H. J. Sinnige, *J. Org. Chem.*, **32**, 622 (1967).

(19) N. A. LeBel and A. DeBoer, *J. Amer. Chem. Soc.*, **89**, 2784 (1967).

(20) P. D. Readie and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).

(21) P. S. Skell in "Organic Reaction Mechanisms," Special Publication No. 19, International Symposium, The Chemical Society, Burlington House, London W. 1, 1965, p 131.

(22) B. Helferich, E. N. Mulcahy, and H. Ziegler, *Chem. Ber.*, **87**, 233 (1954).

(23) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Col. Vol III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 482.

Reactions were carried out with a concentration of 0.734 M D-glucal triacetate in the solvents and appropriate amounts of IBD.

Product Isolation.—A mixture of 1.0 g of D-glucal triacetate, 1.21 g of IBD, and 50 ml of carbon tetrachloride was degassed by a freeze-thaw method, and nitrogen gas dried with concentrated sulfuric acid was introduced. The ampoule was sealed and placed in a thermostated bath adjusted at $30 \pm 0.1^\circ$. When the mixture was irradiated by a 200-W incandescent light bulb, the reaction proceeded very quickly. After 2 min of irradiation,

the ampoule was opened and the reaction mixture was washed with sodium thiosulfate and water, dried, and evaporated. The residue was fractionated by repeated preparative tlc on silica gel using benzene-ether (1:1) as the developer, and 543 mg (43.1%) of 5, mp $63-63.5^\circ$, 81 mg (6.4%) of 2, mp $100-101.5^\circ$, and 140 mg (11.1%) of 4, mp $120-121.5^\circ$, were obtained. These compounds were found to be identical with the authentic samples.

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Steric Parameters in Structure-Activity Correlations. Cholinesterase Inhibitors¹

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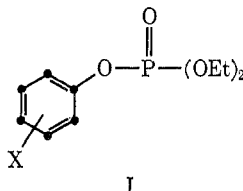
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Newly formulated E_s constants based on Charton's work showing a direct relationship between the steric parameter E_s and van der Waals radii are used to help correlate the chemical structure of diethyl phenylphosphates with their cholinesterase-inhibitory potency.

We have been interested in the correlation of chemical structure and reactivity of organic compounds with enzymes and pharmacological systems.^{2,3} The approach employed is that now termed extrathermodynamic⁴ in which the linear combination of free energy based parameters is used to correlate structure with activity. A generally useful model for enzymic reactions⁵ is shown in eq 1. In some instances higher order equa-

$$\log 1/C(K) = k_1\pi + k_2\sigma + k_3E_s + k_4 \quad (1)$$

tions should be considered.⁶ In eq 1, C represents molar concentration of organic compound causing a standard response (in the present work 50% inhibition of cholinesterase activity). Alternatively, a rate or equilibrium constant, K , may be used. The constants k_1 , k_2 , k_3 , and k_4 are obtained by the method of least squares. The Hammett constant σ or its variations⁴ may be used to represent electronic effects of substituents on $\log 1/C$ or K . The hydrophobic parameter,⁷ π , represents the free energy of transfer of a substituent from an aqueous to an apolar phase and E_s is Taft's steric parameter.⁴ The present analysis is directed toward the application of eq 1 and its simpler forms to cholinesterase inhibitors of structure I. The activity data



($1/C$) come from the extensive studies of Metcalf and Fukuto on the inhibition of fly head cholinesterase by phosphorous esters^{8,9} and carbamates.¹⁰

(1) This work was supported by Grant CA 11110 from the National Institutes of Health.

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(3) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

(4) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963.

(5) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965).

(6) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).

(7) (a) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

Metcalf and Fukuto showed that the inhibitory activity of the esters (I) was strongly related to the electron-withdrawing effect of the substituents (X). In an attempt to sharpen their correlation it was found¹¹ that there was a very good correlation between the *para* isomers and the Hammett constant, but that the *meta* isomers gave an extremely poor correlation. Metcalf and Fukuto¹² have advanced evidence to show that the *meta* substituents appear to fit into a specific enzymic site. The geometry of the substituent could of course be crucial in such a fit. At the time of our first analysis of the *meta*-substituted phenylphosphates only a limited set of E_s values for substituents on the benzene ring were available. While the steric parameter E_s was formulated for intramolecular interactions, we have found that this parameter can be employed when intermolecular interactions may be involved.^{5,11,13,14}

Recently, Charton¹⁵ has shown that E_s can be quantitatively related to van der Waals radii for symmetrical-top-like substituents. He has calculated the maximum van der Waals radii, $r_{V \max}$, and the minimum, $r_{V \min}$, for groups such as methyl, trifluoromethyl, etc. We have found that using $r_{V \text{ av}}$ (an average of $r_{V \max}$ and $r_{V \min}$), E_s values calculated from van der Waals radii can be placed on the same scale as Taft's values. Equa-

$$E_s = -1.839r_{V \text{ av}} + 3.484 \quad \begin{matrix} n & r & s \\ 6 & 0.996 & 0.132 \end{matrix} \quad (2)$$

tion 2 can be used for this purpose. Equation 2 was established¹³ by the correlation of six (n = number of data points employed in the regression) symmetrical-top substituents of known E_s values with $r_{V \text{ av}}$ values taken from the work of Charton.¹⁵ Using eq 2, E_s values formerly not available for the halogens, NO_2 , SF_5 , etc., can be calculated from $r_{V \text{ av}}$ values. Thus we are now

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(12) R. L. Metcalf and T. R. Fukuto, *J. Agr. Food Chem.*, **13**, 220 (1965).

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