Thallium in Organic Synthesis. XXV. Electrophilic Aromatic Bromination Using Bromine and Thallium(III) Acetate[1-3]

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A mixture of thallium(III) acetate and bromine is shown to be a mild and efficient reagent for electrophilic aromatic bromination. The reaction is applicable to the preparation of a wide range of isomerically pure monobromo aromatic compounds but is successful only when the substrate is activated toward electrophilic substitution. Several possible mechanisms are considered and explanations suggested for the role of thallium(III) acetate.

Thallium(III) acetate was first described in 1903 by Meyer and Goldschmidt,[4] but it is only in the last few years that the versatility and synthetic utility of this reagent in organic chemistry have deen demonstrated. The scope[5,6] and status[7] of thallium(III) acetate as an oxidant have been reviewed, and among recent applications to organic synthesis are reports describing its use in the oxidative cleavage of cyclopropanes,[5] the preparation of α-acetoxy ketones from ketones[8] and enamines,[9] the synthesis of 4,5-dihydrofurans from β-dicarbonyl compounds,[10] the direct conversion of chalcones into isoflavones,[11,12] and the hydration of acetylenes.[13] In all of these reactions thallium(III) acetate has been shown to function as a moderately reactive yet highly selective[5,6,11,12] electrophile. As far as we are aware, however, there are no reports on the Friedel–Crafts catalytic activity of the salt with respect to electrophilic aromatic substitution. Studies on the use of the thallium(III) halides as Friedel–Crafts catalysts have established that alkylation,[14,15] acylation,[14,15] chlorination,[16-18] and bromination[19] of aromatic compounds proceed normally but in low yields. The inefficiency of the thallium(III) halides in these reactions is almost certainly due primarily to the thermal instability of these compounds.[20] By contrast, thallium(III) acetate is a readily accessible, stable, crystalline solid which can be stored indefinitely without decomposition.

We have investigated the utility of thallium(III) acetate as a Friedel–Crafts catalyst and describe in this paper a general procedure for electrophilic bromination of activated aromatic compounds.

Results

A mixture of thallium(III) acetate and bromine is an effective and highly selective reagent for electrophilic aromatic bromination. Addition of a solution of bromine in carbon tetrachloride to a suspension of thallium(III) acetate in carbon tetrachloride containing an aromatic substrate results in the instantaneous discharge of the red color of the bromine. Thallium(III) acetate is rapidly converted to thallium(III) bromide, with simultaneous formation of the brominated aromatic compound. In the majority of examples studied the reaction proceeded rapidly at room temperature.

The scope of the reaction can be seen by examination of the data in Table I, in which typical conversions are summarized, and by consideration of the following general observations. Bromination occurs readily only with substrates activated toward electrophilic substitution. Even mildly deactivated compounds such as the halobenzenes were recovered unchanged when carbon tetrachloride was employed as solvent. These compounds underwent bromination smoothly, however, when excess of the aromatic substrate was employed as solvent, and the reaction was conducted at 80–90°. All other electron-withdrawing groups completely inhibited bromination in monosubstituted benzenes. A number of substituent groups were efficiently oxidized by thallium(III) acetate and bromine in carbon tetrachloride and nuclear substitution was not observed with such monosubstituted benzenes. Thus, benzaldehyde and benzyl alcohol, both of which could be recovered unchanged after being heated with thallium(III) acetate in carbon tetrachloride, were converted to benzoic acid (58%) and benzaldehyde (62%), respectively, when bromine was added to the reaction mixture. In polysubstituted benzenoid compounds, however, oxidation of these substituents was suppressed in favor of substitution when powerfully electron-donating groups were present. Thus 4-methoxybenzaldehyde was smoothly converted into 3-bromo-4-methoxy-

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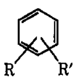
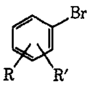
TABLE I

SYNTHESIS OF AROMATIC BROMIDES USING $Tl(OOCCH_3)_3/Br_2$

	Starting material		Product		
					
No.	R	R′	R	R′	Yield, %[a]
1	H	H	H	H	83
2	CH_3	H	4-CH_3	H	60[b,c]
3	C_2H_5	H	4-C_2H_5	H	60[b]
4	C_6H_5	H	4-C_6H_5	H	93
5	CH_3O	H	4-CH_3O	H	91
6	CH_3NH	H	4-CH_3NH	H	62
7	$(CH_3)_2N$	H	4-$(CH_3)_2N$	H	75
8	CH_3CONH	H	4-CH_3CONH	H	95
9	CH_3S	H	4-CH_3S	H	73
10	F	H	4-F	H	70[d]
11	Cl	H	4-Cl	H	70[d]
12	Br	H	4-Br	H	73[d]
13	I	H	4-I	H	69[d]
14	CH_3	2-CH_3	3-CH_3	4-CH_3	85
15	CH_3	3-CH_3	2-CH_3	4-CH_3	88
16	CH_3	4-CH_3	2-CH_3	5-CH_3	76
17	CH_3O	2-CH_3O	3-CH_3O	4-CH_3O	85
18	CH_3O	3-CH_3O	2-CH_3O	4-CH_3O	87
19	NO_2	2-CH_3O	3-NO_2	4-CH_3O	90
20	NO_2	2-C_6H_5	4-(2′-$NO_2C_6H_4$)	H	70
21	CHO	4-CH_3O	5-CHO	2-CH_3O	66
22	$COOCH_3$	3-CH_3O	2-$COOCH_3$	4-CH_3O	93
23	$COOCH_3$	4-CH_3O	5-$COOCH_3$	2-CH_3O	90
24	Thiophene		2-Bromothiophene		82[e]
25	2-Methylthiophene		2-Bromo-5-methylthiophene		75
26	3-Methylthiophene		2-Bromo-3-methylthiophene		72
27	Naphthalene		1-Bromonaphthalene		71
28	1-Methylnaphthalene		4-Bromo-1-methylnaphthalene		84
29	1-Methoxynaphthalene		4-Bromo-1-methoxynaphthalene		70
30	2-Methoxynaphthalene		1-Bromo-2-methoxynaphthalene		68
31	1-Nitronaphthalene		5-Bromo-1-nitronaphthalene		75
32	Anthracene		9-Bromoanthracene		89
33	Biphenylene		2-Bromobiphenylene		88
34	Fluorene		2-Bromofluorene		80
35	Phenanthrene		9-Bromophenanthrene		78
36	*p*-Terphenyl		4-Bromo-*p*-terphenyl		79[f]

[a] Calculated on pure recrystallized or redistilled material. [b] Reaction conducted at 0° throughout. [c] Accompanied by 8% *o*-bromotoluene. [d] Excess of the aromatic substrate was used as solvent; reaction conducted at 80–90°. [e] Accompanied by 8% of 2,5-dibromothiophene. [f] Accompanied by 2–4% of 4,4′-dibromo-*p*-terphenyl.

benzaldehyde in 66% yield on treatment with thallium(III) acetate and bromine in carbon tetrachloride.

The rate of addition of the bromine solution in these reactions is critical; the presence of free bromine in the reaction mixture leads to mixtures of isomers and should be avoided. For example, addition of the bromine solution all at once to a mixture of ethylbenzene and thallium(III) acetate in carbon tetrachloride resulted in formation of both 2- and 4-bromoethylbenzene (15:85).

From the above results and the data in Table I, it is evident that the thallium(III) acetate/bromine reaction involves a species of low electrophilicity. This conclusion is compatible with the two most outstanding features of the reaction: (1) monobromination was observed in almost all of the aromatic substrates studied and (2) exclusive para bromination was observed with almost all of the monosubstituted benzenes. The latter feature, which distinguishes the present method from the majority of electrophilic aromatic bromination reactions, is indicative of an electrophile of low reactivity but high steric requirement.[21]

Bromination of phenol, aniline, thiophene, 1,4-dimethoxybenzene, and *p*-terphenyl with thallium(III) acetate and bromine gave mixtures of mono- and dibrominated products. The yield of dibromo compounds was low with thiophene (8%) and *p*-terphenyl (2–4%) but considerably higher with phenol, aniline, and 1,4-dimethoxybenzene (10–25%). We interpret these results as reflecting the relative rates with which these compounds and their monobromo derivatives undergo electrophilic bromination. Thus competitive substitution by molecular bromine and by the thallium(III) acetate/bromine reagent would be expected with phenol, aniline, thiophene, and 1,4-dimethoxybenzene provided that the relative electrophilicities of the reagents were comparable. In 4-bromo-*p*-terphenyl, the initial substitution product of *p*-terphenyl, deactivation of the 4′ position by the bromine substituent should be considerably reduced relative to the 4′ position in bromobenzene, and a small amount of dibromination is predictable.

Discussion

Many procedures have been described for the direct introduction of bromine into an aromatic nucleus. The majority of these can be classified into one of three categories depending on the nature of the bromine source which is employed, namely (a) molecular bromine, as such, or generated *in situ*, (b) molecular bromine activated by a catalyst, or (c) a positive bromine species.[22] The general trend of increasing electrophilicity in this series is a < b < c. With respect to this classification, and in view of the unusually high selectivity of substitution encountered with thallium(III) acetate/bromine, we have examined a number of possible mechanisms for this reaction. Our objective in this work was to elucidate two interrelated aspects of the reaction, namely the nature of the bromine electrophile involved and the specific role of the thallium(III) acetate.

There are three obvious pathways for electrophilic aromatic bromination using thallium(III) acetate and bromine: (1) formation of acetyl hypobromite as the active bromine reagent; (2) generation of an arylthallium diacetate by electrophilic thallation and subsequent reaction of this intermediate with bromine; (3) bromination by molecular bromine catalyzed either by thallium(III) bromide or by thallium(III) acetate. The results summarized below clearly eliminate the first two of these possibilities and are in general agreement with the third.

(1) **Acetyl Hypobromite Formation.**—Preparation of acyl hypohalites by treatment of metal carboxylates with molecular halogen is a well-documented process[23] which has been used to generate "positive" halogen

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[21] R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, New York, N. Y., 1965.

[22] Reference 21, pp 119–155.

[23] M. Anbar and D. Ginsburg, *Chem. Rev.*, **54**, 925 (1954).

(by decomposition of the acyl hypohalite[24,25]). Evidence that an analogous pathway (eq 1 and 2) is not

$$3Br_2 + Tl(OOCCH_3)_3 \longrightarrow 3CH_3COOBr + TlBr_3 \quad (1)$$

$$3CH_3COOBr + 3ArH \longrightarrow 3CH_3COOH + 3ArBr \quad (2)$$

involved in the thallium(III) acetate/bromine reaction was obtained as follows. Thalluim(III) acetate was shaken with a solution of bromine in carbon tetrachloride, aliquots were withdrawn periodically, and the uv spectra were recorded. The characteristic absorption maximum at 265 nm due to acetyl hypobromite[26] was not observed; a solution of genuine acetyl hypobromite[26] in carbon tetrachloride was used as reference standard. Identical results were obtained using acetonitrile as solvent [in which thallium(III) acetate is soluble]. Aliquots were also withdrawn from reaction mixtures consisting of thallium(III) acetate, bromine, and an aromatic substrate, both in carbon tetrachloride and acetonitrile. Again, examination of the uv spectra showed that acetyl hypobromite was not formed in these reactions.

(2) **Electrophilic Thallation.**—The reactions shown in eq 3 and 4 constitute a plausible explanation for the

$$ArH + Tl(OOCCH_3)_3 \longrightarrow ArTl(OOCCH_3)_2 + CH_3COOH \quad (3)$$

$$ArTl(OOCCH_3)_2 + 2Br_2 \longrightarrow ArBr + TlBr + CH_3COOBr \quad (4)$$

bromination of aromatic compounds with thallium(III) acetate and bromine. Electrophilic aromatic thallation with thallium(III) trifluoroacetate[27] and isobutyrate[28,29] has been described; arylthallium dicarboxylates (eq 3) are known to undergo C–Tl bond cleavage on treatment with molecular halogen to give aromatic halides.[30] As discussed above, acetyl hypobromite is not produced in the thallium(III) acetate/bromine reaction (*cf.* eq 4). Acyl hypobromites have been shown to react with thallium(I) bromide, however, to give the unstable sesquihalide Tl_2Br_4, which readily decomposes to a mixture of thallium(I) and thallium(III) bromides.[31] Consequently, failure to detect the presence of acetyl hypobromite in the reaction mixture does not necessarily negate the feasibility of bromination as shown in eq 3 and 4.

Equation 3 was shown to be untenable as follows. Attempted thallation of a variety of aromatic substrates by heating with thallium(III) acetate in carbon tetrachloride was totally unsuccessful, and the reactants were recovered unchanged. Under more forcing conditions (absence of solvent, 100–150°), extensive decomposition resulted and led to intractable tars. In an alternative approach designed to test the validity of eq 4, phenylthallium and 4-*o*-xylylthallium diacetates were prepared independently (see Experimental Section) and treated with solutions of bromine in carbon tetrachloride. In both cases, extensive decomposition of the organothallium derivatives was observed, and complex reaction mixtures were obtained. The major constituents of these mixtures were *p*-dibromobenzene and 4,5-dibromo-*o*-xylene, respectively.

(3) **Molecular Bromine as Electrophile.**—The stoichiometry of the thallium(III) acetate/bromine reaction is shown in eq 5. Thallium(III) bromide is insoluble

$$Tl(OOCCH_3)_3 + 3ArH + 3Br_2 \longrightarrow 3ArBr + 3CH_3COOH + TlBr_3 \quad (5)$$

in carbon tetrachloride, the solvent used in preparative scale operations, and separated during reaction. It is, however, soluble in acetonitrile and its formation during reactions conducted in this solvent was confirmed by observation of its characteristic uv absorption maxima at 275 and 300 nm. Solutions of freshly prepared thallium(III) bromide in acetonitrile (see Experimental Section) were used as reference standards.

As mentioned above, the thallium(III) halides are mild but inefficient Lewis acid catalysts in electrophilic aromatic halogenation reactions. Their thermal instability severely limits their application to synthesis; the bromide, for example, disproportionates at temperatures in excess of 40° (eq 6). Nevertheless, we

$$TlBr_3 \underset{<40°}{\overset{>40°}{\rightleftharpoons}} TlBr + Br_2 \quad (6)$$

considered that some portion of the product formed in the thallium(III) acetate/bromine substitution of aromatic compounds might be derived by processes involving catalysis of substitution by molecular bromine either by thallium(I) or thallium(III) bromide. The following control experiments were undertaken to test these possibilities. Anisole was added to a freshly prepared solution of thallium(III) bromide in acetonitrile and the reaction mixture was monitored by uv spectroscopy during the course of several days. No diminution was observed in the absorption maxima due to thallium(III) bromide. On a preparative scale, a mixture of equimolar amounts of anisole and thallium(III) bromide in acetonitrile was stirred at room temperature for 7 days; anisole was recovered unchanged. Thallium(III) bromide itself is not therefore the active reagent in the bromination reaction.

The rate of bromination of toluene by bromine in acetonitrile was then studied, both in the presence and absence of thallium(III) bromide. The concentration of thallium(III) bromide was varied from 0.1 to 1.0 *M* with respect to the aromatic substrate. There was no evidence of rate enhancement in reactions conducted in the presence of thallium(III) bromide. This latter result, though indicative, does not however conclusively eliminate the possibility that in acetonitrile solution part of the product may be formed by bromination of the aromatic substrate by a mixture of thallium(III) bromide and bromine. Acetonitrile is a relatively strong base which may effectively quench the catalytic activity of Lewis acids. Thus, Stock and Himoe have observed that the second-order rate constants for the chlorination of toluene in acetonitrile are little changed by the addition of aluminum chloride.[32]

It proved impossible to assess the extent (if any) to which thallium(III) bromide might function as a catalyst in reactions in which carbon tetrachloride was

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[25] R. N. Haszeldine and A. G. Sharpe, *ibid.*, 993 (1952).

[26] M. Anbar and I. Dostrovsky, *ibid.*, 1105 (1954).

[27] A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423 (1969).

[28] V. P. Glushkova and K. A. Kocheshkov, *Izv. Akad. Nauk USSR, Otd. Khim. Nauk*, 1186 (1957).

[29] V. P. Glushkova and K. A. Kocheshkov, *Zh. Obshch. Khim.*, **36**, 1690 (1966).

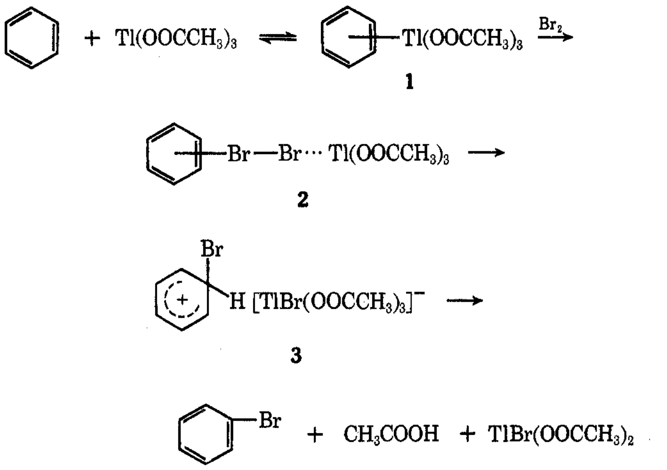
[30] A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Vol. 1. The Organic Compounds of Boron, Aluminium, Gallium, Indium and Thallium," North Holland Publishing Co., Amsterdam, 1967, p 587.

[31] A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, **34**, 1172 (1969).

[32] L. M. Stock and A. Himoe, personal communication.

employed as solvent. These reaction mixtures were heterogeneous, and attempts to obtain satisfactory kinetic data both by spectroscopic and quenching techniques were unsuccessful. Thallium(III) halides are known to be ineffective Friedel–Crafts catalysts,[14–19] however, and the yields of products obtained in thallium(III) halide-catalyzed halogenations of aromatic compounds are much inferior to those realized when thallium(III) acetate is employed. Consequently, we believe that the reaction pathway involving molecular bromine activated by thallium(III) acetate is the more important and that the mechanism is best represented as shown in Scheme I. Decomposition of the ion pair **3** into product and bromothallium diacetate is presumably followed by similar reaction sequences involving bromothallium diacetate and dibromothallium acetate as catalysts. The high degree of positional selectivity observed in substitution can then be attributed primarily to the steric bulk of the electrophile, species such as **2** and **3** representing highly ordered arrays.

SCHEME I



Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Where appropriate, identity of compounds was confirmed by comparison of ir spectra determined by the normal Nujol mull or liquid film techniques on a Perkin-Elmer Model 237 grating infrared spectrophotometer. Analytical gas–liquid chromatograms were carried out using Perkin-Elmer Model PE 452 and F 11 gas chromatographs. Standard columns comprising 1-m and 2-m Apiezon and 2-m silicon oil packing were used throughout with the PE 452; a 50-m PPG capillary column was employed with the F 11 instrument. Quantitative analyses of chromatograms were performed using a Vitatron UR 400 digital readout integrator. Ultraviolet spectra were recorded on a Perkin-Elmer Model 137 uv spectrophotometer and on a Unicam SP 500 Series 2 ultraviolet and visible spectrophotometer.

Starting Materials.—Compounds **1–21**, **24–32**, and **34–36** were commercial samples and were purified prior to use. Methyl 3-methoxybenzoate[33] and methyl 4-methoxybenzoate[34] were prepared by literature procedures; compound **33** was kindly donated by Dr. J. F. W. McOmie of the University of Bristol.

Purification of Solvents.—Carbon tetrachloride was dried by stirring over phosphorus pentoxide for at least 24 hr, followed by distillation on to molecular sieves which had been previously heated under vacuum at 80° for 10 hr. Acetonitrile was distilled off phosphorus pentoxide, the fraction bp 81° being collected. Acetic acid was purified by the procedure of Orton and Bradfield,[35] and bromine was dried over phosphorus pentoxide for 24 hr prior to use.

Reaction of Aromatic Compounds with Thallium(III) Acetate and Bromine in Carbon Tetrachloride. Standard Procedure.—To 0.01 mol of the aromatic substrate was added 0.03 mol of thallium(III) acetate. The mixture was stirred in 100 ml of carbon tetrachloride under an atmosphere of dry nitrogen in a flask fitted with a dropping funnel and reflux condenser, both of which were protected by silica gel drying tubes. Maintaining a vigorous rate of stirring, a solution of 0.01 mol of bromine in 50 ml of carbon tetrachloride was added dropwise, the concentration of free bromine being maintained at a minimum throughout reaction. Addition of bromine was generally complete within 15–20 min. The mixture was then heated under reflux for 30 min. The cooled reaction mixture was filtered through a sintered glass funnel and then washed with approximately 150-ml quantities of aqueous sodium metabisulfite, aqueous sodium bicarbonate, and finally water. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed to give the crude product. To remove traces of thallium, this material was filtered down a short alumina column using chloroform as eluent. Distillation or recrystallization then gave the pure product.

Procedure for the Bromination of Halobenzenes with Thallium(III) Acetate and Bromine.—To 20 ml of the halobenzene was added 0.01 mol of thallium(III) acetate. The mixture was stirred under an atmosphere of dry nitrogen and heated to 80–90°. A solution of 0.03 mol of bromine in 10 ml of the halobenzene was added slowly. The mixture was stirred at 80–90° for 1 hr and allowed to cool. The mixture was then worked up as in the above procedure.

Preparation of Phenylthallium Diacetate.—To a solution of 5 g (0.06 mol) of sodium acetate in 20 ml of acetic acid was added 2.5 g (0.005 mol) of phenylthallium ditrifluoroacetate.[27] The mixture was stirred for 48 hr and filtered, and the colorless product was dried under high vacuum. This gave 2.0 g (50%) of phenylthallium diacetate as a colorless solid, mp 205–209° (lit.[36] mp 193–195°).

The general method of Glushkova and Kocheshkov[37] was also employed to prepare this compound, yield 43%, mp 204–208°.

Preparation of 4-*o*-Xylylthallium Diacetate.—The procedure used was the same as for phenylthallium diacetate, using as starting material 4-*o*-xylylthallium ditrifluoroacetate,[27] yield 52%, mp 201–206°. Satisfactory analytical data could not be obtained for this compound because of the ease with which it underwent symmetrization to the diarylthallium acetate.[38,39] The identity of the compound was, however, easily confirmed by examination of its ir and nmr spectra.[40]

Reaction of Phenylthallium Diacetate with Bromine in Carbon Tetrachloride.—To a stirred suspension of 4 g (0.01 mol) of phenylthallium diacetate in 30 ml of carbon tetrachloride was added, from a graduated dropping funnel, a solution of 4.8 g (0.03 mol) of bromine in 10 ml of carbon tetrachloride. After one-third of the solution had been added the mixture was stirred for 5 min; the color of the bromine did not discharge at a detectable rate. The mixture was thus heated to reflux and the rest of the bromine solution was added. Total decolorization of the bromine required heating under reflux for 12 hr. The mixture was worked up as described above in the general procedure to give 0.5 g of a thick, yellow oil; distillation gave 0.3 g of a pale yellow oil, bp 200–220° (1 mm), glc analysis of which showed it to be a mixture of four products. One of these components was identified as *p*-dibromobenzene by comparison of its retention time with that of an authentic sample.

Reaction of 4-*o*-Xylylthallium Diacetate with Bromine in Carbon Tetrachloride.—To a stirred suspension of 4.3 g (0.01 mol) of 4-*o*-xylylthallium diacetate in 30 ml of carbon tetrachloride was added a solution of 1.66 g (0.01 mol) of bromine in 10 ml of carbon tetrachloride. The bromine was decolorized after 5 hr. The work-up used was similar to that described above and gave 0.1 g of a yellow oil which could not be identified.

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(33) K. Kindler, *Justus Liebigs Ann. Chem.*, **452**, 90 (1927).

(34) E. Votecek and J. Matejka, *Chem. Ber.*, **46**, 1755 (1913).

(35) K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, **130**, 983 (1927).

(36) H.-J. Kabbe, *Justus Liebigs Ann. Chem.*, **656**, 204 (1962).

(37) V. P. Glushkova and K. A. Kocheshkov, *Dokl. Akad. Nauk USSR*, **116**, 233 (1957).

(38) K. Yasuda and R. Okawara, *Organometal. Chem. Rev.*, **2**, 255 (1968).

(39) Reference 30, pp 581, 582.

(40) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Organometal. Chem.*, **24**, 77 (1970).

The above experiment was repeated using 4.8 g (0.03 mol) of bromine in 20 ml of carbon tetrachloride. Work-up gave 0.4 g of a brown gum which, after filtration through an alumina column, using chloroform as eluent, gave 0.3 g of a yellow oil which had the same retention time on glc analysis as 4,5-dibromo-*o*-xylene. Its ir spectrum was superimposable on that of authentic 4,5-dibromo-*o*-xylene.

Reaction of Thallium(I) Bromide with Bromine in Acetonitrile. Preparation of Thallium(III) Bromide.—A suspension of 0.28 g (0.001 mol) of thallium(I) bromide in 20 ml of acetonitrile was stirred vigorously while 0.16 g (0.001 mol) of bromine in 10 ml of acetonitrile was added. The bromine was decolorized, and the solid dissolved to give a solution of thallium(III) bromide. Dilution of an aliquot of this solution (0.1 ml made up to 10 ml) gave a solution whose uv spectrum showed an intense absorption band at 275 nm, with a shoulder at 300 nm.

Registry No.—Bromine, 7726-95-6; thallium(III) acetate, 2570-63-0; phenylthallium diacetate, 20425-82-5; 4-*o*-xylylthallium diacetate, 31947-39-4; thallium(III) bromide, 13701-90-1.

Structure–Activity Relationship in the Chymotrypsin Hydrolysis of *p*-Nitrophenyl Esters[1]

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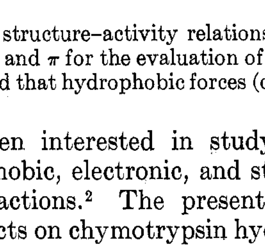
The structure–activity relationship in chymotrypsin substrates is examined using the substituent constants σ^*, E_s, and π for the evaluation of electronic, steric, and hydrophobic effects on the relative rates of reaction. It is found that hydrophobic forces (defined by π) play a positive role in the deacylation step.

We have been interested in studying substituent effects (hydrophobic, electronic, and steric) on enzyme substrate interactions.[2] The present paper analyzes substituent effects on chymotrypsin hydrolysis from the work of Dupaix, Béchet, and Roucous[3] and compares this with earlier studies. The structure–activity problem with chymotrypsin has been approached from many points of view.[4,5] In this report our primary purpose is to consider the role of hydrophobic forces in the hydrolysis step *via* extrathermodynamic correlations. There appears to be a role for these forces independent of specific steric and electronic effects of substituents.

In a recent study[6] of chymotrypsin substrates and inhibitors, the Hein–Niemann[7,8] model of the active site was employed in an analysis of the structure–activity relationship. This model pictures four sections in space into which the four substituents attached to the α carbon of an amino acid moiety of a protein or peptide would fit. This is depicted as in I. In I the hydrogen atom on the α carbon is not shown. It is in the space below the plane of the page. The ρ_H region into which the hydrogen fits is assumed to be occupied only by solvent. The ρ_1, ρ_2, and ρ_3 regions have quite different binding characteristics for substrates and inhibitors. We[6] have attempted a characterization of these areas using linear modeling techniques[9] employing four types of physicochemical parameters: hydrophobic ($\log P$, π), electronic (σ), steric (E_s), and polarizability (P_E). Our general model[10] is formulated in eq 1. In eq 1, k may



I

$$\log k = k_1\pi + k_2\sigma + k_3E_s + k_4 \qquad (1)$$

be a rate or equilibrium constant and the disposable parameters, k_1–k_4, are evaluated *via* the method of least squares.[9] The parameter π is obtained from octanol–water partition coefficients[11,12] and is an operationally defined "hydrophobic bonding" constant analogous to the familiar Hammett constant.[13] E_s is Taft's steric parameter.[13] Atomic refractivities[14] have been used as a measure of polarizability.[15]

In a review of the chymotrypsin literature it was found[6] that, for eight sets of substrates and inhibitors with hydrophobic groups attached to an α carbon, the coefficient with the hydrophobic term (π or $\log P$) in eq 1 or its simpler forms had a mean value with standard deviation of 1.21 ± 0.23. The dependent variable in these correlations was either $\log 1/K_m$, $\log K_i$, or $\log 1/C$. K_i is an inhibition constant and C is the molar concentration causing 50% inhibition. There was no apparent difference in the coefficients for substrates or inhibitors. This high coefficient (1.21) was suggested to be a ρ_2 area characteristic. For four sets of congeners with groups fitting the ρ_3 area, the mean coefficient with the apolar term was 0.29 ± 0.1. Binding in the ρ_3 area was found to be quite different; the ρ_3 area does not behave by our operationally defined hydrophobic

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