Thallium in Organic Synthesis. XXIII. Electrophilic Aromatic Thallation. Kinetics and Applications to Orientation Control in the Synthesis of Aromatic Iodides[1]

Edward C. Taylor,*[2a] Frank Kienzle,[2a,3] Roger L. Robey,[2a] Alexander McKillop,[2b] and John D. Hunt[2b]

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey 08540, and the School of Chemical Sciences, University of East Anglia, Norwich, England.
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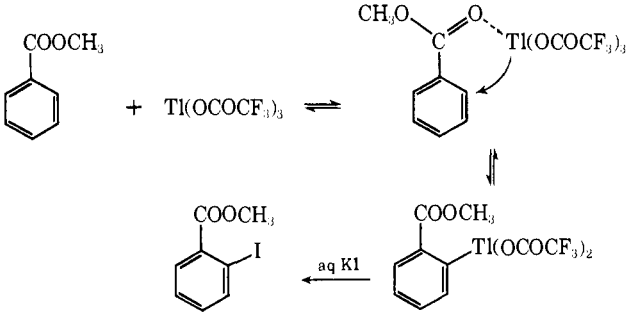
Abstract: Aromatic thallation is shown to be a reversible, electrophilic substitution reaction with an energy of activation of 27 kcal/mol and a large steric requirement. The process of thallation followed by addition of aqueous potassium iodide represents a simple and facile synthesis of aromatic iodo compounds, and the factors (kinetic, thermodynamic, steric) which control the position of thallation (and hence of iodination) have been systematically explored. Meta substitution is achieved under conditions of thermodynamic control. Under conditions of kinetic control, ortho substitution results when chelation of the reagent (thallium(III) trifluoroacetate, TTFA) with the directing substituent permits intramolecular delivery of the electrophile, and para substitution results when such capabilities are absent. Thus appropriate manipulation of conditions can lead to control over orientation (ortho or meta or para) in the same electrophilic substitution reaction. The application of these observations to the selective synthesis of a number of aromatic iodo compounds is described.

In the preceding paper[1b] we have described the preparation of thallium(III) trifluoroacetate (TTFA), its use as a reagent for effecting electrophilic aromatic thallation, and a facile synthesis of aromatic iodides by treatment of the resulting arylthallium ditrifluoroacetates with aqueous potassium iodide. In the course of this work it was noted that unexpectedly high ortho thallation (95%) was obtained with benzoic acid. An attractive rationale for this almost exclusive ortho substitution was intramolecular delivery of thallium to the ortho position from a mixed thallium(III) carboxylate, presumably formed *in situ*. However, methyl benzoate also gives almost exclusive ortho thallation (95%), indicating the more probable intermediacy of a substrate–electrophile complex.



The present work[4] was undertaken in order to examine the validity of this postulate and its potential synthetic applications. Table I lists the compounds examined and our experimental results.

Table I. Isomer Distributions in the Thallation of Aromatic Compounds at Room Temperature

Compd	Substrate C_6H_5R, R =	Isomer distribution[a] Ortho	Meta	Para
1	CH_3	9	4	87
2	$CH_2CH_2CH_3$	3	6	91
3	$CH(CH_3)_2$	1	5	94
4	COOH	95	5	0
5	CH_2COOH	92	3	5
6	$CH(CH_3)COOH$	65	11	24
7	$C(CH_3)_2COOH$	0	37	63
8	CH_2CH_2COOH	29	13	58
9	$CH(CH_3)CH_2COOH$	37	14	49
10	$CH_2CH_2CH_2COOH$	6	10	84
11	$CH_2CH_2CH_2CH_2COOH$	5	9	86
12	$COOCH_3$	95	5	0
13	CH_2COOCH_3	92	3	5
14	$CH_2CH_2COOCH_3$	53	7	40
15	CH_2OH	>99		
16	CH_2OCOCH_3	50	21	29
17	CH_2CH_2OH	83	6	11
18	$CH_2CH_2OCOCH_3$	3	13	84
19	$CH_2CH_2CH_2OH$	10	10	80
20	$CH_2CH_2CH_2OCOCH_3$	5	12	83
21	OCH_3	7		93[b]
22	CH_2OCH_3	>99		
23	$CH_2CH_2OCH_3$	85	3	12
24	$CH_2CH_2CH_2OCH_3$	27	6	67
25	CH_2OCOCF_3	49	24	27
26	$OCOCH_3$	21		79
27	*o*-$CH_3C_6H_4CH_2COOH$	31% thallation in position 6[c]		

[a] Determined by glc analysis of the corresponding aromatic iodides (see Experimental Section). [b] Determined by nmr. Thallation was carried out at −25°. [c] Exact values for the percentage of thallation in the other positions were not obtained.

Inspection of the results obtained upon thallation and subsequent iodination of the homologous series of carboxylic acids [benzoic acid (**4**), phenylacetic acid (**5**), 3-phenylpropanoic acid (**8**), 4-phenylbutyric acid (**10**), and 5-phenylpentanoic acid (**11**)] (see Table I) indicate conclusively that the degree of ortho substitution is dramatically affected by the size of the carboxylate-

(1) (a) We gratefully acknowledge financial support of part of this work by the Smith Kline & French Laboratories, Philadelphia, Pa. 19101, and by Eli Lilly and Co., Indianapolis, Ind. 46206. (b) Part XXII: A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Amer. Chem. Soc.*, **93**, 4841 (1971).
(2) (a) Princeton University; (b) University of East Anglia.
(3) NRCC Postdoctoral Fellow, 1968–1970.
(4) For a preliminary report on this work, see E. C. Taylor, F. Kienzle, R. L. Robey, and A. McKillop, *J. Amer. Chem. Soc.*, **92**, 2175 (1970).

electrophile chelate. Thus, both benzoic and phenylacetic acid, and their methyl esters, give almost exclusively *o*-iodo derivatives through five- and six-membered chelate rings, respectively.[5] On the other hand, ortho thallation with 3-phenylpropanoic acid can only occur by intramolecular delivery through a seven-membered chelate ring, which is clearly less favorable (30% ortho thallation). A further increase in the size of the intermediate chelate (to eight- and nine-membered rings, respectively) with compounds **10** and **11** effectively eliminates ortho substitution *via* substrate–electrophile complexation.

In order to study further the influence on isomer distribution of this (presumed) intramolecular delivery of thallium *via* an intermediate Lewis acid–Lewis base chelate,[6,7] we have examined thallation–iodination of a number of homologous series of compounds substituted in the side chain with a substituent capable of complexing with TTFA. Once again, five- and six-membered intermediate chelates lead to exclusive or predominant ortho substitution (benzyl alcohol (**15**), 99%; benzyl methyl ether (**22**), 99%; β-phenylethanol (**17**), 83%; β-phenylethyl methyl ether (**23**), 85%).[8] And once again, increasing the size of the intermediate chelate by increasing further the distance of the complexed electrophile from the aromatic ring (**19** and **24**) results in a sharp decrease in ortho substitution. The degree of ortho substitution within any given size of chelate ring (five, six, or seven membered) appears to be a function of the nature of the Lewis base substituent on the side chain with ortho substitution decreasing in the order ester > acetate > acid > ether > alcohol.[9]

Intramolecular chelate-controlled ortho delivery of thallium appears to be extremely sensitive to steric hindrance. Replacement of one α hydrogen atom by a methyl group in phenylacetic acid (*i.e.*, **6**) results in a decrease in ortho substitution from 92 to 65%; replacement of both α hydrogens by methyl groups (*i.e.*, **7**) totally eliminates ortho substitution. Comparing compounds **8** and **9**, it would appear that, as expected, steric hindrance to ortho substitution is greater the closer the interfering group is to the site of complex formation.

The presumed intermediacy of a substrate–electrophile complex formed prior to thallation is supported by the following observations.

(a) Thallation of compounds bearing an activating substituent (*i.e.*, alkyl) which cannot react (other than sterically) with TTFA is complete within a few minutes at room temperature. However, the presence of a basic substituent on the side chain, independent of its distance from the ring, markedly increases the time required for thallation (*i.e.*, benzyl methyl ether (**22**), 5 hr; β-phenylethanol (**17**), 7 hr; β-phenylethyl acetate (**18**), 24 hr; 3-phenylpropanoic acid (**8**), 24 hr; 3-phenylpropanol (**19**), 24 hr; phenylacetic acid (**5**), 48 hr).

(b) Meta substitution is highest with those compounds where an intermediate eight-membered chelate ring can be formed to the meta position (and thus a seven-membered ring to the ortho position); *i.e.*, **8**, **19**, **23**, and **24**. A particularly striking orientation effect which can only have its origin in chelation is observed with 2-phenyl-2-methylpropanoic acid (**7**). Ortho thallation (through a six-membered chelate ring) is apparently sterically prohibited, resulting in a significant amount (37%) of meta substitution. By comparison, cumene (**3**), with comparable steric requirements for the side chain but without a complexing substituent, gives only 5% meta substitution.[10]

(c) Electrophilic aromatic thallation is extremely sensitive to steric factors because of the size of the thallium electrophile (compare toluene (**1**) with cumene (**3**)). It is therefore striking that 2-methylphenylacetic acid (**27**) thallates to the extent of 31% *in the sterically most hindered and electronically least favored position.*

Aromatic thallation is a freely reversible electrophilic substitution reaction (see Experimental Section); the principle of microscopic reversibility predicts that, under equilibrating conditions, the meta isomer should accumulate at the expense of the kinetically favored ortho and para isomers. In agreement with this prediction, we have found that the amount of *m*-iodocumene is increased *17-fold* by carrying out the thallation of cumene at 73° (refluxing TFA) rather than at room temperature[11] prior to addition of aqueous potassium iodide. Analogous results with other substrates are summarized in Table II. It should be noted that compounds carrying side-chain substituents capable of complexing with TTFA required much longer times for equilibration. This places a limitation on the synthetic utility of this procedure for meta substitution, since prolonged heating of TTFA in TFA results in gradual decomposition of the reagent, with concomitant regeneration of the nonthallated substrate. Furthermore, some substrates may not survive prolonged refluxing in TFA.[12]

(5) For comparison, mercuration of benzoic acid with mercury(II) acetate at 130° for 1.5 hr gives 57% ortho, 25% meta, and 18% para substitution [G. R. Jackson and M. S. Frank, *J. Amer. Chem. Soc.*, 77, 5625 (1955)], and at 110° for 2.5 hr 80% ortho, 20% meta, and no para substitution [Y. Ogata and M. Tsuchida, *J. Org. Chem.*, 20, 1644 (1955)]. Mercuration of phenylacetic acid with mercury(II) acetate has been reported to give primarily para substitution (Y. Ogata and M. Tsuchida).

(6) Intermediate Lewis acid–Lewis base chelates have been postulated previously to account for unusually high ortho substitution in some nitrations and formylations, and in alkylations of primary and secondary amines with olefins (R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, New York, N. Y., 1965, pp 303–304).

(7) P. Kovacic and J. J. Hiller, Jr., *J. Org. Chem.*, 30, 1581 (1965).

(8) For comparison, mercuration of benzyl alcohol with mercury(II) acetate gives 60% ortho, 15% meta, and 25% poly substitution and mercuration of β-phenylethanol gives 20% ortho, 60% meta, and 20% poly substitution [T. Ukai, Y. Yamamoto, M. Yotsuzuka, and F. Ichimura, *J. Pharm. Soc. Jap.*, 76, 657 (1956)].

(9) Anisole (**21**) and phenyl acetate (**26**) represent special cases in that the substituent, although capable of chelating with TTFA, also activates the aromatic ring toward electrophilic substitution (thallation of anisole is complete within 1 min at room temperature). It is perhaps noteworthy that phenyl acetate gives 21% ortho thallation, possibly *via* a six-membered intermediate chelate.

(10) It is interesting to note that mercuration of cumene with mercury(II) trifluoroacetate gives 2.4% ortho, 9.8% meta, and 87.8% para substitution, indicating a slightly larger steric requirement for thallation [H. C. Brown and R. A. Wirkkala, *J. Amer. Chem. Soc.*, **88**, 1453 (1956)].

(11) A similar but much smaller effect has been noted with aromatic mercuration, which is also reversible. Thus, fluorobenzene gave (at 25°) 28.7% ortho, 1.8% meta, and 69.5% para substitution, whereas (at 90°) 33.7% ortho, 6.9% meta, and 59.4% para substitution was observed [H. C. Brown and G. Goldman, *J. Amer. Chem. Soc.*, **84**, 1650 (1962)]. Similarly, *tert*-butylbenzene gave no ortho, 28.4% meta, and 71.6% para at 25°, but 34.9% meta and 65.1% para substitution at 90° [H. C. Brown and M. Dubeck, *ibid.*, **81**, 5608 (1959)].

(12) Meta substitution may be increased by addition of various bases to the thallation mixture. In the most favorable example of such catalysis observed thus far, addition of morpholine to cumene–TTFA–

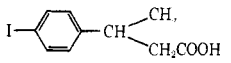
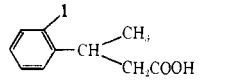
Table II. Isomer Distribution in the Thallation of Aromatic Compounds at 73°

Compd	Reaction time[a]	Isomer distribution[b] Ortho	Meta	Para	m 73°/ m 20°
2	24 hr	9	78	13	13
3	5 hr	12	85	3	17
5	6 days	79	15	6	3.7
8	3 days	28	52	20	3.7
9	1 day[c]	25	45	30	3.2
11	1 day[c]	18	55	27	6.1
17	4 days	6	54	40	9
19	3 days	7	64	29	6.4
23	1 day[c]	65	20	15	6.7

[a] The reaction was stopped when the isomer distribution remained constant. [b] Determined by glc of the corresponding iodo compounds. [c] The reaction was stopped after 1 day. The isomer distribution does not, therefore, represent the equilibrium value.

The structures of the first four iodo compounds in Table III (**28–31**) were easily established by elemental analyses and infrared and nmr data, and in some cases also by their photolytic conversion to the corresponding (known) chloro compounds.[13] The establishment of the structures of **32** and **33**, however, requires further comment. The structure of 6-iodo-2-methylphenylacetic acid (**32**) could be deduced from the fact that its nmr spectrum showed a singlet for the methylene hydrogens at a substantially lower field (τ 6.03) than was observed for the isomeric 5-iodo compound **33**, where the methylene hydrogens appeared at τ 6.48. The deshielding effect of the iodine was not so pronounced in the signals for the methyl groups (τ 7.64 for **32**, τ 7.79 for **33**). The signals for the aromatic protons also supported these structural assignments.

Table III. Miscellaneous Iodoaromatic Compounds Prepared by the TTFA–KI Procedure

Compd	Iodo compound	Mp, °C	Mol formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
28	*p*-$IC_6H_4CH_2CH_2COOCH_3$	47	$C_{10}H_{11}O_2I$	41.40	3.82	41.62	3.81
29		95–96	$C_{10}H_{11}O_2I$	41.40	3.82	41.90	3.90
30		84–85	$C_{10}H_{11}O_2I$	41.40	3.82	41.74	3.99
31	*o*-$IC_6H_4CH(CH_3)COOH$	112–114	$C_9H_9O_2I$	39.15	3.29	39.53	3.42
32	2-CH_3-6-$IC_6H_3CH_2COOH$	156	$C_9H_9O_2I$	39.15	3.29	39.03	3.33
33	2-CH_3-5-$IC_6H_3CH_2COOH$	99–101	$C_9H_9O_2I$	39.15	3.29	39.16	3.26

The synthetic utility of the orientation control discussed above is further illustrated by the selective conversion of β-phenylethanol to its *o*-, *m*-, or *p*-iodo derivative. Thus, thallation of β-phenylethanol at room temperature, followed by treatment with aqueous potassium iodide, gives predominately ortho substitution (83%), while thallation under equilibrating conditions (73°) gives predominately meta substitution (56%). On the other hand, thallation of the *acetate* of β-phenylethanol (**18**, Table I) results in 84% para substitution (here the size of the intermediate chelate required for kinetically controlled ortho substitution has been increased from a six-membered ring to an eight-membered ring by the conversion of –OH to $-OCOCH_3$).

In summary, therefore, appropriate manipulation of conditions can lead to control over orientation in the same electrophilic substitution reaction (thallation). Meta substitution is achieved under conditions of thermodynamic control. Under conditions of kinetic control, ortho substitution results when chelation of the reagent (TTFA) with the directing substituent permits intramolecular delivery of the electrophile, and para substitution results when such capabilities are absent.

In the course of this work several new aromatic iodo compounds were synthesized (see Table III).

TFA resulted in 53% meta substitution within 1 hr, as contrasted with 19% meta substitution in the absence of added morpholine. Similarly, iodination of *n*-propylbenzene (thallation with TTFA–TFA at 73° for 8 hr, in the presence of morpholine, followed by addition of aqueous potassium iodide) gave a mixture of iodo compounds (ortho:meta:para ratio of 18:60:22) unusually rich in the meta isomer. This unexpected catalysis of meta substitution by added bases is under further investigation.

Compound **32** showed one downfield hydrogen (H-5) at τ 2.40, and two upfield hydrogens (H-3, H-4) at τ 3.05. The corresponding signals in **33** were at τ 2.60 (H-4, H-6) and τ 3.20 (H-3). These data establish the structure of **32**, since an iodine atom in position 3, although giving rise to a similar pattern for the aromatic protons, should have a greater effect than was actually observed on the chemical shift of the methyl group. It would not, however, be expected to exert a deshielding effect on the side chain methylene group.

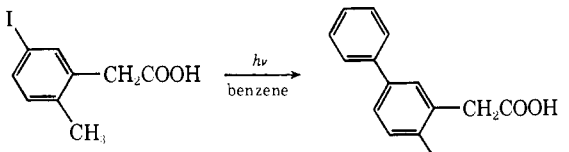
However, nmr data alone are insufficient to define unequivocally the structure of **33**, since rather similar spectra might be predicted for the 4- and the 5-iodo isomers. To distinguish between these two possible structures, **33** was photolyzed in the presence of benzene. It is known[14] that irradiation of aromatic iodides in benzene solution results in the formation of biphenyls where the iodine has been replaced by a phenyl group. Photolysis of **33** under these conditions should thus give either 2-methyl-4-phenyl- or 2-methyl-5-phenylphenylacetic acid, depending upon the position of the iodine substituent. Of these two possible isomers, only 2-methyl-4-phenylphenylacetic acid is known (mp 107–108°).[15] The compound isolated upon photolysis of **33** in benzene, which gave correct microanalytical values and the expected nmr spectrum, melted at 127–128°, and must therefore be 2-methyl-5-phenylphenylacetic acid (**34**). Consequently, the initial iodo compound must be the 5-iodo isomer **33**.

(13) F. Kienzle and E. C. Taylor, *J. Org. Chem.*, **35**, 528 (1970).
(14) W. Wolf and N. Kharasch, *ibid.*, **30**, 2493 (1965).
(15) Netherlands Patent Appl., 6,500,865; *Chem. Abstr.*, **64**, 5005 (1966).

Table IV. Arylthallium Trifluoroacetates

Substrate	Yield of crude product,[a] %	Mp, °C, crystal shape, position of Tl, in recrystallized material[b]	Mol formula	Calcd,[c] % C	Calcd,[c] % H	Calcd,[c] % F	Found,[c] % C	Found,[c] % H	Found,[c] % F
5	72	189–191, prisms, ortho	$C_{10}H_6F_3O_4Tl$	26.54	1.37	12.60[d]	26.30	1.50	12.76
6	80	212, ortho	$C_{11}H_8F_3O_4Tl$	28.38	1.73	12.20	27.91	1.83	12.74
8	89	227–228, needles, para	$C_{11}H_8F_3O_4Tl$	28.38	1.73	12.20[e]	28.54	1.87	12.20
9	66	211, para	$C_{12}H_{10}F_3O_4Tl$	30.05	2.10	11.89	29.84	2.13	11.81
10	76	205–206, prisms, para	$C_{12}H_{10}F_3O_4Tl$	30.05	2.10	11.89	29.98	2.06	11.52
11	94	201–203, prisms, para	$C_{13}H_{12}F_3O_4Tl$	31.64	2.45	11.55	31.48	2.43	11.57
13	9	148–152, prisms, ortho	$C_{13}H_9F_6O_6Tl$	26.94	1.56	19.67	26.94	1.64	19.89
14	67	139–148, prisms, mixture	$C_{14}H_{11}F_6O_6Tl$	28.33	1.88	19.20	28.32	1.87	17.95
17	33	155-167, ortho	$C_{14}H_8F_9O_6Tl$	25.97	1.24	26.43	26.03	1.42	25.23
18	95	188[f]	$C_{14}H_{11}F_6O_6Tl$	28.33	1.87	19.23	28.27	2.05	17.50
19	11	144–150, mixture	$C_{15}H_{10}F_9O_6Tl$	27.23	1.52	25.85	27.38	1.58	25.13
20	97	135–145[f]	$C_{18}H_{18}F_6O_6Tl$	29.65	2.16	18.76	29.64	2.32	16.68
22	66	160–163[f], ortho	$C_{12}H_9F_6O_5Tl$	26.10	1.63	20.70	26.78	1.88	18.52
23	57	185, ortho	$C_{13}H_{11}F_6O_5Tl$	27.61	1.98	20.02	29.98	2.18	17.52
24	40	170–178[f]	$C_{14}H_{13}F_6O_5Tl$	29.01	2.20	19.67	29.30	2.35	16.84
27	92	212, needles, 6	$C_{13}H_9F_6O_6Tl$	26.94	1.56	19.67	27.13	1.68	18.48

[a] The percentage yield was calculated on the basis of a molecular formula determined by elemental analysis of the *recrystallized* product. [b] As determined by subsequent iodination. [c] See ref 19–21. [d] For comparison, analysis of the crude material gave C, 26.15; H, 1.41; F, 14.95. Calcd for a compound with *two* trifluoroacetic acid residues: C, 25.49; H, 1.25; F, 20.15. [e] Analysis of the crude product gave C, 27.52; H, 1.67; F, 14.70. Calcd for a compound with *two* trifluoroacetic acid residues: C, 26.94; H, 1.56; F, 19.67. [f] Not recrystallized.



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Experimental Section[16,17]

Thallation of Arylcarboxylic Acids and Esters. General Procedure. The aromatic compound (0.01 mol) was dissolved in 10 ml of the TTFA solution and the mixture stirred at room temperature, protected from light, for at least 48 hr.[18] Evaporation of excess TFA, followed by two coevaporations with 1,2-dichloroethane, left the solid arylthallium trifluoroacetate which was suspended in cold 1,2-dichloroethane, and then collected by filtration.

All products, except those derived from esters, could be recrystallized from TFA. The thallated esters were recrystallized from 1,2-dichloroethane. No attempt was made to optimize yields.

Acids and esters thallated in this way are listed in Table IV.[19–21]

Thallation of Aryl Alcohols and Their Acetates. General Procedure. The aromatic compound (0.01 mol) (cooled) was dissolved in 10 ml of cold TTFA solution, and the mixture was kept at 0° for 3 hr. The green to brown solution was then allowed to reach room temperature and (protected from light) stirred for another 20 hr. Evaporation of excess TFA followed by several coevaporations with 1,2-dichloroethane left the solid product which was suspended in 1,2-dichloroethane, collected by filtration, and recrystallized from 1,2-dichloroethane.

Alcohols and acetates thallated using this procedure are listed in Table IV.[20,21]

Thallation of Aryl Ethers. Ethers were thallated in the same manner as described for the acids. The products are listed in Table IV.[21]

Isomer-Ratio Studies. Iodination. General Procedure. All compounds were thallated as described above, but the thallated compound was not isolated after the two coevaporations with 1,2-dichloroethane. Instead, the reaction mixture was suspended in 100 ml of water and potassium iodide (8 g, 0.05 mol) was added. The suspension was heated under reflux for 5 hr, and sodium metabisulfite (1 g) was then added to reduce iodine which had been formed during the reaction. Heating was continued for another 30 min, and the precipitated thallium(I) iodide filtered off (without prior cooling). The collected inorganic material was thoroughly washed with acetone, and the filtrate and washings were evaporated. Depending on the starting material, work-up for the isomer ratio studies had to be modified to give compounds suitable for glc inspection.[22]

(16) Unless otherwise indicated, evaporations were carried out *in vacuo* at 35–40° (bath temperature). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Infrared data refer to Nujol mull spectra taken on a Perkin–Elmer 237B grating infrared spectrometer; nmr data were obtained on a Varian A-60A instrument. Gas chromatographic studies were carried out using an Aerograph A90-P3 instrument equipped with a 30 × 3/8 in. column with 30% QF-1 on 45–60 Chrom W; for the kinetic studies reported herein, Perkin-Elmer Models F11 and 452 flame ionization instruments, equipped with 2-m Apiezon columns, were used. A 1 *M* solution of TTFA in TFA (TTFA solution), prepared by dissolving solid TTFA in TFA, was used in all thallations.[1b]

(17) Thallium and thallium compounds are extremely toxic and must be handled with care. Rubber gloves should be worn at all times, all operations carried out in a well-ventilated hood, and good housekeeping rules enforced. For more detailed comments, see E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 3, 338 (1970).

(18) See Discussion section.

(19) It should be noted that, with the exception of 2-methylphenylacetic acid (27), all of the arylthallium trifluoroacetates prepared from side-chain carboxylic acids gave good microanalytical values for molecular formulae containing only one trifluoroacetic acid residue.

(20) Fluorine analyses on the arylthallium trifluoroacetates derived from the thallated derivatives of the homologous side-chain primary alcohols indicated that, in most cases, *three* trifluoroacetate residues were present. This appears to be due to trifluoroacetylation of the arylthallium ditrifluoroacetates initially formed, since glc analysis of several of the crude iodo alcohols prepared by the normal aqueous potassium iodide treatment showed the presence of varying amounts (20–60%) of the corresponding trifluoroacetate esters. Furthermore, β-phenylethanol is readily trifluoroacetylated (82% yield) upon standing at room temperature for 48 hr in a slight excess of TFA.

(21) It proved to be difficult to obtain good microanalytical values on thallated derivatives of ethers and acetates because of some concomitant ether cleavage (up to 5%), hydrolysis, and possibly complexation of the thallated products with traces of unreacted substrate.

(22) The identities of the individual iodo compounds were confirmed either by glc comparison with authentic samples or by glc separation followed by inspection of each compound by nmr and infrared spectroscopy. In almost all cases the sequence of elution from the column was ortho before meta before para (however, this sequence was exactly reversed with the isomeric methyl iodobenzoates). The position of the substituent in individual compounds could be recognized easily by inspection of the chemical shifts of the ring hydrogens, which showed a characteristic pattern for each type of substitution. The isomer ratio was determined by a comparison of the areas under the peaks of the chromatogram. It is recognized that it is not always possible to relate peak area to percentage composition, and in many cases we did not have sufficient material available to show that such a relation indeed existed. We did establish, however, that a mixture of equal portions of the three methyl iodobenzoates gave peaks of equal area. Isomer distribution

The following work-up procedures were used. **For acids,** the aqueous acetone solution of the iodo compounds was extracted with three 40-ml portions of ether, and the ether extracts were dried over anhydrous sodium sulfate and evaporated.[23] The crude mixture of acids was redissolved in anhydrous ether and methylated with an ether solution of diazomethane. Evaporation left a mixture of methyl esters which was inspected by glc.

For methyl esters, the work-up was the same as for the acids. The ether solution of the esters was treated with diazomethane to remethylate any product that might have been hydrolyzed during the reaction.

For alcohols, the aqueous acetone solution of the iodo alcohols was extracted with ether, the extracts were evaporated, and the residue was heated under reflux for 1 hr in 50 ml of 10% potassium hydroxide (to hydrolyze any trifluoroacetates which might have been present). The alcohols were isolated by three extractions of the basic mixture with 40-ml portions of ether. Evaporation of the combined ether extracts gave the crude alcohols which were quantitatively converted to their corresponding acetates by addition of 10 g of acetic anhydride and three drops of boron trifluoride etherate catalyst.[24] Water (50 ml) was then added to destroy excess acetic anhydride, and the solution was extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and evaporated; the residual acetates were then inspected by glc.

For acetates, the aqueous acetone solution of the acetates was extracted with ether and the extract then treated as described above for alcohols.

For ethers, the aqueous acetone suspension of the iodo compounds was made alkaline by addition of 10% sodium hydroxide. The mixture was then extracted with ether, the dried ether extracts were evaporated, and the residue was inspected by glc.

Results are summarized in Table I. Since no attempt was made to achieve maximum yields in the actual isolation of the crude iodo compounds, yields are not recorded; they usually were in the range of 70–90% for thallations at room temperature, and 20–50% for thallations at 73°. In the latter case, taking into account recovered starting material, actual yields are much higher (>60%).

Extent of thallation was determined by withdrawing small samples from the reaction mixture. Normal work-up, followed by glc inspection, gave an indication of the progress of the reaction. In this way it was found that thallation of *n*-propylbenzene and of cumene was complete in less than 10 min; benzyl methyl ether, 5 hr; β-phenylethanol, 7 hr; 3-phenylpropanoic acid, 25 hr; phenylacetic acid, 48 hr.

In the equilibration studies thallation was carried out in boiling TFA (73°); after cooling, the work-up was as described above.

In order to demonstrate the potential synthetic value of the thallation–iodination procedure, several iodo compounds were prepared on a larger scale as described below.

***o*-Iodophenylacetic Acid.** A solution of 2.72 g (0.02 mol) of phenylacetic acid in 20 ml of the standard TTFA solution was stirred for 48 hr at room temperature and then, without isolation of the intermediate thallated derivative, treated with aqueous potassium iodide as described above. On work-up crude *o*-iodophenylacetic acid (5.10 g, 97.5%), mp 80–90°, was obtained. Recrystallization from petroleum ether gave 3.80 g, mp 108–110°.[25] Methylation of a small sample with diazomethane and subsequent inspection of the resulting methyl ester by glc showed the compound to be pure methyl *o*-iodophenylacetate.

In a separate experiment, the *isolated* thallated phenylacetic acid was iodinated by addition of a hot TFA solution containing 1 equiv of potassium iodide. There was no precipitate of thallium(I) iodide; evaporation of the clear solution gave a residual syrup which was suspended in 50 ml of water and thrice extracted with 40-ml portions of ether. Evaporation of the dried ether solution gave pure *o*-iodophenylacetic acid (63%) after recrystallization from hexane. Addition of a sodium chloride solution to the aqueous layer resulted in the precipitation of thallium(I) chloride (91%).

When the above experiment was carried out in cold instead of boiling TFA, and the reaction allowed to stand for 48 hr at 0°, violet needles of iodine (12.6%) could be isolated. Work-up of the filtrate as described above afforded *o*-iodophenylacetic acid (49%).

***o*-Iodobenzyl Methyl Ether.** Benzyl methyl ether (4.88 g, 0.04 mol) was treated first with the standard TTFA solution and subsequently with aqueous potassium iodide as described above. Work-up gave 7.73 g (78%) of crude *o*-iodobenzyl methyl ether which on distillation yielded 7.11 g of the pure compound, bp 80° (2 mm).

3-(Iodophenyl)propanols. Thallation, iodination, and acetylation as described above of 4.77 g (0.035 mol) of 3-phenylpropanol afforded 8.24 g (77.3%) of 3-(iodophenyl)propyl acetate, with an isomer distribution of 11% ortho, 9% meta, and 80% para. Distillation (148–152° (5 mm)) gave 7.19 g (63%), but with essentially the same isomer distribution.

Methyl 3-(4-Iodophenyl)propanoate (28). 3-(4-Iodophenyl)propanoic acid (1 g)[26] was methylated in ether solution with diazomethane. Evaporation left the solid ester which upon recrystallization from 80% ethanol gave colorless needles (see Table III).

3-(4-Iodophenyl)butanoic Acid (29). 3-Phenylbutanoic acid was thallated by the normal procedure, and the recrystallized thallated derivative (1.6 g) was heated under reflux in 50 ml of water containing 2 g of potassium iodide for 5 hr. Filtration, extraction of the filtrate with three 25-ml portions of ether, and evaporation of the dried ether extracts gave a solid (44%), mp 93–94°. Recrystallization from petroleum ether gave thin prisms (see Table III).

The nmr spectrum (in $CDCl_3$) showed a symmetrical A_2B_2 splitting pattern (4 H) for the aromatic protons characteristic for para substitution.

3-(2-Iodophenyl)butanoic Acid (30). The mixture of isomeric methyl 3-(iodophenyl)butanoates (6% ortho, 10% meta, 84% para), obtained above in the isomer-ratio study of the thallation of 3-phenylbutanoic acid, was subjected to preparative gas chromatography and the isolated methyl 3-(2-iodophenyl)butanoate saponified with 10% potassium hydroxide. Acidification gave the solid acid which was recrystallized from heptane to yield prisms (see Table III).

Its nmr spectrum (in $CDCl_3$) showed the same complex pattern for the aromatic protons as was observed for all the other ortho-substituted iodo compounds encountered during this work (*e.g.*, *o*-iodophenylacetic acid).

2-(2-Iodophenyl)propanoic Acid (31). The recrystallized thallated derivative of 2-phenylpropanoic acid (430 mg) was treated as described above in the synthesis of 3-(4-iodophenyl)butanoic acid. The crude acid (61.5%), mp 97–101°, was recrystallized from heptane to give prisms (see Table III).

6-Iodo-2-methylphenylacetic Acid (32). The recrystallized thallated derivative of 2-methylphenylacetic acid (2.9 g) (from TFA) was treated with aqueous potassium iodide as described above for the synthesis of 3-(4-iodophenyl)butanoic acid. The crude acid (1.06 g, 77%), mp 154–155°, was recrystallized from heptane to give needles (see Table III; for the nmr spectrum of this compound, see Discussion): ir 3300–2600 (broad), 1700, 1590, 1340, 1240, 1115, 935, 765, and 670 cm^{-1}.

5-Iodo-2-methylphenylacetic Acid (33). 2-Methylphenylacetic acid (6 g, 0.04 mol) was thallated as described above to yield 15.6 g (67.5%) of the crude thallated derivative. Recrystallization from TFA gave 2.9 g (20%) of the isomer thallated in position 6, and this was converted to 6-iodo-2-methylphenylacetic acid as described above. The filtrate from the recrystallization of the crude thallation product was concentrated *in vacuo* and treated with aqueous potassium iodide. Work-up in the normal manner followed by recrystallization of the crude product gave 1.08 g (10%) of 5-iodo-2-methylphenylacetic acid (see Table III): ir 3300–2500 (broad), 1695, 1590, 1300, 1285, 1270, 1175, 1160, 940, 905, 890, 815, 775, and 735 cm^{-1}. A small sample was methylated with diazomethane and the resulting methyl ester inspected by glc. It showed a single sharp peak, which travelled considerably more slowly than the methylated 6-iodo isomer **32**.

2-Methyl-5-phenylphenylacetic Acid (34). 5-Iodo-2-methylphenylacetic acid (500 mg) was dissolved in benzene (300 ml) and the solution irradiated with 3000 Å light (Rayonet photochemical reactor) in a 30 × 5 cm quartz tube for 20 hr. Evaporation of the violet solution gave a solid residue which was redissolved in 100 ml of benzene and extracted with 20 ml of a 5% sodium bisulfite solution. Evaporation of the dried (Na_2SO_4) organic layer left a solid which was dissolved in ether, treated with activated charcoal,

values obtained from nmr measurements were also found to be identical with those obtained by gas chromatography.

(23) Some acids could be isolated at this stage.

(24) H. H. Baer, F. Kienzle, and F. Rajabalee, *Can. J. Chem.*, **46**, 80 (1968).

(25) Mp 110° [W. Raum, *Ber.*, 27, 3233 (1894)]; mp 114.5° [J. Frederik, J. Dippy, and R. H. Lewis, *J. Chem. Soc.*, 644 (1936)].

(26) This was prepared by the thallation–iodination procedure from 3-phenylpropanoic acid.

Table V. k_{obsd} Values for Reaction of Chlorobenzene with Excess TTFA in TFA

Temp, °C	Concn, $[C_6H_5Cl]$	[TTFA], mol/l.	k_{obsd}, sec^{-1}
25	0.043	0.222	3.19×10^{-5}
	0.043	0.446	3.34×10^{-5}
	0.043	0.561	3.98×10^{-5}
30	0.043	0.222	0.85×10^{-4}
	0.043	0.446	0.96×10^{-4}
	0.043	0.561	3.51×10^{-4}
35	0.043	0.222	1.05×10^{-4}
	0.043	0.446	3.61×10^{-4}
	0.043	0.561	4.52×10^{-4}

and again evaporated. Recrystallization of the residue from petroleum ether gave 62 mg (15.2%) of 2-methyl-5-phenylphenylacetic acid, mp 115–120°. Two more recrystallizations from the same solvent raised the mp to 127–128°.

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.22: H, 6.26.

Its nmr spectrum ($CDCl_3$) showed a singlet at τ 7.68 (3 H), a singlet at 6.34 (2 H), and a multiplet for the aromatic protons (8 H); ir 3250–2500 (broad), 1700, 765 (both strong), 1240, 1225 (both medium), 1335, 1305, 935, 830, 730, 695, and 685 cm^{-1} (all weak).

Determination of the Energy of Activation for Thallation of Chlorobenzene.[27] Chlorobenzene was employed as aromatic substrate,[28] pure, dry TFA as solvent, and pure recrystallized TTFA as reagent. Aliquots were withdrawn from the reaction mixture (see Table V) at appropriate time intervals and added to an excess of an aqueous solution of potassium iodide. A calculated amount of a standard solution of pure *p*-iodotoluene in benzene was then added and the resulting mixture shaken vigorously for 12 hr to ensure complete partition of the iodoaromatics between the aqueous and benzene phases. The benzene layer was analyzed by glc, and the relative areas of the peaks due to *p*-chloroiodobenzene and *p*-iodotoluene were determined. Prior to the kinetic runs, it was established by using mixtures of the two iodoaromatics of known concentrations that the concentration of *p*-chloroiodobenzene present was directly proportional to the ratio of the area of its peak in the glc trace to that of the standard, *p*-iodotoluene. This ratio therefore gave a direct reading of the concentration of *p*-chloroiodobenzene.

The data obtained for the reaction of chlorobenzene with an equimolar amount of TTFA were inconsistent with simple first- and second-order kinetic expressions; a 10 molar excess of TTFA was therefore employed. The data obtained under these conditions were fully consistent with eq 1,

$$\ln\left(\frac{x_e}{x_e - x}\right) = t\{k_1[\text{TTFA}] + k_{-1}[\text{TFA}]\} \quad (1)$$

where x = concentration at time t and x_e = concentration at equilibrium, which was adapted from an expression derived to account for pseudo-first-order kinetics in a reversible reaction.[29] Equation 1 can be simplified to eq 2, since TTFA was present in excess, TFA was employed as solvent, and the concentration x is proportional to the ratio r of the areas of the glc peaks for *p*-chloroiodobenzene and *p*-iodotoluene

$$\ln\left(\frac{r_e}{r_e - r}\right) = k_{obsd}t \quad (2)$$

where r = ratio at time t and r_e = ratio at equilibrium. For kinetic runs at 25, 30, and 35°, straight line plots were obtained for each concentration of TTFA; k_{obsd} values are listed in Table V. From eq 3, derived from eq 1 and 2, values for k_1 at 25, 30, and 35°

$$k_{obsd} = k_1[\text{TTFA}] + k_{-1}[\text{TFA}] \quad (3)$$

were calculated by plotting k_{obsd} against [TTFA], k_1 being given by the slope of the plot, and were found to be, respectively, 2.36×10^{-4}, 7.88×10^{-4}, and 10.24×10^{-4} sec^{-1}. From these data, the computed[30] energy of activation was found to be 27 kcal mol.

(27) An indirect method was employed in which the extent of thallation was estimated by quenching of the reaction mixture with aqueous KI; the amount of iodoaromatic thus formed was assumed to be equal to the amount of arylthallium ditrifluoroacetate in the reaction mixture [A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969)].

(28) Thallation of benzene and alkylbenzenes was so rapid under the pseudo-first-order conditions described that no suitable technique for kinetic evaluation could be developed. The reaction is slower in aqueous TFA and in TFA containing acetic acid, but erratic results were obtained (*cf.* J. M. Briody and R. A. Moore, *Chem. Ind.* (London), 803 (1970)).

(29) D. Bethell and A. F. Cockerill, *J. Chem. Soc.*, 920 (1966).

(30) Program written in Fortran IV for ICL 1905 E, based on H. Eyring, *J. Amer. Chem. Soc.*, **73**, 5628 (1951).

The Structure of the "Symmetrical Cedrone"

J. A. Beisler, J. V. Silverton, A. Penttila,[1a] D. H. S. Horn,[1b] and H. M. Fales*

Contribution from the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, and Laboratory of Chemistry, National Heart and Lung Institute, Bethesda, Maryland 20014. *Received November 9, 1970*

Abstract: The structure of the symmetrical form of cedrone has been determined by X-ray analysis. On this basis the structures of the three acetates of cedrone have been deduced. Cedrone and its monoacetate appear to exist in tautomeric forms in solution.

Several years ago, during a study of the oxidative dimerization of acylphloroglucinols,[2] *e.g.*, **1** + **2** → **3**, we became aware of the presence of, but did not report, substances corresponding to the abstraction of 4 hydrogen atoms from 2 mol of **1**. In the interim, these compounds have been extensively studied by Erdtman and his coworkers,[3] who very reasonably assigned them tricyclic structures such as **4** based on chemical degradations.

(1) (a) Visiting Scientist from OY Medica AB, Helsinki, Finland; (b) Division of Applied Chemistry, C. S. I. R. O., Melbourne, Australia.

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