RADIOIODINATIONS OF ORGANIC MOLECULES ON SILICA GEL SURFACES[*]

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SUMMARY

To investigate radioiodinations on chromatographic surfaces, $^{131}I^-$ has been allowed to react with various organic compounds on silica gel chromatography plates. Antipyrine, which reacts with $^{131}I^-$ to give 4-[^{131}I]iodoantipyrine, was used as a model compound. The yield varied as a function of the initial solvent used; hydrogen ion concentration; contact time on the surface; and temperature. These results were extended to other reactive compounds such as substituted 3H-pyrazol-3-ones; substituted phenols, including L-tyrosine; substituted anilines; 5-iodouracil; some secondary alkyliodides and alkylbromides; alkylboranes; and aryl-and vinylboronic acids.

Key Words: Surface Catalysis, 4-[^{131}I]Iodoantipyrine, No-Carrier-Added $^{131}I^-$.

INTRODUCTION

Previous investigations indicated that certain radioiodinations occur on chromatographic surfaces, especially silica gel (1-4). Most of these investigations dealt with the preparation of 4-[^{131}I]iodoantipyrine (4-^{131}IAP) by reaction of $^{131}I^-$ with antipyrine (AP) on silica gel chromatography plates (1,2) or on silica gel columns (3,4). Shiue and Wolf (4) concluded that the radiochemical yield of the 4-^{131}IAP was dependent on the reaction time of AP

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with $^{131}I^-$ in acidic solution but was not dependent on the contact time of the solution with the silica gel.

Our recent studies of the reaction of $^{131}I^-$ with the activated aromatic compounds phenol and aniline showed that the yield of radioiodinated products varied with contact time on a silica surface (2). Phenol was the most reactive and resulted in both 4-[^{131}I]iodophenol and 2-[^{131}I]iodophenol in >80% yield after one hour on the surface. The absolute yield and the 2:4 substitution ratio also varied as a function of the initial solvent. The results indicated that with aromatic compounds the reactions occur by electrophilic substitution, the iodinating species arising from surface catalyzed oxidation of $^{131}I^-$.

Because of the apparent differences between our results (1,2) and those of other investigators (3,4), a thorough study was performed on the reaction of $^{131}I^-$ with AP on a silica gel surface. The investigation was extended to gain insight into the types of compounds which might be reactive toward radioiodination on a silica gel surface.

MATERIALS AND METHODS

General. Therapeutic Na^{131}I solution was purchased from Syncor, Inc., Miami, Florida. The formulation was claimed to be carrier free and was supplied in phosphate buffered sodium chloride containing up to 0.16% sodium thiosulfate with a pH of 7.5-9.0, adjusted with sodium hydroxide. Reactions and thin-layer chromatography (TLC) were performed on Analtech precoated glass plates of the appropriate chromatographic material (250 μm). Spots for standards were visualized by ultraviolet light or by exposure to iodine vapor; those for radiolabelled materials were detected by autoradiography using Polaroid 52 film. After isolation, the sections containing the radiolabelled compounds were assayed on a Nuclear Data 60A (ND60A) Multichannel Analyzer equipped with a NaI (Tl) detector.

All solvents for high performance liquid chromatographic (HPLC) analyses were of high purity grade obtained from Burdick and Jackson Laboratories and were degassed ultrasonically under vacuum before use. Separations were

performed using an Altex Model 330 liquid chromatograph equipped with an Altex Model 155-40 variable wavelength ultraviolet (UV) detector. Eluates were continuously monitored for radioactivity using the ND60A in the multichannel scaling mode.

Labelling Procedure. In a typical reaction, $Na^{131}I$ (1-3 μl, 50-100 μCi/μl) was added to a solution of the reactant (0.5 ml, 5-10 mg/ml) in either water, acetonitrile, ethanol, or dimethylformamide (DMF). The hydrogen ion concentration can be adjusted with H_2SO_4. Samples (5 μl) were removed and spotted on the chromatographic surface and allowed to dry at room temperature for specified lengths of time; a similar aliquot, used as a standard, was sealed for radioassay. The drying of samples at elevated temperatures was performed using a Thermolyne 1400 Furnace. Specific reaction conditions are given in the Results section. When necessary, solutions containing the reactants were checked by appropriate HPLC methods to determine if any reaction was occurring in solution, and, if so, to what extent.

Synthesis of 3-[^{131}I]iodo-L-tyrosine. The procedure for the reaction of L-tyrosine with $^{131}I^-$ is presented because the yield of 3-[^{131}I]iodo-L-tyrosine could not be determined accurately by TLC. Isolation of the product and HPLC analysis were therefore necessary. L-Tyrosine (Aldrich Chemical Co.) was converted to the hydrochloride salt. L-Tyrosine hydrochloride (∿5mg) was dissolved in 0.5 ml of water. To 100 μl of the solution was added 10 μl of $Na^{131}I$ (50-100 μCi/μl). Of this, 20 μl was spotted on a silica gel plate; a total activity reading was taken in a Capintec CRC-30 radioisotope calibrator, and the plate allowed to dry at room temperature for one hour. The section of the plate containing the activity was removed and the silica gel placed in a microfiltration - centrifugation tube (Bioanalytical Systems) with a 1.0 μm filter and washed with 1:1 ethanol:water until the amount of activity extracted was constant (2 x 200 μl). The extract was examined by HPLC using an Alltech LiChrosorb RP-18 column (10 μ, 25 cm x 4.6 mm i.d.) fitted with a Brownlee C-18 guard column (3 cm x 4.6 mm i.d.); the mobile phase was a mixture of 90% 2.5 x $10^{-3}M$ Na_2HPO_4, pH = 4.0 (H_3PO_4) and 10% acetonitrile. At a flow rate of 2
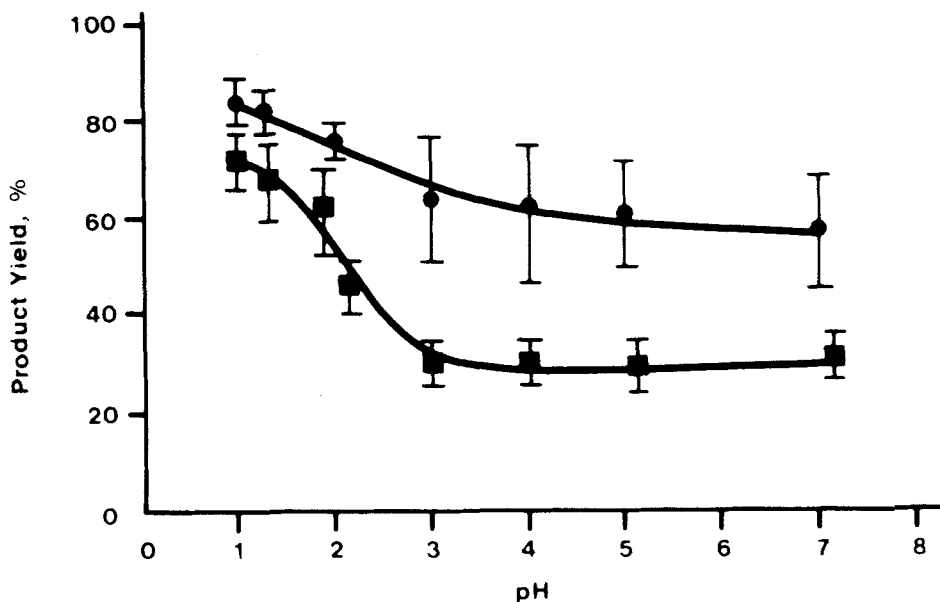
Figure 1. Yield of 4-[^{131}I] iodoantipyrine obtained from the reaction of ^{131}I$^-$ with antipyrine on a silica gel surface as a function of pH (adjusted with H_2SO_4) after spotting from water (■) and ethanol (●). Drying time was 0.5 hr.

ml/min, the retention times for L-tyrosine and 3-iodo-L-tyrosine were 1.9 and 4.5 min, respectively.

RESULTS

The reaction of ^{131}I$^-$ with AP on silica gel chromatographic plates has been thoroughly investigated. The yield of 4-^{131}IAP was found to be pH dependent after spotting on silica gel from either water or ethanol (Figure 1). As observed previously with phenol (2), the yield of radioiodinated product was higher in ethanol. Acetonitrile and DMF gave similar results to ethanol over the pH range.

The yield of 4-^{131}IAP varied as a function of the contact or drying time on the surface (Figure 2). After spotting from water the maximum yield was obtained in 60 min, whereas after application from ethanol the reaction was more
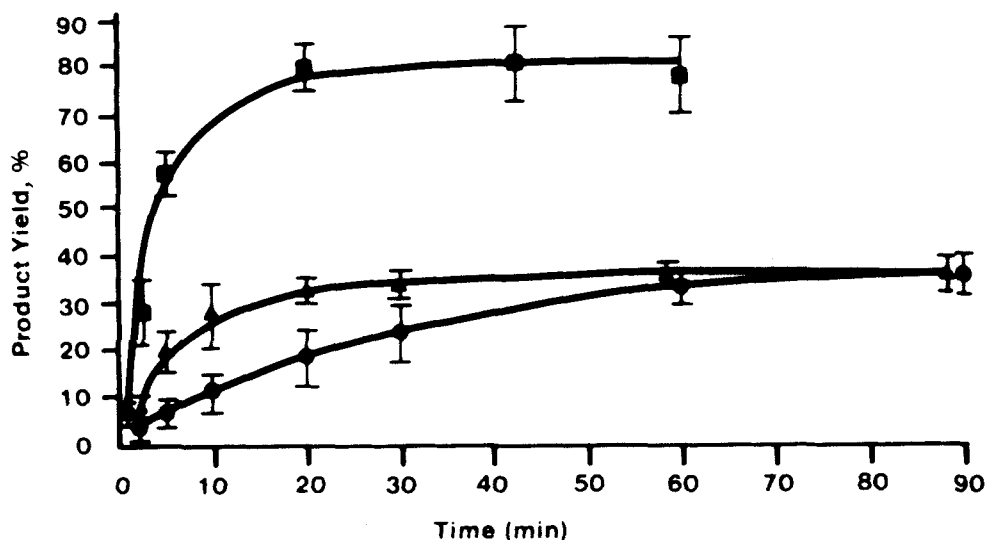
Figure 2. Yield of 4-[^{131}I]iodoantipyrine formed from the reaction of ^{131}I⁻ with antipyrine as a function of contact time on a silica gel surface after spotting from ethanol (■), after application to surface immediately after mixing AP and ^{131}I⁻ in water (●) and after spotting from same water solution after more than 5 hr (▲).

rapid and resulted in a higher yield after 5 min of contact with the surface. An experimentally significant difference in the yield of 4-^{131}IAP as a function of contact time was observed depending upon the "age" of the aqueous AP, ^{131}I⁻ mixture (Figure 2). Control experiments indicated that both AP and ^{131}I⁻ had to be present together in solution before this effect was observed. There is evidence to indicate that halogens can associate with AP and other pyrazolones by means other than covalent bonding (5). HPLC analysis of solutions at essentially neutral pH indicated that only 1.0-1.5% of 4-^{131}IAP was formed after 24 hr.

The yield of 4-^{131}IAP was also found to be a function of contact time after spotting from aqueous solutions adjusted to pH 1.2, the pH of maximum yield (Figure 3). The amount of 4-^{131}IAP formed in solution at pH 1.2 was examined by HPLC analysis. After 1 hr ∿10% of the ^{131}I⁻ reacted with AP (Figure 3). The

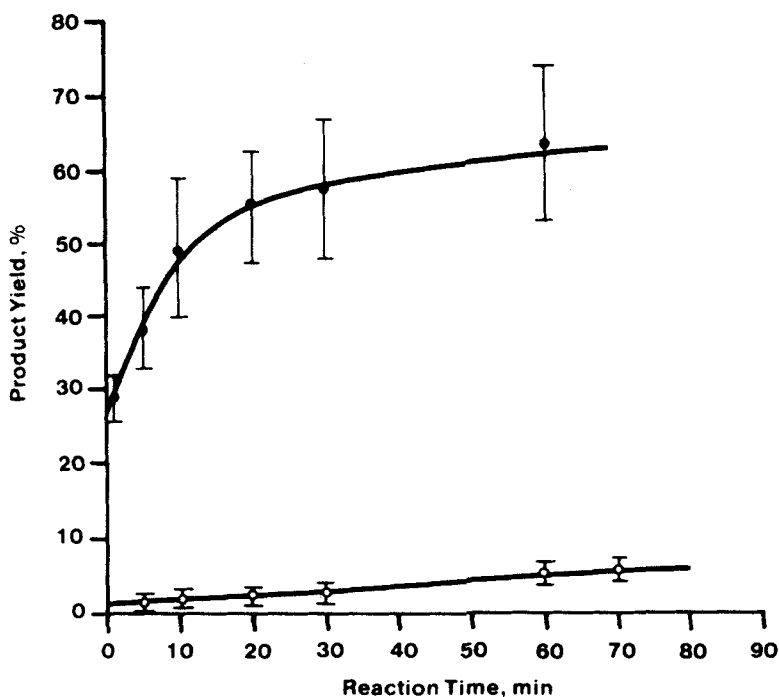Figure 3.   Yield of 4-[131 I]iodoantipyrine formed from the
reaction of 131 I⁻ with antipyrine on a silica surface after spotting
from water at pH 1.2 as a function of contact time (●) compared to 4-
[131 I]iodoantipyrine formed in the aqueous solution at pH 1.2 as
determined by HPLC analysis (O).

extent of the reaction was determined to be 39.7% and 57.4% after 17 hr and 42

hr respectively, thus indicating significant reaction in solution. Previously,

we had not observed significant amounts of $4-^{131}IAP$ being formed in solution at

low pH (1). This could be related to the type of antioxidant in solution. If

there is no antioxidant, $^{131}I^-$ is subject to air (O_2) oxidation (6), particu-

larly in solutions at low pH as a result of acid catalysis (7).

The influence of antioxidants was investigated. Solutions of $Na ^{131}I$ from

different manufacturers vary regarding the antioxidant. Some have no anti-

oxidant (3,4); others contain either bisulfite, HSO_3^- (1,6) or thiosulfate,

$S_2O_3^{-2}$ (2). Our initial experiments (1) were performed using $Na^{131}I$ containing

HSO_3^-, whereas our most recent work (2) and the present investigation were with

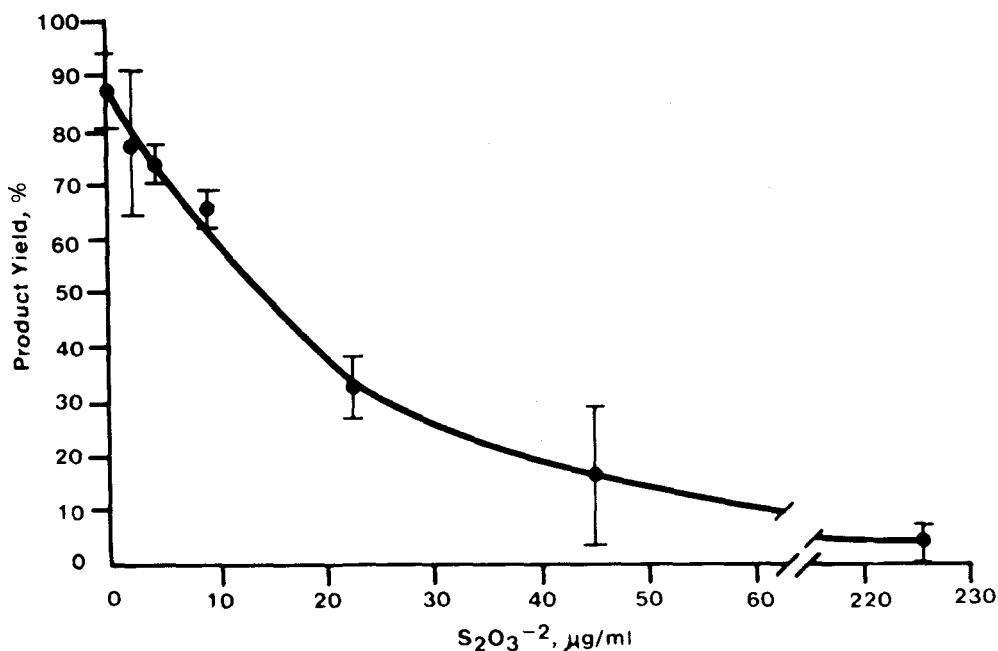solutions containing $S_2O_3^{-2}$. The effects of the addition of $S_2O_3^{-2}$ and HSO_3^-

Figure 4. Yield of 4-[^{131}I]iodoantipyrine formed as a function of added thiosulfate. Samples spotted from ethanol solutions and allowed to dry for 0.5 hr.

(either added as $NaHSO_3$ or as $Na_2S_2O_5$) were studied. The addition of $S_2O_3^{-2}$ in µg/ml amounts resulted in a rapid decrease in the 4-^{131}IAP formed on the surface after spotting from ethanol solutions of AP and ^{131}I$^-$ at pH ∿7 (Figure 4). The same effect was observed after spotting from solutions adjusted to pH 1.2. Concentrations as low as 4-5 µg/ml were sufficient to reduce the extent of reaction occurring in solution at pH 1.2 to zero. On the other hand, the addition of HSO_3^- to the solution at concentrations as high as 10 mg/ml had no effect on the yield of 4-^{131}IAP formed after application to the surface.

These results explain the variations observed in our work using solutions containing HSO_3^- and $S_2O_3^{-2}$ and the work of other investigators using solutions containing no antioxidant. The yield of 4-^{131}IAP formed on a surface and the extent of the reaction in solution were greater when less $S_2O_3^{-2}$ was present.
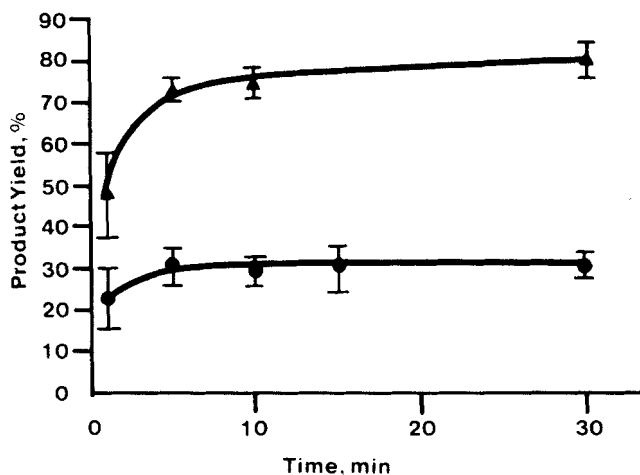
Figure 5. Yield of 4-[^{131}I]iodoantipyrine formed after spotting from ethanol
(▲) and water (●) on a silica gel surface and heating at 100 C.

The largest amount of $S_2O_3^{-2}$ that could be introduced from the $Na^{131}I$ solution in these current experiements was $7\,\mu g/ml$.

Effect of Temperature. The yield of the radiolabelled product should be a function of the reactivity of a compound with the oxidized $^{131}I^-$. Elevating the temperature of the plate from room temperature to a temperature that does not result in volatilization of the $^{131}I^-$ or the radiolabelled product would be expected to result in more rapid formation of the product. The reaction of $^{131}I^-$ and AP on a silica surface at 100°C after spotting from water and ethanol resulted in a more rapid formation of product (Figure 5, compared to Figure 2). The 4-^{131}IAP reached a maximum yield in 10 min.

As AP is a reactive compound toward iodination even at room temperature, we decided to investigate a compound of lower reactivity. Previously (2) we had shown that aniline gave less than 20% 4-[^{131}I]iodoaniline (4-^{131}IA) and less than 0.5% 2-[^{131}I]iodoaniline (2-^{131}IA) at room temperature on a silica gel surface after spotting from ethanol. Heating a silica gel plate at 70°C after
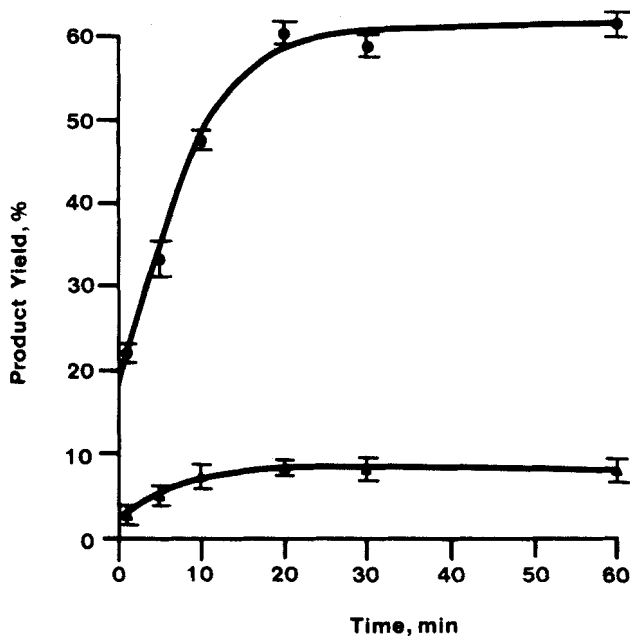
Figure 6. Yield of 4-[^{131}I] iodoaniline (●) and 2-[^{131}I]iodoaniline (▲) formed from the reaction of ^{131}I$^-$ with aniline on a silica gel surface after spotting from ethanol and heating at 70 C.

application of aniline and ^{131}I$^-$ resulted in high yields of radioiodinated anilines (Figure 6). The yield varies as a function of contact time and reaches a maximum for both 4-^{131}IA and 2-^{131}IA at 20 min.

The reaction of the ^{131}I$^-$ with aniline on a silica gel surface at 70°C could be similar to the "melt-method" (8,9) of radioiodination. Therefore, the specific chromatographic surface should have no effect on the yield. By allowing aniline to react with ^{131}I$^-$ on an alumina surface at 70°C, the yields of 4-^{131}IA and 2-^{131}IA were only 16.5 ± 1.5 and 1.6 ± 0.3%, respectively; thus proving that the type of surface has an effect on the yield.

<u>Reaction of ^{131}I$^-$ with Substituted Phenols and Anilines</u>. To further investigate the applicability of the surface catalyzed labelling, ^{131}I$^-$ was allowed to react with variously substituted phenols and anilines. Reaction with

iodinated and brominated phenol have been reported (2). For phenols blocked in
the 4-position, the 2-position substitution occurred in yields of 17.6 to 26.1%
(Table I). The highly activated position adjacent to the hydroxyls in
2,6-dihydroxytoluene resulted in a labelling yield of 71.2 ± 4.2%. Radioiodine
for boron exchange occurred in an arylboronic acid to give 1-[^{131}I]iodo-4-
methyl benzene. With substituted anilines, the 4-position was found to be the
most reactive (Table I).

Table I also shows the results of the reaction of ^{131}I$^-$ on a silica gel
chromatographic surface with L-tyrosine. The L-tyrosine was converted to the
hydrochloride salt to increase its solubility in water. The yield of
2-[^{131}I]iodo-L-tyrosine was greater than 50% after 1.0 hr drying time at room
temperature. The yield from the reaction of ^{131}I$^-$ with 3-methoxy-L-tyrosine was

TABLE I

Percent Yield of Radioiodinated Products from Reaction of ^{131}I$^-$ with

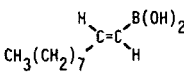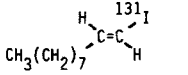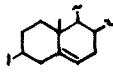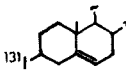Variously Substituted Aromatic Compounds on a Silica Gel Surface

Reactant[a]	Product (%)
4-methylphenol	2-[^{131}I]iodo-4-methylphenol (26.1 ± 9.3)
2,4-dimethylphenol	2,4-dimethyl-6-[^{131}I]iodophenol (23.8 ± 9.2)
4-hydroxy-3-methoxybenzaldehyde	4-hydroxy-5-[^{131}I]iodo-3-methoxybenzaldehyde (17.6 ± 5.7)
4-hydroxy-5-iodo-3-methoxybenzaldehyde	4-hydroxy-5-[^{131}I]iodo-3-methoxybenzaldehyde (21.3 ± 2.6)
2,6-dihydroxytoluene	2,6-dihydroxy-3-[^{131}I]iodotoluene (71.2 ± 4.2)
L-tyrosine hydrochloride[b]	3-[^{131}I]iodo-L-tyrosine (54.6± 6.0)
3-methoxy-L-tyrosine[c]	3-methoxy-5-[^{131}I]iodo-L-tyrosine (30.6 ± 9.6)
3-methoxy-L-tyrosine[d]	3-methoxy-5-[^{131}I]iodo-L-tyrosine (42.4 ± 11.7)
4-methylbenzene boronic acid[e]	1-[^{131}I]iodo-4-methylbenzene (11.2 ± 0.5)
2,6-dimethylaniline	2,6-dimethyl-4-[^{131}I]iodoaniline (45.8 ± 4.2)

a) Unless otherwise indicated, samples were spotted from ethanol on silica gel GHLF. Phenols were dried
at room temperature for 0.5 hr; anilines were heated on the surface at 70°C for 0.5 hr. b) Dissolved in
water, dried at room temperature for 1.0 hr. c) Dissolved in ethanol/water (1:1), dried at room
temperature for 0.5 hr. d) Dissolved in ethanol/water (1:1), heated on surface at 110°C for 0.25 hr.
e) 10 mg/ml dissolved in methanol/water (1:1); dried at room temperature for 0.5 hr.

higher when heated at 110°C as compared to room temperature reactions (Table I).

Reactions of $^{131}I^-$ with non-aromatic compounds. The reactions of $^{131}I^-$ on a silica gel surface with various compounds other than aromatics were investigated (Table II). These reactions included iodine for iodine exchange with 4-iodoantipyrine, iodine for hydrogen and iodine for bromine exchange in

TABLE II

Radioiodination of Various Compounds on a Silica Gel Surface

Reactant	Product	Reaction conditions[a]	Yield (%)
4-IAP	4-[^{131}I]IAP	Ethanol, R.T., 0.5 hr	7.1 ± 0.4
		Ethanol, 100°C, 0.25 hr	23.4 ± 0.5
MPP[b]	4-[^{131}I]IMPP[c]	Ethanol, pH ∿1, R.T., 0.5 hr	47.4 ± 3.0
4-BrMPP[d]	4-[^{131}I]IMPP[c]	Ethanol, 100°C, 0.25 hr	14.4 ± 0.4
5-iodouracil	5-[^{131}I]iodouracil	DMF, R.T., 1.0 hr	65.0 ± 5.0
$(C_{10}H_{21})_3B$[e]	1-[^{131}I]iododecane	THF, R.T., 0.5 hr	20.2 ± 5.3
$CH_3(CH_2)_7$ $\overset{H}{\underset{}{C=C}}\overset{B(OH)_2}{\underset{H}{}}$	$CH_3(CH_2)_7$ $\overset{H}{\underset{}{C=C}}\overset{^{131}I}{\underset{H}{}}$	THF/H_2O(1:1), R.T., 0.5 hr	7.2 ± 0.6
1-iododecane	1-[^{131}I]iododecane	Ethanol, R.T., 0.5 hr	0.5 ± 0.1
		Ethanol, 70°C, 0.5 hr	21.6 ± 8.9
1-bromodecane	1-[^{131}I]iododecane	Ethanol, R.T., 0.5 hr	0.6 ± 0.2
		Ethanol, 70°C, 0.5 hr	8.0 ± 3.4
(Cholesteryl iodide)	(Cholesteryl [^{131}I]iodide)	Ethanol, R.T., 0.5 hr	0.8 ± 0.2
		Ethanol/CHCl$_3$(1:1), R.T., 70 hr	14.1 ± 6.2
		Ethanol/CHCl$_3$(1:1), 65°C, 0.5 hr	23.8 ± 11.6
Cholesteryl bromide	Cholesteryl [^{131}I]iodide	Ethanol/CHCl$_3$(1:1), 65°C, 0.5 hr	21.8 ± 10.8

a) Samples were spotted from the solvent and allowed to dry at the appropriate temperature for specified lengths of time; R.T. = room temp. b) 1,2-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one. c) 1,2-dihydro-4-[^{131}I]iodo-5-methyl-2-phenyl-3H-pyrazol-3-one. d) 1,2-dihydro-4-bromo-5- methyl-2-phenyl-3H-pyrazol-3-one. e) 1.0 molar.

the appropriate 1,2-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-ones, and iodine for iodine exchange with 5-iodouracil.

Iodine for iodine and iodine for bromine exchange were also studied with primary and secondary alkylhalides (Table II). HPLC analysis indicated that exchange with 1-iododecane and 1-bromodecane was also occurring in solution and, therefore, was the result of nucleophilic displacement. However, HPLC analysis demonstrated that iodine exchange with the secondary alkylhalides cholesteryl iodide and cholesteryl bromide was not occurring in solution but rather the reaction occurred on the surface. Radioiodine for boron exchange occurred with decylborane and with a vinylboronic acid.

DISCUSSION

Numerous methods are available for the incorporation of radioiodine into organic and biologic molecules (8,9). One of the most popular methods involves oxidation of the iodide to a reactive intermediate with chloramine-T (C-T) or reagents similar to C-T (8-11). Radioiodinations with C-T occur readily with activated aromatics such as phenols and anilines, including L-tyrosine (11) as well as other aromatics as anisole and toluene (10). Uracil and cytosine are also easily iodinated (11). The reaction of carrier-added $^{125}I^-$ with AP in the presence of C-T gave a 48% yield of 4-^{131}IAP (12). Studies using C-T and no-carrier-added $^{131}I^-$ with AP indicated that 4-^{131}IAP can be prepared in greater than 98% yield (13).

The goals of the methods employing chromatographic surfaces for radio labelling were neither to develop oxidative procedures to compete with C-T nor to develop preparative methods for synthesizing radiopharmaceuticals, although it was used preparatively to make 4-^{131}IAP (1). The objectives were to gain insight into the types of compounds that are reactive toward $^{131}I^-$ on a chromatographic surface and the reaction conditions condusive to such labelling. From a preparative point of view, the use of C-T has far greater applicability for radioiodinations by electrophilic iodine.

Based on our previous results (1,2), the results of other groups (3,4) and the results of this study, the following conclusions and predictions can be made

regarding radioiodinations on chromatographic surfaces: 1) The reactions occur more readily on silica surfaces (1-4) but can occur to some extent on other surfaces (1,2). 2) The source of the $^{131}I^-$, particularly the absence, presence, or type of antioxidant, can influence the labelling (2-4). 3) The reactions appear to occur by oxidation of $^{131}I^-$ on the surface resulting in electrophilic substitution (2). 4) The initial solvent used to mix the reagents influences the course of the reaction. This could be the result of either the influence of the solvent on the tautomeric forms of the reactant (5) or the influence of the solvent on the interaction of the reactant with the surface (2). A possible explanation for the apparent accelerated reactivity of some of the compounds in organic solvents as compared to water could be the more rapid concentration of the reactants during evaporation of the solvent. 5) The reactions occur readily with carrier-free $^{131}I^-$ and to a lesser extent with increasing carrier iodide (up to 80 μg/ml) (2). 6) Electrophilic substitution of activated aromatics such as phenols and anilines occur under certain conditions. Less highly activated aromatics such as anisole and toluene were not reactive. Aryl compounds having groups capable of undergoing electrophilic substitution (14-16), such as arylboronic acids, reacted on the surface. 7) In some cases alkyl halides will undergo iodine for halide exchange, but at room temperature the reactions occur only to a limited extent. Alkyl- and vinylboranes reacted on the surface at room temperature. It is possible that certain organo-tin, organo-thallium, and organo-silicon compounds could also react on a silica gel surface. These type of compounds have been found to be reactive with oxidized radioiodine (8,9). 8) Other compounds are less predictable and labelling may vary with conditions. For example, AP exhibited a pH effect. A compound similar to AP, i.e., MPP (see Table II), was reactive only at low pH. Uracil and 2-deoxyuridine were unreactive, but iodine for iodine exchange occurred with 5-iodouracil. The surface may have an affect on the tautomeric conformations of the compounds thus influencing the reactivity with the iodinating species. 9) The reliance upon TLC as a sole tool to monitor radioiodinations and to perform quality control should be avoided unless the particular system has been thoroughly investigated to preclude surface catalyzed reactions.

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