Catalytic Effect of Copper(II) Chloride on the Radioiodination of L-p-Iodophenylalanine

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Summary

The various iodophenylalanine isomers have been used for pancreatic imaging studies. In this work a convenient method was developed for incorporating radioactive iodine onto L-p-iodophenylalanine (p-IPA) using copper(II) chloride to promote radioiodination. Radioiodination conditions were optimized in terms of reaction time, temperature, copper(II) chloride and p-IPA concentration. Catalytic effect of other metal salts such as $MgCl_2.6H_2O$, $Ni(NO_3).6H_2O$, also pivalic acid and acetamide as a molten solvent were tested. Radioiodination of p-IPA with $Na^{131}I$ in organic media such as dimethyl sulfoxide(DMSO), dimethyl formamide(DMF) and Dioxane were achieved and a comparison was made as to the labelling rates. The rate order was found to be as follows:

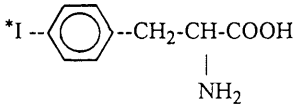
Dioxane > DMSO > DMF

The results showed that copper(II) chloride was effective for facilitating the exchange reaction with maximum yield (~87%) after 60 min at 150°C. Activation energy of 13.3 kcal/mol was also determined.

Key Words: *radioiodination, L-p-iodophenylalanine, copper(II) chloride, HPLC separations*, activation energy.

Introduction

Special interest has been concentrated on the labelling of p-iodophenylalanine (p-IPA) with different iodine isotopes by exchange reaction [1,2] due to their potential use for pancreatic imaging studies (Tumor localization)



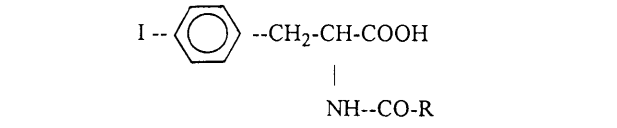
L-p-Iodophenylalanine

CCC 0362–4803/97/080631–14$17.50

Received 8 November 1996
Revised 4 March 1997

The normal radioiodine exchange with iodine containing organic molecules follows a nucleophilic mechanism[3]. The decisive step in this reaction is the attack of the radioactive iodide ($^*I^-$) to the positive charged carbon atom, which already carries the inactive iodine. In a series of compounds this mechanism works highly efficiently, requiring only short reaction times[4]. However, these is another series of iodine containing organic compounds which does not behave comparably, p-IPA belong to this group.

N-acylderivatives of p-IPA have been labelled by radioiododide exchange method which was based on a solid phase reaction in the presence of ammonium sulfate[5,6]. A radiochemical yield more than 55% was achieved.

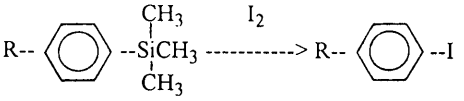


1: R = $--C_3H_7$ 2: R = $--C_2H_4COOH$

N-acylderivatives of L-p-IPA

Isotopic exchange in melt is limited by the necessity of melting the substrate to be labelled without decomposition[7]. Molten "Unreactive" solvents with low melting points such as acetamide[8], benzoic acid[9], and pivalic acid[10], which have a good solubility for many organic compounds have been used, in order to avoid the problem of decomposition in melt method.

The methods for introducing iodine onto a phenyl ring are numerous[1,11]. Furthermore two methods[12] have been used separately for the production of aryl iodides. The first method was the use of trimethylsilyl group $(CH_3)_3Si$ to direct the introduction of iodine onto a phenyl ring (eq. 1)



(1)

R = H , CH_3 , CH_2 - CH - COOH
NH2

The very stable $(CH_3)_3Si$ substituent might be used as a masked iodine precurser for the synthesis of affinity ligands or other labelled precursers, where the radioactive $^*I$ is inserted as the final step in the synthesis[12].

In the second method, silver salts [1.1 equiv. of silver tetrafluoroborate ($AgBF_4$) or silver trifluoroacetate (CF_3CO_2Ag)] have been used as catalysts for the introduction of iodine onto phenyl rings at ambient temperature within an hour with a maximum yield>95%[12]. Silver iodide AgI (formed from the reaction) must be removed to prevent the interference with other functional groups.

Copper(I) salts have been shown to catalize the isotopic exchange of radioiodide onto aromatic rings with high radiochemical yields[13]. High specific activity [^{75}Br]- and [^{77}Br]-p-bromophenylalanine has been achieved via copper-assisted nucleophilic aromatic substitution[14]. No-carrier added(NCA) L-p-[^{18}F] flourophenylalanine has been synthesized using nucleophilic displacement of the activated nitro group of p-nitrobenzaldehyde by NCA ^{18}F obtained from the ^{18}O(p,n) reaction on enriched water[15].

In this work the utility of cupric chloride for promotion of the radioiodination of p-IPA in different organic solvent have been investigated. [^{131}I] and [^{125}I] were utilized in these experiments. Radioisotope exchange at high temperature reaction conditions using pivalic acid and acetamide as molten reaction media have been also studied.

Experimental

Materials:

p-IPA used in this work was purchased in 98-99% purity from the Aldrich chemical Co. Copper(II) chloride (99± %purified), anhydrous dimethylsulfoxide (DMSO, 99± % gold label), N,N-dimethylformamide (DMF) and $CuSO_4.5H_2O$. All other reagents were of analytical grade and used as received without any further purification.
$Na^{131}I$ (nca) in 0.1N NaOH was locally produced in our laboratory.

Optimization of the reaction conditions:

The effect of different labelling conditions on the labelling yield was investigated in several series of experiments as changing reaction time, temperature, concentrations of the precursor, catalyst and solvents. In every experimental series only one of the parameters was varied within the following limits; Reaction time: 5-180 min, temperaure: 115 - 170°C, amount of the precursor p-IPA: 50-600μg and copper(II) chloride 50-500 μg.

Labelling procedure:

The general labelling sequence used was to place the 10 μl $^{131}I^-$ into V shaped reaction vial, 0.5mg of p-IPA followed by addition of 100 μg $CuCl_2$ in 100 μl DMSO. The reaction was allowed to proceed for a chosen time interval before the vessel contents were removed for analysis.

HPLC analysis:

Paraiodophenylalanine, $^{131}I^-$ as well as the corresponding radioactive p-*IPA were analyzed by HPLC using an u.v. detector operating at 254 nm. The analytical column used was an Rp-C18. The mobile phase used was acetonitril: water (1:1), at a flow rate of 1 ml/min. An example of the final p-*IPA (iodoproduct) separation is given in Fig.1 showing good separation capability of this simple HPLC solvent mixture.

Radioiodination via isotope exchange in pivalic acid as an exchange medium:

In a tightly-sealed 2ml glass reaction vial, 10μl Na*I plus 1 mg pivalic acid (trimethylacetic acid m.p 33°C, b.p. 164°C) were added followed by adding 1 mg p-IPA. The vial was sealed with teflon-rubber septum and partially immersed in a preheated (170°C) oil bath. The reaction was allowed to proceed for a chosen interval before the vessel contents were removed for analysis. The reaction vial was allowed to cool, then acetonitrile (100μl) was added to dissolve the residue and the vial swirled gently. Exess pivalic acid can be removed prior to chromatography by inserting a disposable syringe containing granulated characoal as a trap into the reaction vial while heating and allowing the pivalic acid to distill into the trap[10]. A TLC sample (1-2μl) was taken for TLC with a syringe at different time intervals and analyzed by TLC (Silica gel 60 Merck). Solvent system used was n-butanol: acetic acid: water (4:1:1). The R_f value of radioiodide found to be near the start point (R_f=0.3), while the labelled p-*IPA was near the front (R_f=0.9). The radioactivity was assayed using SR- 7 gamma-counter and labelling percent yield at time t was measured according to the following equation.

$$\text{Radiochemical yield(\%)} = \frac{\text{Activity of the product}}{\text{total activity}} \times 100$$

Results and Discussion

Reaction time:

The influence of reaction time on the labelling yield of p-^{131}IPA is shown in table (1). It is clearly shown that the radiochemical yield increased rapidly between 5 and 60 min from 18 to 88 % respectively and remains constant with increasing the time of reaction from 60-120 min. This indicates that at least 60 min labelling time is necessary for a suitable yield.

Influence of concentration of p-IPA

The effect of p-IPA concentration on the radiochemical yield has been studied in presence of $CuCl_2$ at 150°C within 60 min and the result is shown in table (2). It is clearly that a very poor labelling yield ≃ 28 % is obtained when using different amounts of p-IPA (50-100μg). The radiochemical yield is increased by increasing the amount of p-IPA from 100-600μg reaching a maximum value of 87.8 %. Increasing the amount of p-IPA > 500μg did not produce an imporovement in the yield.

Influence of copper(II) chloride:

The extent of isotopic exchange of p-IPA and Na*I was followed, using different concentrations of cupric chloride in DMSO during several time intervals from 0 to 140 min. The amount of p-IPA (500μg) and Na*I (10μl) were kept constant. The labelling

Table (1): Variation of the radiochemical yield of p-^{131}IPA as a function of time. (0.5mg p-IPA in 100μl DMSO+ 100μg $CuCl_2$ in 10μl DMSO + 100μCi $Na^{131}I$). temp.=150°C.

Time (min)	Radiochemical yield (%)
0	0
5	18
10	35
15	45
30	58.49
60	87.84
90	87.9
120	86.81

Table (2): Variation of the radiochemical yield of p-^{131}IPA as a function of the added amounts of p-IPA. (x mg p-IPA in 100μl DMSO + 100μg $CuCl_2$ in 10μl DMSO + 100 μCi $Na^{131}I$) temp.=150°C, reaction time =60 min.

Quantity (mg)	Radiochemical yield (%)
25	17.24
50	21.79
100	28.58
200	40.41
300	56.67
400	64.59
500	87.84
600	87.00

yield is illustrated in table (3). The results show that copper(II) chloride is effective for facilitating the exchange reactions. A higher labelling yield (~92%) was obtained when the reaction was carried out in presence of $CuCl_2$ (500μg in 100μl DMSO) whithin 30min at 150°C. Low concentration of cupric chloride (50μg in 100μl DMSO) led to decrease in labelling yield (<14% within 30min), probably due to insufficient interaction between copper species and aromatic substrate[13].

$$[R\text{-}Ar\text{-}I^{\cdot -}]\text{---}Cu^{++}\text{---}{}^{*}I^{-}]$$

The possible mechanism could be illustrated [13] by the following reaction scheme:

$$R\text{-}Ar\text{-}I + Cu^{+} + {}^{*}I^{-} \text{-----} > R\text{-}Ar\text{-}I \text{----} Cu^{+} + {}^{*}I^{-} \text{----} >$$
$$\{[R\text{-}Ar\text{-}I\cdot^{-}] \text{---} Cu^{++} \text{---} {}^{*}I^{-}\}$$
$$\{[R\text{-}Ar\text{-}{}^{*}I\cdot^{-}] \text{---} Cu^{++} \text{---} I^{-}\} \text{-----} >$$
$$Cu^{+} + R\text{-}Ar\text{-}{}^{*}I^{-} + I^{-}$$

The labelling yield of p-*IPA under the same conditions but in the absence of the cupric chloride was negligible <5% at 5min and increased to ~10% after 1 h. table (3). It was previously reported that the most effective catalyst for an isotopic exchange was copper and its monovalent compounds[16]. Our application of Cu(I) chloride methodology to the pharmaceutical p-IPA was not effective (<5%).

Table (3): Dependence of the radiochemical yield of p-^{131}IPA on the quantity of $CuCl_2$ and time. (0.5mg p-IPA in 100 µl DMSO + x µg $CuCl_2$ in 10 µl DMSO+100µCi Na^{131}I) temp=150°C.

Time (min)	Radiochemical yield (%) No $CuCl_2$ –	$CuCl_2$ 50µg	$CuCl_2$ 100µg	$CuCl_2$ 300µg	$CuCl_2$ 500µg
5	5.68	9.78	18	28.59	10.15
10			35		
15	1.96	10.25	45	65.47	67.0
30	2.11	13.53	58.49	82.47	91.4
60	10.0	30.79	87.84	85.87	91.52
120		71.21	86.81	85.47	88.16

Effect of trace metal ions:

Initial attempts have been made to radiolabel of p-IPA using other metal salts such as $MgCl_2.6H_2O$ and $Ni(NO_3)_2.6H_2O$ in addition to $CuSO_4.5H_2O$ and $CuCl_2$ (those mentioned in the table 4) in order to investigate their effects on the labelling yield. From this table it is clear that copper metal is effective as cupric sulfate for facilitating the exchange reaction> 90% within 30 minutes. The high radiochemical yield that was obtained utilizing copper sulfate may be due to production of I_2:[17]

$$2\ Cu^{2+} + 4\ I^{-} \xrightarrow{H_2O} 2\ Cu\ I + I_2$$

The formation of I_2 occurs because the oxidation potential of the half-cell reaction:

$$Cu\ I = Cu^{2+} + I^{-} + e^{-} \qquad E^{o} = -0.860\ V$$

is high enough to oxidize the I^{-} ions to I_2:

$$2\ I^{-} = I_2 + 2\ e^{-} \qquad E^{o} = -0.536\ V$$

The cupric sulfate tends not only to promote the production of I^+ but also to remove any free I^- which fails to react[17]. Satisfactory labelling efficiency (>85%) could also be achieved using $CuCl_2$. This high radiochemical yield can be attributed to the preferential coordination of [^{131}I] iodo-copper species to the substituent prior to ipso substitution[16]. According to HSAB throry, copper(I) is classified as a class(b), or soft, acid whose affinity for interacting with halogens increases in the rank order F< Cl< Br< I [18]. On the other hand, no significant catalytic effect was observed using $MgCl_2.6H_2O$ and $Ni(NO_3)_2.6H_2O$. A radiochemical yield of <15% was obtained for each salt with the formation of two unknown radioiodinated side products (have no chemical correspondent by u.v. detector on HPLC). Mg^{+2} and Ni^{+2} have been previously used with satisfactory labelling efficiency[19].

Table (4): Variation of the radiochemical yield of p-^{131}IPA as a function of time using different catalysts.(0.5mg p-IPA in 100 µl DMSO + 100 µg catalysts in 10 µl DMSO +100 µCi Na^{131}I) temp=150°C.

Time (min)	Radiochemical yield (%)				
	No Catalyst	$CuCl_2$	$CuSO_4.5H_2O$	$MgCl_2.6H_2O$	$Ni(NO_3)_2.6H_2O$
0	0	0	0	0	0
5	7.68	18	45		
15	1.96	43.8	70	3	4
30	2.11	58.49	91.28	4.06	5.4
60	10.0	87.84	91.8	20.07	6.8
90		87.9	92.0		

Effect of temperature:

Fig.2 illustrates the relationship between the radiochemical yield of p-*IPA and the reaction time at different temperatures. It is clear that heating the reaction and the pressence of $CuCl_2$ in DMOS are necessary for radioiodination to be achieved. It was found that the maximum yield (~87%) is obtained within 60 min at 150°C. A higher temperature (170°C) decreases the radioiodination efficiency due to a thermal decomposition of the product. Lower temperature 120°C and 135°C led to a minimum radiochemical yield(20%) within 2hrs.

The effect of temperature on reaction rate: Energy of activation

Mckay has shown that[20] homogeneous exchange reactions are always first order with respect to time, irrespective of the mechanism of the process. The exchange reaction between [$^{131}I^-$] iodide and p-IPA is a simple homogeneous radioisotope exchange reaction and its kinetics will follow the exponential exchange law:

$$-\ln (1-F) = \frac{(A) + (B)}{(A) \cdot (B)} Rt$$

where F= fraction of exchange, (A)= the concentration of p-IPA in mol L^{-1}, (B)= the concentration of Na^*I(nca), R= isotope exchange rate, t= time in min.

The data in Fig.2 was recalculated to $F = \frac{X}{X_{oo}}$

where X and X_{oo} are the radiochemical yield(%) at time t and at equilibrium (t=oo), respectively, when log $(1-X/X_{oo})$ was plotted vs time, a straight line with a negative slope passing through the organic was obtained for all reaction temperature studied Fig.3. This strongly suggests that the labelling reactions followed the first-order kinetics with respect of each of the reactants.

The rate of exchange (R) for the bimolecular reaction is given by:

$$R = k (A) (B)$$

The specific rate constant (k) was calculated from the slope (p) of the plot of log $(1-X/X_{oo})$ against t Fig.3 according to the formula [21].

$$k = \frac{2.303 \times p}{a}$$

where $a = [*I^-] + [p\text{-IPA}] \simeq [p\text{-IPA}] = 0.0143$ mol L^{-1},
$[*I^-]$ iodide tracer was negligible considering the radioactivity used in each run only (10µl, 80µCi) compared to the quantity of p-IPA.

The half-time of exchange ($t_{1/2}$) which is the time necessary for F=0.5 is given by

$$t_{1/2} = \frac{0.693}{k[(A) + (B)]} = \frac{0.693}{ka}$$

The values of slope (P), k and $t_{1/2}$ at different temperatures are shown in Table (5)

Table (5): Variation of p, k and $t_{1/2}$ with temperature

Temp. (°C)	(p-IPA) mol.L^{-1} (M)	Slope (min^{-1})	k ($M^{-1}min^{-1}$)	$t_{1/2}$ (min.)
120	0.0143	0.008	1.288	37.66
135	0.0143	0.01	1.61	30.1
150	0.0143	0.02	3.22	15.05
170	0.0143	0.18	28.98	1.6713

It is evident that the value of k increases and $t_{1/2}$ decreases with an increase in the temperature. The activation energy was obtained based on the Arrhenius equation:

$$k = A\, e^{-\Delta E/Rt}$$

where A is a constant known as the frequency factor for the reaction. R= universal gas constant= 1.987 cal/mol.deg., T= absolute temperature.

Plotting log k versus 1/T, a straight line was obtained (Fig.4) its slope= -E/2.303 R. The activation energy (E) was calculated to be 13.6 k cal/mol.

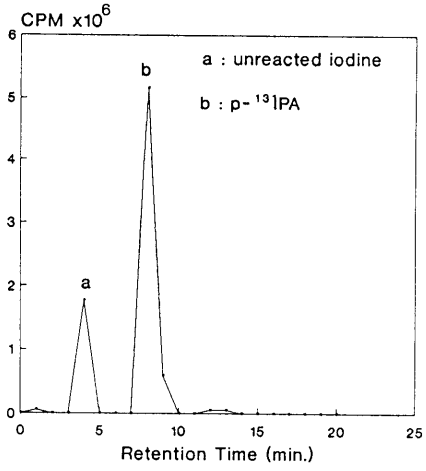


Fig. 1: Radiochromatogram of p-^{131}IPA obtained after HPLC separation. [0.5 mg p-IPA in 100 µl DMSO + 100 µg $CuSO_4$. 5 H_2O in 10 µl DMSO + 100 µci $Na^{131}I$]. Temp. =150°C, Time = 30 min.

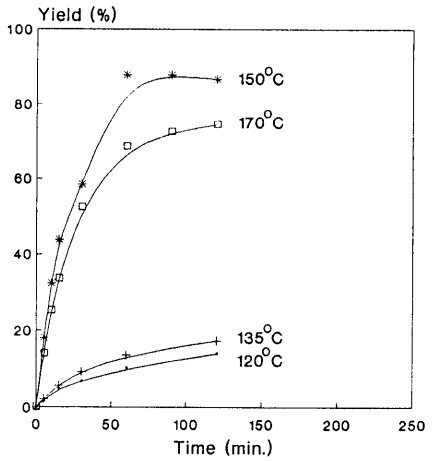


Fig. 2 : Effect of time of heating on the radiochemical yield of p-^{131}IPA at different temperatures. [0.5 mg p-IPA in 100 µl DMSO + 100 µg $CuCl_2$ in 10 µl DMSO + 100 µci $Na^{131}I$]

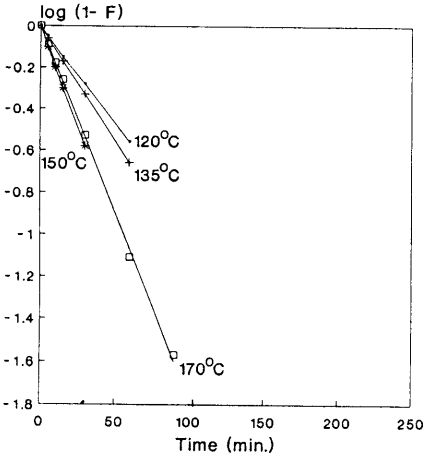


Fig. 3: Variation of Log (1-F) as a function of reaction time at different temperatures. [0.5 mg p-IPA in 100 µl DMSO + 100 µg $CuCl_2$ in 10 µl DMSO + 100 µci $Na^{131}I$

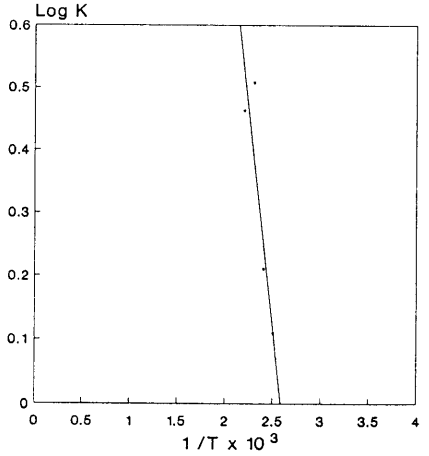


Fig. 4 : Relationship between Log K and reciprocal of absolute temperature {1/T}

The simplest interpretation of the Arrhenius equation for a bimolecular reaction is that, for a reaction to occur, the two reactants must collide and the total energy possessed by them must be at least to E. The necessary activation energy is acquired by the reactant molecule as the result if its collision with other molecules.

Effect of solvent

In this study some organic solvents like DMSO, DMF, Dioxane and aqueous HCl acid were tested. DMSO was employed as the reaction solvent in all investigations due to its versatility under radiolabelling conditions. Advantageous characteristics of this dipolar aprotic solvent (DMSO) include a high boiling point, ability to solvate a broad variety of solutes, promotion of high rate constants for copper-catalysed nucleophilic aromatic halogenation[22] and to usefulness in isotopic exchange reaction[23,13].

Fig.5 shows that heating the reaction mixture and the presence of $CuCl_2$ were necessary for radioiodination yields to be achieved. For all experiments, a reaction temperature of 150°C was selected, because at higher temperature the yield tends to decrease again. The Fig.5 illustrates the effect of reaction time on the NCA nucleophilic exchange reaction of p-IPA using Dioxane only without $CuCl_2$. Higher radioiodination yields (80-90%) were obtained after a reaction period of ~40 min. Similar yield (~90%) was achieved within 60 min using DMSO as a solvent. High radiochemical yields (70-90%) were also achieved using DMF, but after longer reaction times (60-120 min.).

Labelling of p-IPA in HCl was found to be slow to meet practical needs (~28%). This is may be due to solubility problems.

Labelling percent at time t was thus measured. The fractional exchange F was derived from the relationship $F= X/X_{oo}$ Fig.5 where X and X_{oo} were radiochemical yield (% labelling) at time t and at equilibrium (~24 h after the initiation of exchange reaction).

A plot log(1-F) vs. time gave a straight line (Fig.6), suggesting that the labelling reactions under these conditions followed the Mckay's first-order exchange law describing homogenous isotopic exchange processes[21].

$$-\ln (1-F) = Pt$$

where P is the slope of the corresponding straight line (Fig.6).

The rate constant k can be calculated from the slope P of a given straight line in (Fig.6) according to the formula[21,24]:

$$k = 2.303\ P/a$$

where,

$a = [*I-] + [p\text{-}IPA] \sim [p\text{-}IPA] = 0.0143$ M

Na *I (no-carrier added) was negligible considering the radioactive used in each run very tracer compared to the chemical quantity of p-IPA.

The half-time of exchange ($t_{1/2}$) was calsulated by the relation:

$$t_{1/2} = \frac{0.0693}{ka}$$

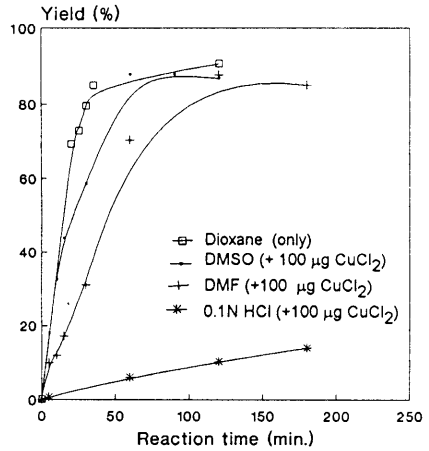


Fig. 5: Effect of various media on the radiochemical yield of p-^{131}IPA as a function of time. [0.5 mg p-IPA in 100 µl media + 100 µci $Na^{131}I$]. at 150°C.

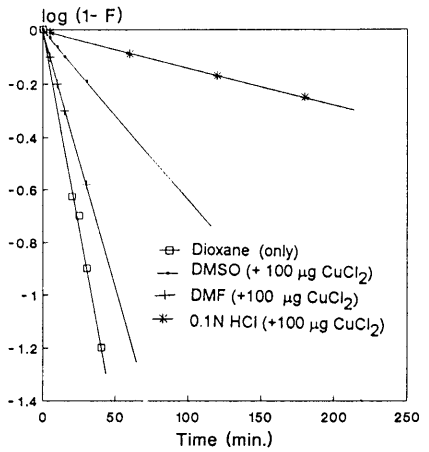


Fig. 6 : Variation of Log (1-F) as a function of reaction time using different solvents [0.5 mg p-IPA in 100 µl media + 100 µci $Na^{131}I$].at 150°C.

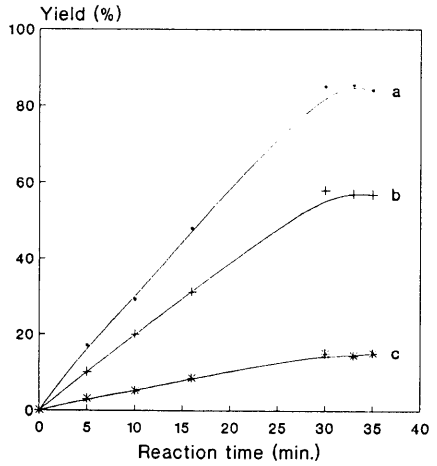


Fig. 7: Radiochemical yield of p-^{131}IPA as a function of time at 170°C in pivalic acid (a, b,), in acetamide (c). (a): mixing 1 mg pivalic acid with $Na^{131}I$ prior to adding 1 mg p-IPA. (b): mixing 1mg p-IPA with $Na^{131}I$ prior to adding 1 mg pivalic acid. (c): mixing 1 mg acetamide with $Na^{131}I$ prior to adding 1 mg p-IPA.

Slopes, specific rate constant (k) and half-time of exchange $t_{1/2}$ are listed in table (6).

Table (6): Comparison of rate constants of the isotopic exchange p-IPA + $Na^{131}I$---> p-^{131}IPA + NaI in different organic solvent and aqueous HCl (0.1N)

Solvent	(p-IPA) mol.L^{-1} (M)	Slope (min^{-1})	k ($M^{-1}min^{-1}$)	$t_{1/2}$ (min.)
Dioxane	0.0143	0.04	6.442	7.522
DMSO	0.0143	0.02	3.220	15.05
DMF	0.0143	0.006	0.966	50.16
HCl(0.1N)	0.0143	0.0015	0.241	201.08

The experimental labelling rates in different solvents as shown above were of the following order.

Dioxane > DMSO > DMF >HCl

It is clear that Dioxane was the most favourable medium for the reactions. This is may attributed to increased anion (i.e, the nucleophilic iodide ion, $*I^-$) solvation [25]. The effect of solvents (Dioxaane, DMSO and DMF) was not associated with the dielectric constant but determined by specific interactions possibly due to the nature of the transient state [13].

Radioiodination via Isotope Exchange in Pivalic Acid as an Exchange Medium:

Based on the results and the finding that acidic conditions facilitate the exchange [10], we sought a new exchange medium. In fulfilling the desired requirements, it was necessary that the medium possess sufficient acidity, appropriate melting, boiling points and relative chemical inertness[10]. It was found that a homolog of acetic acid, pivalic acid (trimethylacetic acid), more closely fits the desired physical properties (m.p. 33°C, b.p.164°C). Moreover, the steric hindrance associated with this acid also decreased the likelihood of it becoming a reactant or promoter of side reactions under conditions of the exchange reaction.

Initial studies with pivalic acid as the exchange medium were promising and in fact afforded p-*IPA in over 90% radiochemical yield. Since Na*I was supplied in 0.1N sodium hydroxide, the small quantity of it was found to have an effect on the radiochemical yield when the isotope exchange reaction was carried out using molten pivalic acid[26], depending on the order in which the reagent were mixed. The results obtained with the two methods (a&b) are shown in Fig.7. The high radiochemical yield (method a) may be attributed to neutralization of sodium hydroxide present by adding pivalic acid to $Na^{131}I$ prior to adding of p-IPA, so that the substrate (p-IPA) was exposed only to the mildly acidic conditions of the pivalic acid melt. The optimum

time for maximum radiochemical yield (>90%) was obtained after thirty minutes. The decrease of radiochemical yield (55%) in method b, is likely due to decomposition of p-IPA in the presence of sodium hydroxide prior to addition of pivalic acid and initiation of the isotope exchange reaction[26]. The use of reaction times longer than thirty minutes for labelling of p-IPA was not expected to increase net radiochemical yield because of accelarated decomposition of radiolabelled product in method b. Because exchange occurs too rapidly with p-IPA in pivalic acid at 170°C, acetamide was also utilized as molten reaction medium to compare the relative labelling efficiencies of pivalic acid and acetamide. As shown in Fig.7, the relative efficiencies of the two media were: pivalic acid >> acetamide. The results imply that in addition to its solvent role, pivalic acid apparently also has a catalytic influence on the exchange reaction.

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