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ORGANIC CHEMISTRY OF ASTATINE

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ABSTRACT

The paper surveys the investigations on the chemical behaviour of astatine in organic systems and deals with the preparation and identification of its organic compounds. A discussion is given on some of the physico-chemical properties of these compounds determined by extrapolation techniques as well as by direct measurement. The biomedical importance of ^{211}At -labelled compounds is briefly referred to.

АННОТАЦИЯ

Дается обзор современного состояния исследований химического поведения астата в органических системах. Рассматриваются методы получения и идентификации астаторганических соединений. Обсуждаются способы определения некоторых физико-химических свойств этих соединений методом экстраполяции, а также прямого экспериментального определения. Дается также краткий обзор биологического использования меченых астатом-211 органических соединений.

KIVONAT

Összefoglaljuk az asztácium szerves rendszerekben mutatott viselkedésének tanulmányozása, szerves asztácium vegyületek előállítása és azonosítása terén elért legújabb eredményeket. E vegyületek egyes fizikai-kémiai tulajdonságainak extrapoláció illetve közvetlen mérések útján történő meghatározását is tárgyaljuk. Röviden utalunk az ^{211}At -mal jelzett vegyületek biológiai-orvosi jelentőségére.

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I. INTRODUCTION

The peculiar feature of the fifth element of the halogen group is that so far none of its stable isotopes has been occurred in Nature; hence the origine of its name: $\alpha\sigma\tau\alpha\tau\omega\sigma$ = unstable. The longest-lived of the four astatine-descendents of the natural radioactive decay chains, ^{219}At , has a half-life of less than 1 min¹ and the total amount of these four in the Earth's crust does not exceed 50 mg which means that astatine is by far the rarest element².

Isotopes that can be generally used for chemical studies, i.e. those with a half-life of several hours, can be produced only via nuclear reactions in cyclotrons or heavy ion accelerators. This may well be the reason why research work on astatine chemistry has been limited to a select few nuclear centres.

On the other hand, all investigations in this field have to be performed on tracer scale utilizing techniques which allow astatine to be measured by its radioactivity. The highest concentration of astatine that has been obtained³ is 10^{-8} M; that needed for typical chemical experiments is in the region of 10^{-13} - 10^{-15} M. The accompanying radiation sets a limit to the concentration applicable to chemical studies. /For example, because of its specific activity of 1.5×10^{16} α -particles/ min.cm³, 1 M solution of ^{211}At would inevitably be exposed to intensive radiation and heat effects thereby making chemical investigations impossible./ If one works with tracer amounts it often results in poor reproducibility due to the masking effects of impurities which are sometimes present in much higher concentrations, even in high quality commercial reagents, than the investigated astatine compound itself.

Although immediately after the discovery⁴ of element 85 its biological behaviour captured the interest of scientists⁵, systematic studies on the chemistry of organic astatine compounds did not follow for quite a long time. One particular obstacle might have been that astatine has a more pronounced positive character than the lighter members of the halogen group. It was originally described as a metal⁴ and this mistaken view remained prevalent for a while. Inorganic systems were predominantly studied and this is well reflected in numerous reviews /see for example References⁶⁻¹⁰/ dealing almost exclusively with the chemical behaviour of astatine in aqueous solutions.

The main aim of this chapter is to survey the results of mostly very recent investigations on the organic chemistry of astatine. These studies clearly demonstrate that the reactions of astatine in organic systems and also the properties of its organic compounds characterize this element as the fifth halogen.

II. PREPARATION AND MEASUREMENT OF ASTATINE

Only three out of the twenty four known astatine isotopes, viz. ^{209}At , ^{210}At and ^{211}At , are regularly used for chemical studies on account of their longest half-lives and also of favourable conditions for their production by means of nuclear facilities. Experiments carried out with HAt-beams using ^{217}At $T_{1/2} = 0.032$ s/ represent a valuable exception to this rule. Here exactly the advantages of short-lived nuclides for radioactive monitoring are utilized to gain information on some chemical properties of astatine compounds¹¹.

Except for the direct measurement of its atomic absorption spectrum¹², all experimental information concerning the physical and chemical properties of astatine has been obtained by detecting the radioactivity of its isotopes. It is, therefore, of basic importance for any study in this field to prepare well defined astatine isotopes and to measure their radioactivity without interfering radiation from other isotopes present. Only a brief survey of the methods applied for these purposes can be given here.

A. PREPARATION OF SUITABLE ISOTOPES

Nuclear processes used to produce astatine isotopes most suitable for chemical studies are summarized in Table 1. /It is worth mentioning that irradiation of metallic bismuth by 32 MeV α -particles in the sixty-inch cyclotron of the Crocker Radiation Laboratory in Berkeley, California, led to discovery of astatine in 1940./ According to the threshold energies of the $/\alpha, xn/$ reactions¹³, by irradiation of bismuth only ^{211}At can be obtained in a reasonable purity from the other two isotopes using α -particles with energy up to 28 MeV. This is also the most widely favoured At-isotope for chemical studies since the somewhat longer-lived ^{210}At is a health hazard decaying into the radiotoxic ^{210}Po with a half-life of 138 days.

In routine procedures bismuth is irradiated either in metallic form^{3,4,14,15} fused or vaporized on aluminium or copper backing plates, or as bismuth oxide pellets¹⁶ pressed into holes of aluminium plate. The target is water-cooled during the irradiation to avoid the melting of bismuth $/mp : 271^{\circ}\text{C}/$ and evaporation of astatine. The radioactive halogen itself can be removed from the irradiated target by distillation at high temperatures^{14,15,17,18} /dry methods/ or by extraction into organic solvents after dissolving the target in strong inorganic acids¹⁶ occasionally combined with distillation^{14,15} /wet methods/.

Only a mixture of ^{209}At , ^{210}At and ^{211}At isotopes can be obtained /among numerous other spallation products/ by bombarding thorium or uranium with 660 MeV protons in synchrocyclotron^{19,20} /Table 1/. The separation of astatine isotopes in this case is more complicated due to the wide product spectrum forming in spallation reactions /sp/. Nevertheless, a number of wet separation techniques have been developed^{19,21,22} based essentially on selective adsorption of astatide onto metallic tellurium from hydrochloric acid solution. More recently, the introduction of gas thermochromatography^{20,23} has provided a simple and elegant technique for fast and selective separation of astatine from other spallation products - including isotopes of other halogens.

Table 1

Nuclear processes used to produce the longest-lived
astatine isotopes and their decay

Nuclear process	Isotope	Particle energy ¹³ /MeV/	T _{1/2} /n/	Decay
²⁰⁹ Bi/α,4n/	²⁰⁹ At	>34	5.5	EC/95.9%/ α/4.1%/
²⁰⁹ Bi/α,3n/	²¹⁰ At	>28	8.1	EC/99.8%/ α/0.2%/
²⁰⁹ Bi/α,2n/ ²¹¹ Rn/EC/	²¹¹ At	>20	7.2	EC/41.9%/ α/58.1%/
²³² Th/p,sp/ ²³⁸ U /p,sp/	^{209,210,211} At	660		

The same procedures can be utilized to separate neutron deficient noble gas isotopes (decaying into halogens by electron capture /EC/) from the spallation products. Isolation of the radon isotopes from this mixture is easily performed by gas chromatography in a column packed with molecular sieves²⁴. The longest-lived ^{211}Rn / $T_{1/2} = 14.6$ h/ can then be used as a source of ^{211}At /Table 1/. Introducing ^{211}Rn into an organic substance enables us to study the reactions of recoil ^{211}At atoms "in situ"²⁶. /see section IV.B.6./

Radon and astatine isotopes can also be obtained by heavy ion induced nuclear reactions^{14,26,27} or by photospallation²⁸. Especially promising is a recently reported procedure²⁷ for producing ^{211}Rn and hence ^{211}At irradiating bismuth



by 60 MeV ^7Li -ions /equation 1/ in larger cyclotrons and Van de Graaff accelerators. However, this has not yet become a routine technique.

B. NUCLEAR PROPERTIES AND MEASUREMENT

^{211}At decays²⁹ partly by emitting α -particles to the long-lived ^{207}Bi and partly by electron capture to ^{211}Po which, in turn, is an α -emitting isotope, see *Figure 1*. Due to the very short half-life of ^{211}Po /0.5 s/ an equilibrium between the two isotopes is momentarily reached with a controlling half-life of the longer-lived astatine. This means that for each decaying ^{211}At nucleus one α -particle is emitted either by itself or by ^{211}Po with energies of 5.9 and 7.45 MeV, respectively. The characteristic α -spectrum, therefore, serves as a distinctive autograph of the ^{211}At . The other two long-lived astatine isotopes do not interfere since they decay by α -emission only to an insignificant extent /see Table 1/.

The requirement of virtually weightless samples to avoid self-absorption, however, severely restricts α -counting as a means of assaying ^{211}At . Measurement of the 80 keV X-rays originating from the electron capture branch of its decay is much more preferable. This can be carried out with simple NaI/Tl/ scintillation counters. The X-ray radiation of ^{207}Bi , always present as a daughter element of ^{211}At and also decaying by electron capture, can be neglected: due to its long half-life it contributes less than $2 \cdot 10^{-5}$ part of the astatine activity.

Similar techniques apply generally to the measurement of the other astatine isotopes, with specific modifications arising from their decay schemes.

In a number of studies, such as for example, in the identification of newly synthesized organic astatine compounds³⁰⁻³² it does not matter very much if the activity observed originates from the mixture of the three long-lived isotopes. In these cases an average half-life is measured and a comparison of the activities in different samples can be made with satisfactory precision.

If the reactions of ^{211}At originating from ^{211}Rn by electron capture are studied, the measurement is complicated by the presence of ^{207}Po arising from ^{211}Rn by α -decay; a further complication is due to ^{211}Rn itself being in equilibrium with its ^{211}At daughter. Adsorption of polonium on metallic tellurium at higher pH-values is generally used^{22,25} for its removal from aqueous solutions where it usually concentrates. Radon dissolves mainly in organic solutions and its evaporation cannot always be achieved completely. It can, however easily be separated from organic astatine compounds by means of gas chromatographic techniques, and its radioactivity can thus be taken into account²⁵.

Since sufficient activity is usually available, normal radiometric equipment can be used to measure astatine without special requirements of high sensitivity or low background.

Table 2

Physical properties of astatine

Property	Value	Reference
At		
Covalent radius	158 pm	31
Ionic radius, r_{At^-}	/gas/ 197 pm	33
	/cryst/ 230 pm	33
Ionization potentials, IP_1	9.5 eV	34
	IP_2 18.2 eV	34
Electron affinity	2.8 eV	35
Electronegativity	2.2	36
Atomic refraction	19.3 cm ³	36
$\Delta H_f^O[\text{At}^-/\text{g}]$ at 298 K	-195 kJ/mol	9
At₂^a		
Internuclear distance	316 pm	31
Dissociation energy, D_{At_2}	116 kJ/mol	37
	$D_{\text{At}_2}^+$ 232 kJ/mol	37
Ionization potential, IP_{At_2}	8.3 eV	37
Melting point	244°C	10
Boiling point	309°C	10

^a Existence of molecular astatine, more precisely of At_2^+ , has been established recently in the plasma ion source of a mass separator³⁸.

III. PHYSICAL AND CHEMICAL PROPERTIES OF ASTATINE

The physical properties of astatine are generally estimated by extrapolation from the data available for neighbouring elements and for the other members of the halogen group. Some data of this kind are shown in Table 2. Probably the only exception so far is the direct measurement of the atomic absorption spectrum¹² performed with a gaseous sample containing 10^{-9} - 10^{-10} g astatine.

It is difficult to describe the chemical nature of astatine without ambiguity. The first investigators⁴ considered it to show closer resemblance to polonium than to iodine by virtue of its ability to precipitate with hydrogen sulfide and its very reduced tendency to do so with silver nitrate. Somewhat later even the existence of astatine cations in acidic aqueous solutions could be proved^{39,40}. On the other hand, immediately after its discovery astatine was shown to behave in biological systems in a very similar way to iodine⁵. The halogen character is also exhibited in its volatility and extractibility with a number of organic solvents⁴¹.

At this point it is interesting to mention that, according to computer predictions, the next hypothetical member of the halogen family, i.e. the heavier homologue of astatine: element 117, would be a typical metal with prevalent +1 and +3 oxidation states⁴². The observed amphoteric character of astatine⁶⁻¹⁰ is, therefore, not surprising. It is assumed to exist in five different oxidation states in aqueous systems. Appelman⁴³ has made an estimation of the corresponding redox potentials in acidic media compared with those for other halogens /see Table 3/.

In organic media astatine is most probably present in a relatively volatile, elementary state, generally designated as At/C/. Its exact appearance has not yet been clarified. The existence of the At₂ form is excluded by the very low concentrations of astatine. So far as the At· radical is concerned, it is very unlikely to survive due to its reactivity. Most probably, At/O/ is bound in some way or other to the organic species present.

Table 3

Halogen potentials /V/ in 0.1 M acid

X	$X^- - X_2 / \text{aq.} /$	$X_2 / \text{aq.} / - \text{HOX}$	$\text{HOX} - \text{HXO}_2$	$\text{HXO}_3 - \text{HXO}_4$
Cl	-1.40	-1.53	-1.35	-1.13
Br	-1.09	-1.51	-1.42	-
I	-0.62	-1.31	-1.07	/-1.6/
At	/-0.3/	/-1.0/	/-1.5/	<-1.6

/Reproduced from E.H.Appelman, J.Am.Chem.Soc.83, 805/1961/
by permission of the American Chemical Society./

Astatine is capable of both electrophilic and nucleophilic reactions in the presence of oxidizing or reducing reagents, respectively. The more pronounced positive character of astatine as compared with that of iodine is reflected in the milder oxidizing conditions necessary to perform electrophilic substitution /see section IV.B.5/.

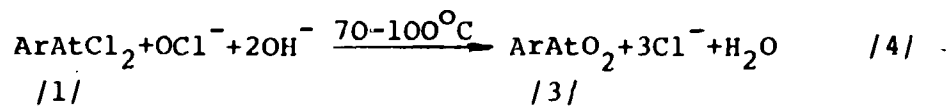
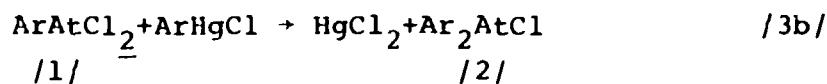
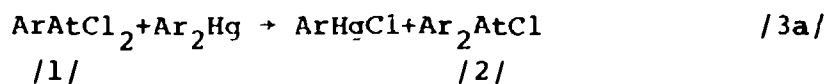
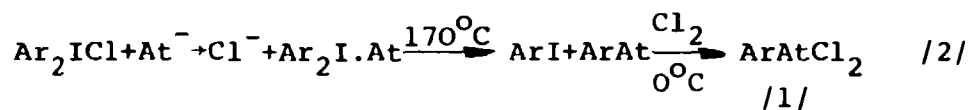
IV. SYNTHESIS AND IDENTIFICATION OF ORGANIC COMPOUNDS

Early reports concerning the preparation of organic astatine compounds of mainly biological importance⁴⁴ were not followed by many others for more than a decade due to often contradictory results^{6,45} leading to the myth that astatine exhibited a capricious character when reacting in organic systems. Besides the interference of impurities, as already mentioned these contradictions and poor reproducibility of results may well have been caused by the use of experimental techniques like coprecipitation, distillation, etc. which were inadequate to separate tracer amounts of astatine compounds from the macro components present. The considerable progress achieved lately in organic astatine chemistry implies the application of chromatographic methods capable of separating and identifying tracer as well as macro amounts^{46,47}.

In the syntheses described below macro amounts of iodine are often used to act as a "non-isotopic" carrier for astatine present in tracer amounts. Sometimes, especially in earlier investigations, the analogous compounds of the two halogens obtained were also identified together. The presence of astatine in the same chemical form as iodine could in these cases be proved by measuring its α -radiation. There is a growing tendency to prepare and use organic compounds of carrier-free astatine. Therefore, in the following mention will be made whenever iodine carrier was used to prepare and/or identify astatine compounds.

A. COMPOUNDS OF MULTIVALENT ASTATINE

According to the more pronounced positive character of astatine compared with that of other halogens, one of the first attempts in this field was aimed at preparing organic derivatives of astatine in +3 and +5 valency state. Norseyev and co-workers^{48,49} obtained the following types of compounds: ArAtCl_2 /1/ Ar_2AtCl /2/ and ArAtO_2 /3/ where $\text{Ar}=\text{C}_6\text{H}_5$ or $\text{p-C}_6\text{H}_4\text{CH}_3$, via the reaction schemes seen below:



Macro amounts of iodine carrier labelled with ^{131}I isotope were always added resulting in the formation of analogous iodine compounds along with those of astatine at each stage of the syntheses*.

To prepare ArI/At/Cl_2 /1/, first KI/At/ is added to the aqueous solution of Ar_2ICl . The crystalline $\text{Ar}_2\text{I} \cdot \text{I/At/}$ formed is centrifuged and washed with small quantities of ethyl alcohol, then sealed in glass ampoules and heated for some minutes at $170-190^\circ\text{C}$. The product of the thermal decomposition: ArI/At/ is

*Although the mixture of the two compounds is referred to in the text, for the sake of clarity it has been omitted when writing the reaction schemes.

dissolved in chloroform, cooled to 0°C and chlorinated into the end product 1 /see equation 2/. It is a yellow precipitate which can be recrystallized from chloroform.

This substance is used as starting material for synthesizing $\text{Ar}_2\text{I}/\text{At}/\text{Cl}$ 2 by adding slowly Ar_2Hg to its hot chloroform solution /equations 3a,b/. After cooling HgCl_2 precipitates leaving a chloroform solution which contains a mixture of 1 and 2. The latter can be extracted into the aqueous phase as it has been proved by paper chromatographic analysis of the two phases⁴⁸.

$\text{ArI}/\text{At}/\text{O}_2$ 3 is formed if to the crystals of substance 1 sodium hydroxide solution and acetic acid is added and the mixture is then chlorinated until the yellow crystals of 1 completely transform into the white amorphous precipitate of 3 /equation 4/.

The carrier iodine compounds were also used for identifying the corresponding astatine derivatives by means of paper chromatography⁴⁸ and thin layer chromatography /TCL/⁴⁹. β - and α -activity for iodine and astatine products was measured, respectively.

B. COMPOUNDS OF MONOVALENT ASTATINE

Quite a few organic compounds containing stable C-At bond have been able to be prepared and unambiguously identified using a variety of chemical procedures principally during the last decade - in spite of the doubts and difficulties previously mentioned. Since progress in this field is likely to continue during and after the appearance of this volume, it seems justifiable to review the results on the basis of the methods most often applied for the synthesis rather than to concentrate on the groups of compounds obtained.

On the other hand, Table 4 summarizes the main groups of organic astatine derivatives successfully synthesized.

Table 4

Preparation and identification of organic compounds of monovalent astatine

I Compound	II Identification ^a	III ^b Preparation	IV Reference
AtCH ₂ COOH	IEC	At ⁻ for I /hom/	50,51
n-C _n H _{2n+1} At /n = 2-6/	GLC	At ⁻ for I /het/ EC recoil At for H	50,52 56,86
i-C _n H _{2n+1} At /n = 3-5/	GLC	At ⁻ for I /het/ EC recoil At for H	56
At  At 	GLC	EC recoil At for H	86

Table 4 /cont./

I	II	III	IV
C_6H_5At	GLC	At^- for I /hom, het/ At^- for Br /het/ At^+ for H /hom/ $/\alpha, 2n/$ recoil in $/C_6H_5/_3Bi$ EC recoil At for H/X Diazonium decomp. $/C_6H_5/_2I.At$ decomp. AtCl, AtBr for X	50,53 30,32 82 50,53 25,85-87 50,53 50,53 14,83
AtC_6H_4X / o,m,p / / X = F,Cl,Br,I /	GLC	At^- for Br /het/ At^+ for H /hom/ EC recoil At for X Diazonium decomp. AtCl, AtBr for H	32 32 14,25,87 14,60,62 14,83

Table 4 /cont./

I	II	III	IV
AtC ₆ H ₄ CH ₃ / o,m,p /	GLC	Diazonium decomp.	14,62
AtC ₆ H ₄ NH ₂ / o,m,p / / o,m,p / / o,p /	HPLC TLC	EC recoil At for H AtCl, AtBr for H Mercury compound	14,87 14,83 65,68
AtC ₆ H ₄ NO ₂ / o,m,p / / o,m,p / / m /	HPLC TLC	At ⁻ for Br /het/ EC recoil At for H Mercury compound	58 58 65
AtC ₆ H ₄ OH / o,p /	HPLC TLC	AtCl, AtBr for H Mercury compound	14,83 65,68
AtC ₆ H ₄ COOH / o,m,p /	Extr. TLC CC	Diazonium decomp.	44 65 68

Table 4 /cont./

I	II	III	IV
4-At-dimethylaniline	TLC	Mercury compound	70
4-At-anisol	TLC PEP PEP	Mercury compound	70
4-At-phenylalanine			
3-At-4-methoxyphenyl- alanine			
3-At-tyrosine	IEC PEP	At ⁺ for H /hom/ Mercury compound	75 59,70
3-At-5-I-tyrosine	PEP	Mercury compound	59

Table 4 /cont./

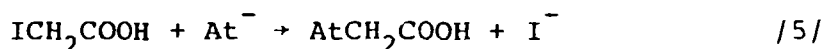
I	II	III	IV
4-At-imidazole 2-At-4-I-imidazole 5-At-4-methylimidazole 2-At-5-I-4-methylimidazole 5-At-histidine	TLC PEP	Mercury compound	69
5-At-uracil	HPLC TLC	Diazonium decomp. AtCl, AtBr for H Mercury compound	14,46 61,64 14 65,69
5-At-deoxyuridine	HPLC	Diazonium decomp. AtCl, AtBr for Br/I	14,46,64

^a GLC=gas liquid chromatography; HPLC=high pressure liquid chromatography; IEC=ion exchange chromatography; PEP=paper electrophoresis; CC=column chromatography; Extr.=extraction

^b /hom/=homogeneous; /het/=heterogeneous

1. Homogeneous halogen exchange

Halogen atoms of the haloacetic acids are readily replaced by another halogen in aqueous solutions. Samson and Aten^{50,51} have taken advantage of this phenomenon to prepare astatoacetic acid. Astatide ion /containing iodide as a carrier/ was let to react in aqueous solution of iodoacetic acid at 40°C according to equation 5:



The product was extracted with ethyl ether, then the solvent evaporated to dryness and the residue recrystallized from carbon tetrachloride. The presence of astatine in the form of astatoacetic acid was proved by ion exchange chromatography. The whole astatine activity could be eluted from the column as a single peak closely following the peak of ICH_2COOH labelled with ^{131}I .

Essentially the same procedure can be used to synthesize a number of n-alkylastatides^{50,52} as well as astatobenzene^{50,53} at room temperature. Intense field of ionizing radiation increases the rate of the exchange reaction leading to formation of astatobenzene.

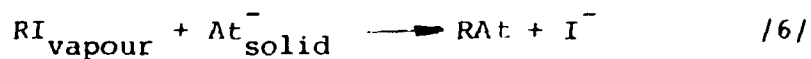
Halogen exchange between $(\text{C}_6\text{H}_5)_2\text{I.I}$ and At^- in hot ethyl alcohol solution /very similar to that described by equation 2 for Ar_2ICl and At^- / gives rise to formation of diphenyliodonium-astatide $/(\text{C}_6\text{H}_5)_2\text{I.At}/$. Decomposition of this compound at 175°C has also been utilized to prepare astatobenzene^{50,53}.

Samson and Aten were the first to use gas-liquid chromatography /GLC/ to isolate the organic products of astatine. This technique not only allows their separation from the corresponding products of iodine but also serves to identify them by means of sequential analysis of the analogous halogen compounds. An example of this for n-pentylhalogenides is shown in Figure 2. . Furthermore, the difference in the GLC retention times $/t_{\text{ret}}/$ for analogous halogen derivatives was made use of when establishing the

boiling points of the corresponding astatine compounds^{50,52,53}. The method was later developed and extended to determine several physico-chemical properties of these compounds, as discussed in section V.B.

2. Heterogeneous halogen exchange

n-Alkylastatides^{50,52} and astatobenzene^{50,53} have also been prepared by means of gas chromatographic halogen exchange, as had been described earlier^{54,55} for radioactive labelling of volatile organic compounds. In this case At^- is adsorbed on the solid phase and the iodine compound is flowing through the GLC column in an inert gas stream.



where $\text{R} = \text{n-C}_n\text{H}_{2n+1} \quad /n=2-6/$

or

$\text{i-C}_n\text{H}_{2n+1} \quad /n=3-5/$

or

C_6H_5

The exchange reaction /equation 6/ was performed at a temperature of 130 to 200°C in a short /15 cm/ column packed with Kieselguhr connected to a longer one for separation and analysis of the products formed. In a simplified procedure Norseyev and coworkers⁵⁶ used only the analysing column, with At^- adsorbed at its inlet, to obtain n- and i-alkylastatides. Each iodide gave rise to the corresponding astatide - as it could be established from the GLC behaviour^{50,52,56,57}. *Figure 3* shows the logarithmic retention time values vs boiling points plot for analogous alkyl iodides and alkylastatides.

Kolachkovsky and Khalkin³⁰ obtained astatobenzene by exchange reaction between At^- adsorbed on sodium iodide and bromobenzene at the boiling temperature of the latter. This technique was further developed by using sealed ampoules which enabled the temperature of reacting systems to be increased^{31,32}.

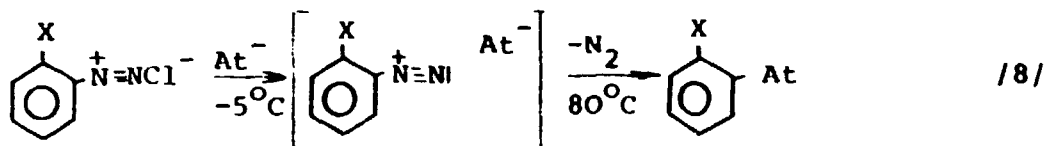
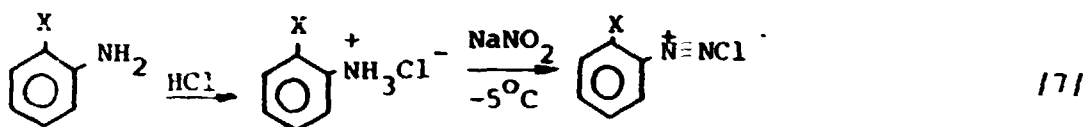
A detailed study concerning the influence of reaction time, temperature and some other factors on the synthesis yields has been carried out. As a result, the following conditions have been found to be optimal for preparing astatobenzene and the isomers of astatohalobenzenes from the corresponding bromine or iodine compounds³². Aqueous solution of astatine containing sodium hydroxide is evaporated to dryness, then a small amount of water is added, the ampoule sealed off and heated for about an hour at 250°C. The isomers of astatonitrobenzene are prepared at lower temperature /50-60°C/ in order to avoid decomposition of the less stable products⁵⁸. GLC and high pressure liquid chromatography /HPLC/ served to identify the compounds formed. Yields of 50-70% and fairly good reproducibility could be obtained with these methods thereby making the use of iodine carrier unnecessary.

Visser and colleagues⁵⁹ reported lower yields /1-5%/ for $\text{At} \rightarrow \text{I}$ exchange in the solid phase when astatine and iodotyrosine or 3,5-diiodotyrosine reacted at 120°C, in vacuum.

3. Decomposition of diazonium salts

In early attempts to produce benzoic acid and hence serum albumin labelled with astatine, Hughes and coworkers⁴⁴ utilized decomposition of the corresponding diazonium salts and so did later Samson and Aten to prepare astatobenzene^{50,53}.

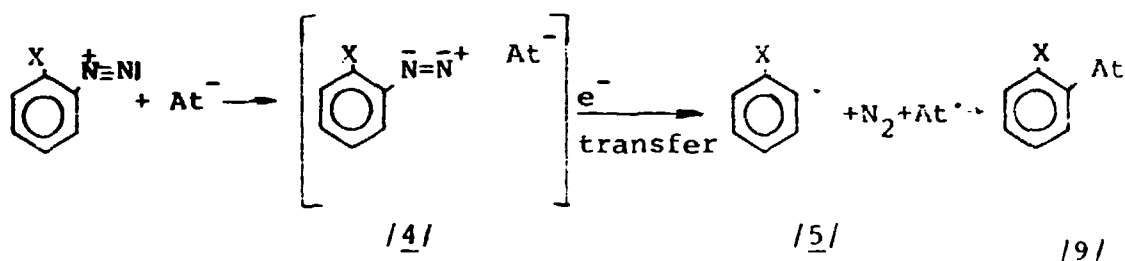
More recently Meyer, Rössler and Stöcklin carried out systematic studies on the application of these reactions for synthesizing astatohalobenzene, astatotoluene and astatoniline isomers^{14,60} as well as 5-astatouracil^{14,61} and 5-astatodeoxyuridine^{14,64}. A comparison with analogous processes of carrier-free ¹³¹I under similar conditions was also made to throw more light on the mechanism of decomposition of the diazonium compounds⁶².



Substituted anilines are used as starting materials to synthesize astatobenzene derivatives. The starting materials are dissolved in hydrochloric acid and converted into the corresponding diazonium salts by adding an aqueous solution of sodium nitrite at -5°C /equation 7/. The excess of sodium nitrite is destroyed by urea. Subsequently At^- in sodium sulfite solution is added and the reaction mixture heated to 80°C for some minutes /equation 8/. The product is extracted with diethyl ether which is then washed with sodium hydroxide, dried and the diethyl ether evaporated at about 30°C . The resulting astatine compound identified by GLC or partition HPLC contains 12-26% of initial radioactivity^{14,60}.

Essentially the same procedure was applied to obtain 5-astatouracil^{14,61} from 5-aminouracil with the only difference that the product can be separated from a yellow precipitate by filtration. The identification in this case can be made by ion exchange or partition HPLC. The liquid chromatographic sequence of uracil and halouracils on different ion exchange columns was used for identification of astatine derivatives as is shown in Figure 4. Iodouracil is analyzed both in macro concentrations and as a carrier-free compound of ^{131}I ($\sim 10^{-17}$ mole/ml) prepared by the same method as astatouracil. The chromatographic pattern indicates that the major radioactive product /~30% yield/ formed by decomposition of the diazonium salt in the presence of At^- , is really 5-astatouracil /see Figure 4/. Reinjection of this fraction gives only one and the same peak again even after keeping it at 80°C for thirty minutes, which shows the stability of the C-At bond in the compound.

Data obtained for astatohalobenzene formation and for the products of carrier-free iodine might provide additional information on the widely discussed mechanism of the diazonium ion decomposition⁶³. Since water is always present in much higher concentration than the trace amounts of carrier-free iodide or astatide, phenol is the product of diazonium ion decomposition to be expected. The fact that iodohalobenzenes and astatohalobenzenes are still formed under these conditions, without catalyst, giving reasonable yields suggests that the halide anions have much higher reactivity than the hydroxide ion. The peculiar selectivity of the decomposition reaction could be explained by the formation of a relatively stable intermediate: according to Meyer and his colleagues^{14,62}, a complex between the halogenide and diazonium ion /4/ in equation 9/. Its formation is followed by an electron transfer which leads to the release of nitrogen while the phenyl and halogen radicals recombine, as is demonstrated in equation 9.



The heavier halogens have a tendency to form complexes which is not expected from hydroxide ion and the high selectivity of this step may suggest an especially favourable interaction between the diazonium group and the I^- or At^- ion. Due to its lower electronegativity and higher polarizability, astatine is the better complex forming agent. This is well in line with the observed 2-3 times higher yields for astatine than for iodine products under comparable conditions. The electron transfer /4-5/ in equation 9 may proceed at lower excitation levels in the presence of I^- and especially At^- as compared with the competitive reaction of hydrolysis because of the relatively low polarizability of the water molecules.

The isomer distribution obtained in competition experiments with equimolar mixtures of ortho, meta and para-diazonium salts^{14,62} seems to confirm the suggested mechanism of intermediary complex formation. As it can be seen from Table 5 both ¹³¹I and ²¹¹At react preferentially with the ortho isomers of haloanilines and this preference decreases in the series from fluorobenzene to iodobenzene. Though the ortho selectivity is stronger for the I⁻ ion, its dependence on the electronegativity of the halogen substituent already present in the molecule is even more clearly expressed for the At⁻ ion.

This phenomenon was explained by the dependence of halogenide - diazonium ion complex stability on the extent of covalency of the participating bonds. Thus, complex 4 might be further stabilized by additional charge delocalization brought about by the substituent present in the ortho position to the diazonium group. Accordingly, the differences in isomer distribution observed in the competition experiments could be attributed to different rates of complex formation, depending on the electronegativity of the ortho substituent. On the other hand, the somewhat lower ortho selectivity of astatide compared with that of iodide was explained by the higher steric hindrance for the bulkier halogen.

5-Astatodeoxyuridine /7/ which is likely to be of special interest for biological studies (see section VI) can be prepared from the corresponding aminoderivative with a yield of only 2-3%, the main product /20-25%/ being 5-astatouracil /8/^{14,64}. The same is true for the iodination of 5-aminodeoxyuridine. Hydrolysis of the N-glycosyl bond of the starting substance /6/ in the course of diazotation is assumed to be responsible for this phenomenon¹⁴.

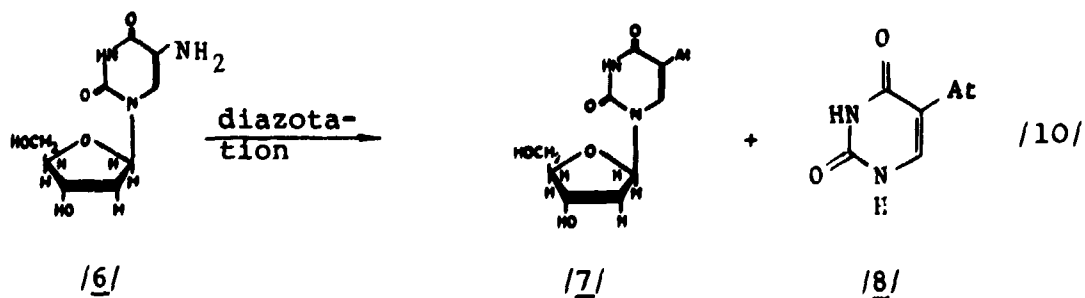


Table 5

Relative isomer distribution of astat- and iodobenzene derivatives
in equimolar mixtures of ortho-, meta-, and para-diazonium salts

Initial substrates	Astatohalobenzenes			Iodohalobenzenes		
	ortho	meta	para	ortho	meta	para
	/ ortho + meta + para = 100 /					
o-,m-,p-FC ₆ H ₄ NH ₂	65 ± 3	25 ± 3	10 ± 3	82 ± 3	11 ± 3	7 ± 4
o-,m-,p-ClC ₆ H ₄ NH ₂	50 ± 3	22 ± 3	28 ± 3	79 ± 2	3 ± 1	18 ± 1
o-,m-,p-BrC ₆ H ₄ NH ₂	44 ± 3	26 ± 3	30 ± 3	59 ± 3	24 ± 1	17 ± 1
o-,m-,p-IC ₆ H ₄ NH ₂	34 ± 4	34 ± 4	32 ± 4	64 ± 6	27 ± 6	9 ± 1

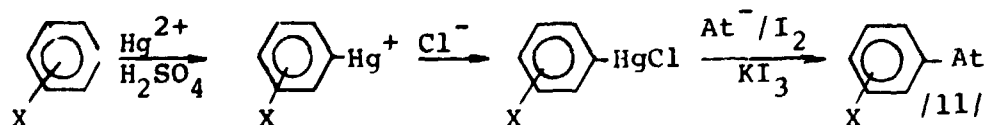
/Reproduced from G.-J. Meyer, K. Rössler and G. Stöcklin, J. Am. Chem. Soc. 101, 3121 /1979/
Table II, by permission of the American Chemical Society/

Other laboratories⁶⁵⁻⁶⁷ have obtained high yields (~90%) of astatobenzoic acid isomers by decomposition of diazonium salts. The products can be identified⁶⁵ by TLC. The para isomer is then used to prepare biologically stable astatinated protein (bovine serum albumin) by a condensation reaction between the carboxylic group and the amine function of the protein, as has been reported by Friedman, Zalutsky and colleagues^{66,67}. Benzoic acid derivative was chosen as an intermediate because aromatic halogen compounds are more stable against halogen displacement than the aliphatic ones. Astatinated protein is separated from the unreacted p-At-benzoic acid by column chromatography, overall yield of labelling being 12%. The labelled protein was found to be stable, in vivo over a 20 h period.

A somewhat modified procedure has been also applied for synthesizing ²¹¹At-labelled antibody proteins⁶⁸ which showed no loss of immunological specificity.

4. Astatination via mercury compounds

Astatine can be built into aromatic and heterocyclic molecules with high yields under relatively mild conditions using the method generally known for converting chloromercury compounds into iodides⁷¹, as it was shown by Visser and colleagues^{59,69,70}. The sequence of the reactions leading to astatinated benzene derivatives is shown schematically by equation 11:



The aromatic or heterocyclic substrate is dissolved or suspended in sulfuric acid and a somewhat less than stoichiometric amount of mercury sulfate is added. The mixture is stirred for several hours at room temperature or at 60°C, depending on the substrate. Thereafter, a twofold stoichiometric amount of sodium chloride is added at room temperature, followed after 5 minutes

by diluted sodium hydroxide - sodium sulfite solution of astatide containing an iodide carrier and by KI_3 . This mixture is stirred for an additional 5-30 minutes. The mercury iodide precipitate is filtered or dissolved by adding an excess of potassium iodide to the system. The astatinated products, except the aminoacids, are extracted with organic solvents and identified by TLC. Astataminoacids are analysed in aqueous solution using paper electrophoresis. Astatine derivatives of phenol, aniline, dimethylaniline, anisol, phenylalanine, uracil⁷⁰ and tyrosine^{69,70} as well as of imidazoles and histidine⁶⁹ can be prepared by this method with 50-95% yields.

Compared with the decomposition of diazonium salts, astatination via chloromercury derivatives - besides the usually higher yields - has the advantage that side reactions can be avoided. This means that after removing the inorganic fraction the required product is generally present in more than 95% purity⁷⁰. On the other hand, it should be kept in mind that the substitution pattern /isomer distribution/ is determined by the mercuriation reaction. Therefore, only ortho and para astatophenol or astataniline can be obtained by this technique, while meta isomer originates if started from nitrobenzene.

For mercuriation of substances such as phenol that possess highly activated substitution sites, it is not necessary to use strong acidic media. Thus, for example ortho and para-chloromercuryphenol can be prepared using $Hg/OAc/2$ followed by the reaction with sodium chloride according to that described earlier⁷². The corresponding astatophenols are then produced smoothly by interaction with At^- containing iodine carrier in chloroform, at room temperature, with 95% yield.

The higher reactivity of astatine compared with iodine in the reactions with chloromercury compounds has been established⁷⁰. This is reflected in the higher yields of some astatinated as compared to those of iodinated products. Furthermore, astatinated products, though with lower yields, are obtainable also without iodine carrier present while carrier-free ^{131}I fails to react

with some substances, such as tyrosine, aniline and nitrobenzene. Both ionic electrophilic and radical mechanism had earlier been proposed for the halogenation of chloromercury compounds. For astatine reacting in the absence of an iodine carrier, however, a strong indication of the radical mechanism has been found⁷⁰ which can be explained by easy oxidation of At^- into $\text{At}/\text{O}/$ at low pH values.

5. Electrophilic substitution

Electrophilic substitution is one of the most characteristic features of halogen atoms. It is surprising, therefore, that not very much is known about this part of astatine chemistry. One of the reasons for this area not yet being clarified is that most investigations related to the substitution of H atom by a positive astatine species were directed towards labelling complicated molecules such as proteins and lymphocytes⁷³⁻⁷⁶. Such systems are, of course, not best suited for studying chemical reaction mechanism. Their investigation is, however, justified by the potential importance of ^{211}At -labelled biomolecules in medical application, as will be discussed in section VI.

Neirinckx and coworkers⁷³ could label lymphocytes by electrolysis in isotonic solution leading to the formation of At^+ ions on the platinum gauze anode. Varying the electrode potential, the highest labelling yields can be obtained if the potential difference is 3-7 V. However, a rapid decomposition of the product is also observed in these cases.

Further information concerning the factors affecting the electrolytic astatination can be obtained from the work of Aaij and colleagues⁷⁴. They investigated different techniques for electrophilic labelling of keyhole limpet hemocyanin /KLH/. Electro-oxidation at pH=7,4 with 1 V potential difference for about thirty minutes led to coupling of about 30% of astatine present to the protein. The value of the electrode potential seems to be crucial as far as the protein denaturation is concerned: Samples obtained under conditions described above do not show any significant denaturation whereas if the voltage is increased to 4-5 V the latter process becomes very fast.

It was proved in the same study that the chloramin-T technique, successfully used to oxidize iodine species to form I^+ for labelling proteins with radioiodine, is very inefficient in the case of astatine. A probable explanation is that due to the difference in oxidation potentials between the two halogens chloramin-T may oxidize astatine to a higher valency state which is not capable of electrophilic substitution in the molecules investigated.

On the other hand, oxidation by hydrogen peroxide at pH=7,4 in the presence of a small amount of potassium iodide resulted in 60% astatination yield of KLH. Both electrolytic oxidation and that with hydrogen peroxide were applied also for labelling human gamma globulin and tuberculin. However, despite successful incorporation of astatine into the proteins under conditions suitable for electrophilic substitution, neither the real mechanism of labelling nor the type or site of At-bond could be determined. Thus, it remained a question whether the astatine built into the KLH by oxidation with hydrogen peroxide is bound in the tyrosine group as a positive ion or forms a complex, as AtI , with the protein molecule⁷⁴. Though several studies have attempted to clarify these questions, we feel that no reliable answer has yet been found.

Thus, according to Vaughan and Fremlin⁷⁵ reaction of astatine with L-tyrosine in the presence of hydrogen peroxide and potassium iodide results in formation of astatotyrosine at pH $\geq$ 9. The product is identified by ion exchange chromatography, however, a loss of astatine with a chemical half-life of 310 minutes is observed. Similar instability is observed⁷⁶ if proteins /rabbit IgG immunoglobulin and the light chain fragment/ are labelled by the same technique at pH=7-7.4. The authors assume that astatine bound originally to the tyrosyl residue of the protein is readily released due to the very unstable C-At bond and reacts non-specifically with other groups, finally being trapped by the tertiary structure of the protein.

Table 6
Stability of astatotyrosine and astatiodotyrosine
at room temperature⁵⁹

Compound	pH	Additive	Chemical half-life
3-astatotyrosine	<1	0.2M H ₂ SO ₄	no decomposition in 20 h
	4	-	- " -
	7	-	14 - 17 h
	7	H ₂ O ₂	0.5 h
	10	-	45 min
	11.5	-	3-4 min
3-astato-5-iodotyrosine	<1	0.2M H ₂ SO ₄	no decomposition in 20 h
	7	-	0.5 - 1.5 h

Investigations carried out by Visser and colleagues⁵⁹ with astatotyrosine have shown, however, that although astatotyrosine is fairly stable in acidic solutions, it decomposes rapidly at $\text{pH} \geq 7$, especially in the presence of oxidizing agents, similarly to astatiodotyrosine as is demonstrated in Table 6. This behaviour was then attributed to the generally known sensitivity of o-halophenols to oxidation⁷⁷ rather than to the weakness of the C-At bond. Fast deastatination at higher pH-values can be explained by the formation of the reactive phenolate ion as was also observed for deiodination of iodotyrosine^{78,79}. Consequently, astatotyrosine is very unlikely to survive the conditions described for electrophilic astatination /hydrogen peroxide in neutral or alkaline media/ of proteins^{75,76}. Instead, a complex formation between oxidized astatine and protein was suggested without specifying its exact structure⁸⁰.

The controversy between different research groups^{80,81} shows that the chemistry of these processes is not wholly understood yet. Further systematic studies and also more unequivocal techniques identifying the products are necessary prior to using electrophilic substitution to produce astatine labelled proteins stable under physiological conditions.

More straightforward work concerning the electrophilic substitution reactions of astatine has been carried out recently with benzene and its monosubstituted derivatives: $\text{C}_6\text{H}_5\text{X}$, where $\text{X} = \text{H}, \text{F}, \text{Cl}, \text{Br}$ ⁸².

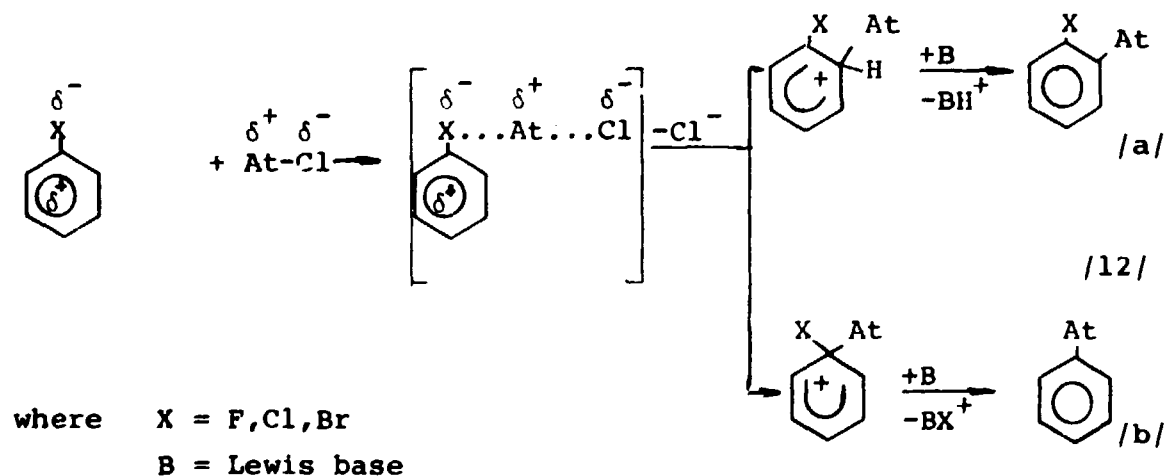
The reactions were performed in homogeneous mixtures of the aromatic compound and acetic acid containing $\text{H}_2\text{Cr}_2\text{O}_7$ as oxidizing agent. The redox potential of the media being ≈ 1.0 V, the astatine is presumably present in the At^+ -form⁸ /see Table 3/.

Under these conditions no significant hydrogen substitution in benzene can be detected below 80°C . At higher temperatures, however, substitution yields of up to 50% are observed in short time periods /see Figure 5/. The isomer distribution of hydrogen substitution products in monohalobenzenes clearly demonstrates the electrophilic character of the reacting astatine /see Table 7/.

Table 7
Yield and isomer distribution as a result of electrophilic
At for H substitution in halobenzenes⁸²

Halobenzenes	Yield %/	Isomer distribution		
		ortho	meta	para
		/ortho + meta + para = 100/		
C ₆ H ₅ F	3.3	7 ± 1		93 ± 6
C ₆ H ₅ Cl	0.2	15.4 ± 0.8	1.6 ± 0.2	83 ± 5
C ₆ H ₅ Br	0.1	20 ± 1	2.0 ± 0.2	78 ± 5

Reactions of AtCl and AtBr* in monosubstituted benzene derivatives: C_6H_5X , where $X = F, Cl, Br, NH_2, OH, CH_3$, were also considered to be mainly electrophilic processes as reported by Meyer and colleagues^{14,64,83}, by analogy with those of carrier-free ^{125}ICl ⁸⁴. This seems to be confirmed by enhanced hydrogen substitution in the activated aromatic compounds such as aniline and phenol as compared with that in halobenzenes and also by the isomer distribution of the products. In contrast to the well established mechanism of the iodine chloride reaction with aromatics, astatine chloride and astatine bromide should react in a different way, as shown by the significant extent of halogen exchange /30-40% / with halobenzenes. This phenomenon together with the high ortho selectivity of hydrogen substitution in halobenzenes and aniline, has been interpreted^{14,83} as being an attack of the polarized interhalogen at the electronegative site of the aromatic substrate /i.e. at the halogen atom / followed by a complex formation. This complex should then react in two different ways: either by normal aromatic substitution /proton removal / or by electrophilic halogen replacement reaction. It has also been assumed that both reactions are assisted by a Lewis base always being present in the reaction mixture.



* These interhalogen compounds can be prepared by interaction of ^{211}At with Cl_2 and Br_2 at room temperature^{14,15}.

It should be emphasized, however, that the mechanism proposed in equation 12 needs further study and more detailed information, especially on the ratio of the observed two directions as a function of reaction conditions. Better statistics of the experimental data would also be necessary to prove the assumption described above^{14,83}.

The high halogen replacement yields observed with halobenzenes, initiated investigations with $^{211}\text{AtCl}$ in order to prepare 5- ^{211}At -deoxyuridine from the corresponding iodine derivative. In this case, however, only yields of 3-4% could be obtained^{14,64}.

6. Reactions of recoil astatine

The fact that astatine can be obtained only via nuclear transformations offers a good opportunity to synthesize its compounds by immediate reactions of recoil astatine. Atoms originated in nuclear processes generally have an excess of kinetic, excitation and also ionization energy which increases their reactivity. This can give rise to chemical reactions prohibited for thermal species due to the activation energy needed.

Samson and Aten^{50,53} were the first to use recoil astatination to synthesize astatobenzene by irradiating triphenylbismuth with α -particles in a synchrocyclotron /see Table 1/. Astatobenzene, as one of the products of recoil astatine formed in nuclear reaction is separated and identified by GLC.

Norsev and colleagues applied reactions of ^{211}At formed by electron capture from ^{211}Rn /see Table 1/ in benzene and aliphatic hydrocarbons to obtain astatobenzene⁸⁵, n- and i-alkyl-astatides⁵⁶ as well as cyclopentyl- and cyclohexylastatide⁸⁶.

More systematic studies were carried out on the replacement reactions of EC produced astatine in gaseous, liquid and crystalline benzene and halobenzenes^{25,82} as well as in liquid nitrobenzene⁵⁹ and aniline⁸⁷.

After its separation from the other spallation products and its subsequent purification as described in section II.B, carrier-free ^{211}Rn is introduced into thoroughly evacuated glass

ampoules containing the organic substrate. The ampoules are sealed and ^{211}Rn is allowed to decay for 14 hours, until the equilibrium with ^{211}At is reached. Organic and inorganic fractions are separated by extraction of the substrate with carbon tetrachloride and aqueous sodium hydroxide solution containing a small amount of sodium sulfite as reducing agent. Identification and determination of the yields of individual organic products is performed by GLC and HPLC.

Considerable amounts of replacement products were obtained for benzene and halobenzenes⁸⁷ with the highest yields for liquid systems. The hydrogen replacement yields in aniline and nitrobenzene⁵⁹ do not differ significantly from those obtained in halobenzenes /as is shown in Table 8/. This finding together with the nearly statistical isomer distribution confirms the assumption that the hydrogen replacement in aromatic compounds by decay activated astatine is a hot homolytic process rather than thermal electrophilic one.

Whereas the extent of hydrogen substitution decreases in the series fluoro-, chloro-, bromo-, iodobenzene the replacement of the halogens shows an opposite tendency /see Table 9/. This is especially true for yields observed in the presence of a small amount /0.5 - 1.0 mole% / of iodine commonly used as radical scavenger for thermalized halogen atoms, i.e. to distinguish between the products of hot and thermal reactions of recoil halogens.

Competition between the halogen and hydrogen replacement seems to be responsible for the opposite tendency in their product yields through the series of halobenzenes. This may imply a common activated state for both reactions, e.g. some kind of short-lived excited intermediate complex formed as a result of a highly inelastic atom - molecule collision of astatine with the aromatic molecule, similar to that postulated earlier^{88,89} for the hot replacement reactions of the other halogens in analogous systems:

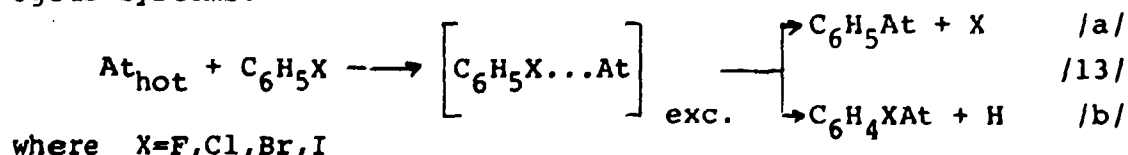


Table 8

Hydrogen replacement of recoil ^{211}At in liquid benzene and
its derivatives^{59,87}

Compound	Yield %	Isomer distribution /ortho + meta + para = 100 /
C_6H_6	22.8 ± 2.5	
$\text{C}_6\text{H}_5\text{F}$	14.4 ± 4.0	38 : 40 : 22
$\text{C}_6\text{H}_5\text{Cl}$	10.7 ± 1.7	40 : 40 : 20
$\text{C}_6\text{H}_5\text{Br}$	7.8 ± 0.9	56 : 30 : 14
$\text{C}_6\text{H}_5\text{I}$	3.7 ± 0.2	48 : 36 : 16
$\text{C}_6\text{H}_5\text{NH}_2$	5.2 ± 1.2	52 : 34 : 14
$\text{C}_6\text{H}_5\text{NO}_2$	6.5 ± 0.4	36 : 44 : 20

Table 9

Halogen replacement of recoil ^{211}At in liquid
halobenzenes⁸⁷

Compound	Yield / % /	
	neet	+ 0.5 mole % I_2
$\text{C}_6\text{H}_5\text{F}$	4.9 ± 0.9	3.6 ± 0.4
$\text{C}_6\text{H}_5\text{Cl}$	35.3 ± 5.2	18.8 ± 0.3
$\text{C}_6\text{H}_5\text{Br}$	41.0 ± 5.0	27.6 ± 3.3
$\text{C}_6\text{H}_5\text{I}$	44.0 ± 2.0	32.8 ± 1.8

Moreover, the halogen replacement yields both in liquid and gas phase show a linear dependence on the reciprocal bond strength of the halogen to be replaced.

This again is consistent with the bond energy dependence of the hot halogen replacement established for other recoil halogens formed in different nuclear reactions^{88,89} and decays^{90,91}. Other factors, such as the increasing polarizability of the substituents in the same series of halobenzenes or steric effects may, however, also be of importance.

On the other hand, investigations on systems diluted with solvents of different ionization potentials /IP/ suggest a more complicated pattern of recoil astatine reactions⁹². Dilution of chlorobenzene with triethylamine /TEA/ having IP lower than astatine increases considerably the replacement of chlorine atoms while decreases that of hydrogen atoms /*Figure 6*/. The opposite tendency was observed when diluting chlorobenzene with carbon tetrachloride or hexafluorobenzene - both having higher IP than astatine. Since astatine is formed in the electron capture originally in the charged state, its neutralization before taking part in the chemical reactions depends on the IP of the surrounding molecules. Therefore, the phenomena observed in different media, as described above, may indicate a significant participation of At^+ in replacing hydrogen while neutral astatine atoms seem to prevail in halogen replacement.

V. PHYSICO-CHEMICAL PROPERTIES OF ORGANIC COMPOUNDS

Even though the number of organic astatine compounds prepared and unequivocally identified has increased rapidly over the past few years, not too many of their properties are known precisely; this is because of the obvious difficulties in measuring micro concentrations. Most of the data concerning the physico-chemical properties of organic astatine compounds have been obtained by making use partly or entirely of extrapolation from the

properties of analogous halogen derivatives. Along with the development of techniques for synthesizing and identifying astatine compounds some direct methods for establishing their characteristics have recently come in sight.

A. EXTRAPOLATION FROM PROPERTIES OF OTHER HALOCOMPOUNDS

In a study aimed at predicting some of the properties of volatile compounds of superheavy elements, Bächmann and Hoffmann⁹³ made a number of estimations also for the corresponding astatine derivatives. The authors found relationships between physico-chemical constants giving monotonic plots for alkyl derivatives of elements which belong to the same group of the periodic system. Extrapolation of the properties according to these plots is possible because the molecule structure of the alkyl derivatives does not change essentially for the elements within one and the same group.

Thus, since both the atomic volume $/v_A/$ and the electronegativity $/x/$ of the heavy atoms exhibit a definite influence on the Van der Waals interactions of their organic derivatives, the boiling temperature $/T_b/$ was plotted vs a relationship of the former quantities:

$$T_b = f / \frac{Z v_A}{x} / \quad /14/$$

where Z = atomic number of the element

Smooth curves were obtained for the methyl as well as the ethyl halogenides. Although both the atomic volume and the electronegativity of astatine were established - likewise by extrapolation - from corresponding values measured for the other halogens, the T_b values determined on the basis of equation 14 agree reasonably well with those obtained using other methods of extrapolation /see Table 10/.

Table 10

Some physico-chemical properties obtained by extrapolation

Property	Quantity used for extrapolation ^a		Value	Reference
$T_b/^{\circ}\text{C}/$	CH_3At			
	$\frac{z v_A}{x}$		73 ± 5	93
	w_M		72 ± 2	94
	p_v		77 ± 5	95
IP/eV/	$\frac{z r_A^2}{x}$		88	95
$D_{\text{C-At}}/\text{kJ/mol}/$	$\frac{z}{x}$		205	95
$T_b/^{\circ}\text{C}/$	$\text{C}_2\text{H}_5\text{At}$			
	$\frac{z v_A}{x}$		103 ± 5	93
	$t_{\text{ret}}/\text{GLC}/$		98 ± 2	50,52
IP/eV/	$\frac{z r_A^2}{x}$		8.65	95

^a w_M = molecular volume; p_v = vapour pressure

The dissociation energy $/D_{C-At}/$ of methylastatides has been determined by extrapolation from other methylhalogenides on the basis of the relationship

$$D_{C-Hal} = f \frac{Z}{x} \quad /15/$$

Furthermore, the ionization potentials for methyl- and ethyl-astatide have also been estimated using the dependence of this former constant on the covalent atomic radius $/r_A/$ and the electronegativity of the heavy atom⁹⁵:

$$IP = f \frac{Z r_A^2}{x} \quad /16/$$

The values for both latter quantities are also given in Table 10.

An other method proposed as a means of estimating the dissociation energy for some aliphatic and aromatic astatine compounds is also primarily based on the assumption of identical molecular structure of analogous derivatives³¹. According to the linear relationship found between D-values and the reciprocal covalent radii for halogen molecules⁹⁶, first the covalent radius of At_2 $/r_{At_2}/$ was estimated by extrapolation /see Figure 7/ using a theoretical value for D_{At_2} ³⁷. Hence the bond distance $/r_{C-At}/$ can easily be calculated and the D_{C-At} can again be determined by extrapolation from corresponding values of analogous halogen compounds, /as is shown in Figure 7 for the methylhalogenide series/. D_{C-At} values for other compounds can also be calculated using Szabo's method⁹⁷ of bond energy decrements. D_{C-At} values for some aliphatic and aromatic astatine derivatives estimated in this way are shown in Table 11 together with calculated and measured values for analogous iodine compounds, for comparison.

B. DETERMINATION BASED ON GAS CHROMATOGRAPHIC BEHAVIOUR

Besides the separation and identification of carrier-free astatine compounds GLC is applied for determining some of their features. Gas chromatographic behaviour of a substrate reflects

Table 11

Dissociation energy values for some organic astatine and
iodine compounds

Compound	$D_{C-X} / \text{kJ/mol} /$			
	X = At		X = I	
	calculated ³¹	experiment ¹⁰⁸	calculated ³¹	experiment ⁹⁶
CH_3X	176		226	226
$\text{C}_2\text{H}_5\text{X}$	167		218	213
$\text{n-C}_3\text{H}_7\text{X}$	163	162 ± 10	213	209
$\text{i-C}_3\text{H}_7\text{X}$	159	152 ± 10	209	192-218
$\text{n-C}_4\text{H}_9\text{X}$	163		213	205
$\text{C}_6\text{H}_5\text{X}$	205	187 ± 20	255	252 ± 24^{108}
$\text{FC}_6\text{H}_4\text{X}$	146		197	
$\text{ClC}_6\text{H}_4\text{X}$	125		175	

its distribution between the stationary /liquid/ and the gas phase; the distribution is determined by intermolecular interaction of this substrate with the molecules of the stationary phase. These interactions, in turn, depend on physico-chemical characteristics of both species. Thus, information can be obtained on particular properties of volatile compounds from systematic gas chromatographic studies using different stationary phases of known characteristics. Actually, this is one of the very few techniques suitable for studying the physico-chemical properties of astatine compounds due to its equal ability to separate species present in micro as well as in macro amounts.

It was first utilized by Samson and Aten⁵² to establish the boiling points of n-alkylastatides $/n-C_nH_{2n+1}At$, where $n = 2-6/$ by extrapolation from the T_b values of other alkylhalogenides. In this case the boiling points were plotted simply vs the logarithmic values of retention time obtained under identical experimental conditions for the analogous alkyl derivatives of the five halogens /see Figure 2/.

Norseyev and coworkers^{56,57} used the same method to establish the boiling points of n- and i-alkylastatides. They could also show that the T_b dependence on the logarithmic retention time is linear for these compounds, similarly to that for the corresponding iodine derivatives /see Figure 3/. The boiling points of astatobenzene^{14,50,53,98}, astatohalobenzenes and astatotoluenes^{14,61} can be likewise estimated. T_b -values established based on gas chromatographic behaviour are summarized in Table 12.

The chromatographic behaviour of astatine compounds in relation to that of other halogenderivatives has also provided a means of calculating the "effective" atomic number of astatine. This latter quantity has allowed a rough estimation of physico-chemical constants, such as T_b , heat of vaporization $/\Delta H_v/$, IP, D and bond distance $/r_{C-At}/$ for a number of simple aliphatic compounds of astatine and also for astatobenzene⁹⁹.

One of the factors limiting the accuracy of estimations described above is that the absolute retention time values depend

Table 12

Boiling points of some organic astatine compounds
based on gas chromatographic behaviour

Compound	$T_b/^{\circ}\text{C}/$	Ref.	Compound	$T_b/^{\circ}\text{C}/$	Ref.
CH_3At	66 ± 3	99	$\text{C}_6\text{H}_5\text{At}$	212 ± 2 219 ± 3 216 ± 2	50,53 14 102
$\text{C}_2\text{H}_5\text{At}$	98 ± 2	50,52	$\text{AtC}_6\text{H}_4\text{CH}_3$	o 237 ± 2 m 237 ± 2 p 236 ± 2	102
$n\text{-C}_3\text{H}_7\text{At}$	123 ± 2	50,52	$\text{AtC}_6\text{H}_4\text{F}$	o 213 ± 2 m 206 ± 2 p 209 ± 2	102
$i\text{-C}_3\text{H}_7\text{At}$	112 ± 2	56	$\text{AtC}_6\text{H}_4\text{Cl}$	o 258 ± 2 m 255 ± 3 p 253 ± 2	102
$n\text{-C}_4\text{H}_9\text{At}$	152 ± 3	50,52	$\text{AtC}_6\text{H}_4\text{Br}$	o 303 ± 3 m 304 ± 3 p 305 ± 3	14
$i\text{-C}_4\text{H}_9\text{At}$	142 ± 3	56	$\text{AtC}_6\text{H}_4\text{I}$	o 336 ± 4 m 337 ± 4 p 337 ± 4	14
$n\text{-C}_5\text{H}_{11}\text{At}$	176 ± 3	50,52	$\text{AtC}_6\text{H}_4\text{NO}_2$	o 303 ± 3 m 297 ± 3 p 303 ± 3	58
$i\text{-C}_5\text{H}_{11}\text{At}$	163 ± 3	56			
$n\text{-C}_6\text{H}_{13}\text{At}$	201 ± 2	50,52			

on the given experimental conditions of the chromatographic separation. Therefore, if we introduce retention index¹⁰⁰/ I_x / which represents a relative value, i.e. retention time of the measured compound compared with that of a standard compound /usually n-hydrocarbon/ under the same conditions*, we are able to considerably improve the precision of determination.

An extensive study has been carried out to establish retention indices for aromatic halocompounds including those of astatine, with a variety of stationary phases^{31,32,101}. Comparison of I_x -values obtained with stationary phases of different polarities allows a more reliable estimation of physico-chemical constants such as T_b , ΔH_v , bond refraction $/R_{C-X}/$ and dipole moment $/\mu/$, for At-derivatives of benzene, halobenzenes, toluene and nitrobenzene^{31,32,102,103}. T_b and ΔH_v can also be directly related to the gas chromatographic parameters.

Known ΔH_v values for halogenated benzene derivatives can be used to construct I_x versus ΔH_v plots from which the corresponding heat of vaporization values for analogous astatine compounds can be determined. Since the heat of vaporization is closely related to the boiling temperature /Trouton's rule/ similar correlation is to be expected for the boiling points of these compounds. Figure 8 shows the linear dependence of retention in-

* I_x can be calculated as follows¹⁰⁰:

$$I_x = 100 \cdot \frac{\lg t/x/ - \lg t/n/}{\lg t/n+1/ - \lg t/n/} + 100 n \quad /17/$$

where $t/x/$ = the retention time of the component x

$t/n/$ = the retention time of the n-alkane with n C-atoms

$t/n+1/$ = the retention time of the n-alkane with n+1 C-atoms
all measured under the same conditions.

$$t/n/ \leq t/x/ \leq t/n+1/$$

dices for monosubstituted benzene derivatives, measured using Squalane stationary phase, on their normal boiling temperature as an example*. Similar linear dependence has been obtained for T_b and ΔH_v in the case of dihalobenzenes, halotoluenes and halonitrobenzenes. This allows one to extrapolate the values of these two quantities for the corresponding astatine derivatives.

It should be stressed at this point that physico-chemical properties governed by dispersion forces, such as T_b , ΔH_v , R , etc., can be established with the greatest accuracy using non-polar stationary phases, such as for example Squalane or Apiezon. Polar phases, frequently used in earlier experiments for determining boiling points of astatine compounds by extrapolation, induce inaccuracy due to the polar interactions between the solute and the solvent /stationary phase/ involved.

ΔH_v can also be established directly from the absolute retention volumes V_g measured at different column temperatures T_c near to the boiling point of the investigated compound by means of the equation¹⁰⁴:

$$\ln V_g = \frac{\Delta H_s}{RT_c} + K \quad /18/$$

where ΔH_s = heat of solution $\approx \Delta H_v$ for non-polar solvents¹⁰⁴

R = gas constant

K = constant

Heat of vaporization values for astatobenzene and astatotoluenes calculated by this method do not differ significantly from those obtained by extrapolation. The average values¹⁰² are given in Table 13.

Boiling temperatures for the the same compounds have also been established by direct calculation using the empirical relationship of Kistiakowsky¹⁰⁵:

*The experimental value for fluorobenzene does not fit the straight line and has, therefore, been omitted in the calculations.

$$\Delta H_v = \left[1 + \frac{2\mu}{100} \right] T_b \left[8.75 + R \ln T_b \right]^* \quad /19/$$

The T_b -values determined by the two different methods¹⁰² are presented in Table 12.

For a series of halobenzenes and substituted halobenzenes a linear relationship has been found¹⁰³ between the retention index increments δI_x observed with non-polar stationary phases and dispersity factors of the corresponding halogens as shown in Figure 9. δI_x can be defined as the change in the retention index of a benzene derivative caused by the introduction of an additional halogen X into the aromatic ring:

$$\delta I_x = I_{ArX} - I_{ArH} \quad /20/$$

The dispersity factor of corresponding halogens d_x can be calculated from the dispersion energy relationship¹⁰⁶ determined by the interactions between the functional groups of the solute and solvent:

$$\delta U_d - A_d \frac{\alpha_x}{(r_o + r_x)^3} = A_d d_x \quad /21/$$

where δU_d = dispersion energy increment

α_x = polarizability of X

r_o = Van der Waals radius of solvent functional group

r_x = Van der Waals radius of X

A_d = constant

From the linear plots between δI_x and d_x the latter value for astatine can be estimated and the α_{At} can be calculated

* μ values of the corresponding iodine compounds were used for these calculations.

Table 13
Physico-chemical constants based on gas chromatographic behaviour
for some aromatic astatine compounds^{102,103}

Compound	ΔH_v /kJ/mol/	R_{C-At} /cm ³ /mol/	μ_{C-At} /Debye/
C_6H_5At	42.8	20.8	1.06 1.60 ^a
ortho AtC₆H₄CH₃ meta para	46.3 46.6 46.7	20.7	0.90
ortho AtC₆H₄F meta para	44.6 43.4 42.5	22.0	
ortho AtC₆H₄Cl meta para	50.8 49.0 47.5	21.5	

^aReference¹⁴

Average: 21.3

according to the equation 21. R_{C-At} is then determined using the relationship between R and α /see for example^{107/}:

$$R = \frac{4\pi N}{3} \alpha \quad /22/$$

where N = Avogadro's constant. The values are given in Table 13.

In order to estimate dipole moments of the C-At group $|\mu_{C-At}|$ for some aromatic astatine compounds, the differences between the retention indices observed with polar /e.g. polyethylene glycol /PEG// and non-polar /e.g. Squalane/ stationary phases have been related to the polarity factors of the halogens $|p_X|$. This latter quantity is determined by the equation of orientation interaction energy¹⁰⁶ determined by the interactions between the functional groups of the solute and solvent:

$$U_{or} \approx A_{or} \frac{\mu_X^2}{T_c / r_o + r_X} = A_{or} p_X \quad /23/$$

where:

- U_{or} = orientation energy
- μ_X = dipole moment of C-X group
- T_c = absolute temperature of the column / K /
- r_o = Van der Waals radius of solvent functional groups
- r_X = Van der Waals radius of X
- A_{or} = constant

Figure 10 shows the $\Delta I_{ArX}^{PEG} = I_{ArX}^{PEG} - I_{ArX}^{Squalane}$ versus p_X plots¹⁰³ for halobenzenes and p-halotoluenes from which the μ_{C-At} values could be determined using equation 23. /This treatment involves the assumption that the difference between the retention indices observed on polar and non-polar stationary phases is controlled mainly by the orientation interactions between the solute and the solvent./ Dipole moments obtained this way for astatobenzene and p-astatotoluene are also given in Table 13. The value of 1.06 Debye for astatobenzene is lower than that reported earlier

by Meyer¹⁴, viz. 1.60 Debye. This latter value was derived from the difference in retention indices observed with Silicon oil /non-polar/ and Silicon oil containing Bentone 34 /polar/ stationary phases for halogenated fluorobenzenes.

* * *

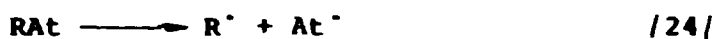
In contrast to the majority of procedures discussed up to this point, in the following two sections techniques are described where the conclusions are drawn from measurements of definite properties /thermal decomposition, solubility/ of the astatine compounds themselves. The application of such direct methods is a very significant step forward in the still obscure field of astatine chemistry.

C. KINETIC DETERMINATION OF C-At DISSOCIATION ENERGY

The dissociation energy of C-At bond for astato-benzene, n- and i-propylastatide has been established experimentally¹⁰⁸ using pyrolytic decomposition of these compounds. The generally used method, well known as the toluene carrier gas technique^{109,110} was slightly modified, by connecting the pyrolytic oven - a Pyrex tube - directly to the gas chromatograph. This ensures continuous removal of non-dissociated original compound from the reaction zone and also its instantaneous separation from the products of pyrolysis as well as measurement. The temperature of the GLC column was kept low enough [$\leq 140^{\circ}\text{C}$] to avoid additional decomposition during the analysis*

The reaction rate of the monomolecular decomposition described in equation 24 follows the first order law and can be calculated according to equations 25 and 26.

*Absence of such decomposition was proved by showing that $98 \pm 2\%$ of injected compound was eluted from the column in the same chemical form.



where $\text{R} = \text{C}_6\text{H}_5, \text{n-Pr}, \text{i-Pr}$

$$\frac{dc}{dt} = kc \quad /25/$$

$$k = \frac{\ln \frac{c}{c_0}}{t} \quad /26/$$

where c_0 = concentration of RAt at $t = 0$
 c = concentration of RAt at the time t
 k = rate constant

Dissociation energy was established using the Arrhenius equation /equation 27/ taking into consideration that in this case $E_a \sim D$ since the energy of the radical recombination does not exceed the limits of the experimental error:

$$k = A e^{-\frac{E_a}{RT}} = A e^{-\frac{D}{RT}} \quad /27/$$

The values of D could then be determined from the slopes of $\ln k$ versus $1/T$ plots. The values obtained in this way for astatine compounds together with those for carrier-free $\text{C}_6\text{H}_5^{131}\text{I}$, measured by the same technique to prove the reliability of the results, are listed in Table 11. The experimental D values are very close to those obtained earlier by extrapolation³¹ and show that the C-At bond in astatobenzene is considerably stronger than in aliphatic, especially secondary, compounds, as is to be expected.

The value of the preexponential factor $A = 3.10^{13}$, obtained for the decomposition of astatobenzene, confirms the monomolecular character of the decomposition reaction studied.

D. DETERMINATION OF DISSOCIATION CONSTANTS

Distribution of acids and bases between organic and aqueous phases at various acidities has been used to establish the dissociation constants $/K_a/$ for astatocetic acid^{50,51}, for the isomers of astatobenzoic acid, astatophenol and astatoniline as well as for astatouracil^{65,70}. According to equations 28 and 29, pK_a values for acids and bases can be evaluated from $1/S$ versus $1/[H^+]$ or versus $[H^+]$ plots, respectively:

$$\frac{1}{S} = \frac{1}{S_o} + \frac{1}{S_o} \frac{K_a}{[H^+]} \quad /28/$$

$$\frac{1}{S} = \frac{1}{S_o} + \frac{1}{S_o} \frac{[H^+]}{K_a} \quad /29/$$

where S = distribution coefficient for dissociated acid or base

S_o = distribution coefficient for undissociated acid or base.

Samson and Aten^{50,51} used diisopropyl ether and water with buffer adjusted acidities to determine the distribution of astatocetic acid and ionexchange chromatography for the analysis. Visser and coworkers^{65,70} chose heptane as the organic extractant for halogenated benzoic acids, phenols and anilines; benzene was chosen for halouracils. The analysis in this case was performed by TLC. The pK_a values for astatocompounds and also for the corresponding iodine derivatives determined in these investigations are shown in Table 14.

An estimation of Hammett σ -constants and hence of the field and resonance effects was made for halophenols and haloanilines, among them for the astatine derivatives, based on the acidity constants. A considerably weaker field effect was found for astatine than for the other halogens. The resonance effect is about the same as for iodine but again much weaker than that obtained for the other members of the halogen family⁶⁵.

Table 14

Dissociation constants for some astato- and iodo-compounds
in aqueous solution at 0°C

Compound	pK _a		Reference
	X = At	X = I	
XCH ₂ COOH	3.78 3.70 ^a	3.14 3.12 ^a	50,51
XC ₆ H ₄ COOH ortho meta para	2.71±0.02 3.77±0.02 4.03±0.02	2.70±0.02 3.70±0.02 3.94±0.03	65
XC ₆ H ₄ NH ₂ ortho meta para	3.03±0.03 3.90±0.03 4.04±0.02	2.65±0.01 3.65±0.02 3.80±0.02	
XC ₆ H ₄ OH ortho meta para	8.92±0.03 9.33±0.03 9.53±0.03	8.50±0.01 9.07±0.02 9.29±0.01	
5-X-uracil	8.97±0.01	8.25±0.01	

^aat 22°C

VI. ^{211}At IN NUCLEAR MEDICINE

Attention paid to organic astatine compounds leading to the recent progress in this field, stems mainly from their potential application in medicine. This is explained by the nuclear characteristics of the ^{211}At isotope and also by its halogenous nature. By virtue of its decay by α -emission /see section II.B/, it provides intensely ionizing radiation in a short range /60 μm in water/. Thus, 1g tissue containing 10 kBq of ^{211}At will receive a dose equivalent of 6 500 $\mu\text{Sv}/\text{min}$ whereas the same activity of ^{125}I will give only 20 μSv . If attached to an appropriate biomolecule, it allows, in principle, a maximal destruction of some target cells with relatively small damage to neighbouring healthy tissues.

Inorganic astatine, similarly to iodine, concentrates in the thyroid gland and can thus provide a unique means for treating hyperthyroidism. It has been shown by Hamilton and colleagues^{111,112} in animal studies that the parathyroid glands remain unaltered even when the thyroid becomes totally destroyed.

Selective cytotoxicity might be applied in tumour therapy, for destroying malignant cells, if tumour specific antibodies are labelled with ^{211}At . Using astatinated DNA-predecessors like astatouracil and astatodeoxyuridine as carriers of α -activity into the centres of cell proliferation seems to have potential importance^{14,46} as has been indicated by radiation therapeutic studies on animals with ^{125}I -deoxyuridine¹¹³. Rössler and co-workers⁶⁴ have found the concentration of ^{211}At in the tumour tissue to be 3 times higher than that of the corresponding radioiodine labelled compounds.

The labelling of red blood cells with ^{211}At may lead to selective α -irradiation of the spleen¹¹⁴ since damaged erythrocytes are rapidly captured by this organ.

The success of organ transplantation can also be influenced by ^{211}At -labelled surface membrane antigens /lymphocytes/. The defence mechanism of the recipient based upon specific recognition and destruction of non-self antigens by host lymphocytes

results in the rejection of the transplanted organ. This often lethal side-effect can be suppressed or avoided by specific elimination of immunocompetent lymphocytes which is, therefore, of paramount importance in transplantation attempts. Neirinckx and coworkers⁷³ were able to suppress to a considerable extent the rejection process by labelling baboon lymphocytes with ^{211}At . The mean survival time for the baboon group receiving astatine labelled lymphocytes has been found to be 3 times longer than that for the untreated group.

Organic molecules tagged with ^{211}At are, therefore, highly needed for biological studies aimed at practical applications in nuclear medicine. To produce controllable circumstances the two main problems chemists are facing in this field are: 1. building ^{211}At selectively into certain positions of appropriate biomolecules; 2. ensuring strong enough binding of astatine in these molecules, so that it remains stable under in vivo conditions. The loss of the ^{211}At label leads most probably to the spreading of α -radioactivity throughout the body thereby damaging healthy organs too.

It is not surprising, therefore, that parallel with the studies on potential immunological and therapeutic applications of ^{211}At quite a few reports have been published on the hazards involved. It has been found, for example that exposure of rats to sublethal amounts of astatine results in the appearance of numerous mammary tumours - including malignant ones¹¹². An extensive study¹¹⁵ of the metabolic effects and embryotoxicity of ^{211}At has shown increased embryo lethality, interuterine growth retardation and induced malformations. The first two effects were found comparable to that produced by external X-ray exposure of similar dose range. Lately, measurable loss of reproductive capacity of cultured mammalian cells in the presence of ^{211}At , even in extremely low concentrations, has been reported¹¹⁶.

Clearly, a great deal more work on the selective labelling of biomolecules with ^{211}At , to yield stable products and to provide knowledge on side-effects, is needed prior to the wide application of astatine compounds in human therapy.

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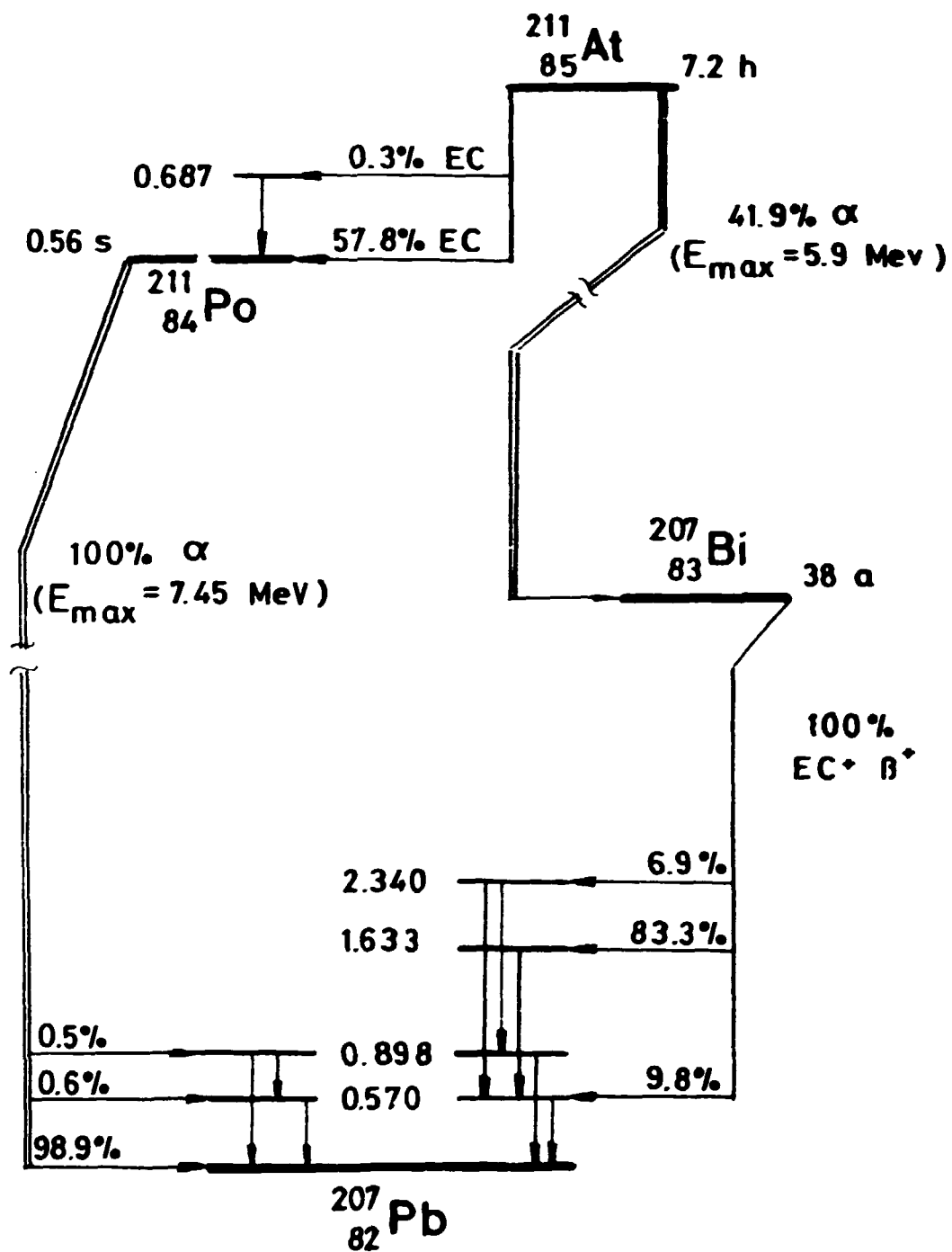


Fig. 1 Simplified decay scheme of ^{211}At after²⁹. Energy values in MeV

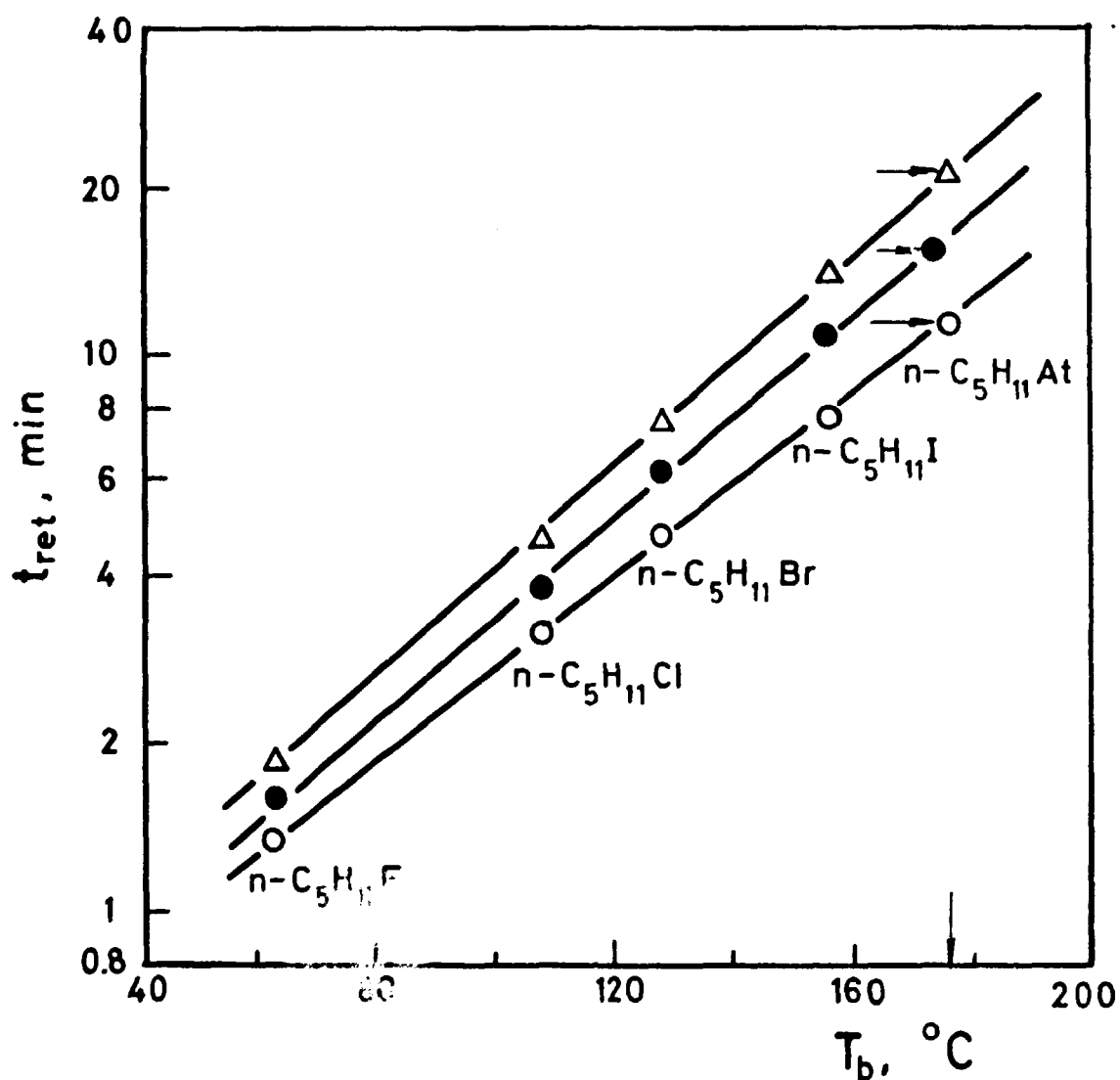


Fig. 2 Logarithmic retention time for *n*-pentylhalogenides, measured using dinonyl phthalate stationary phase at 140°C /Δ/, 150°C /●/ and 160°C /○/ vs respective boiling points of the compound.
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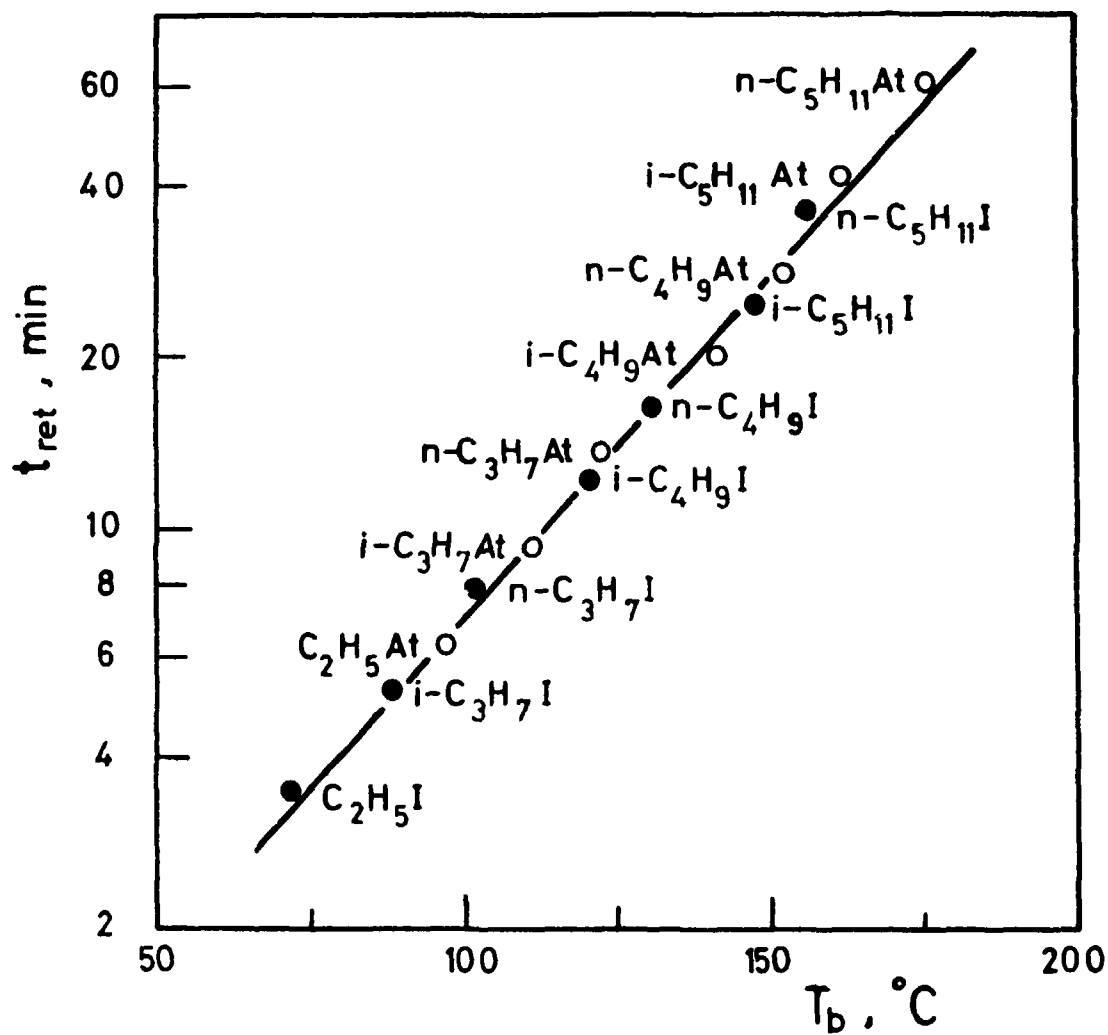


Fig. 3 Dependence of logarithmic retention time for alkyl iodides and alkyl aryl ethers measured using dinonyl phthalate on boiling points of the compounds⁵⁶.

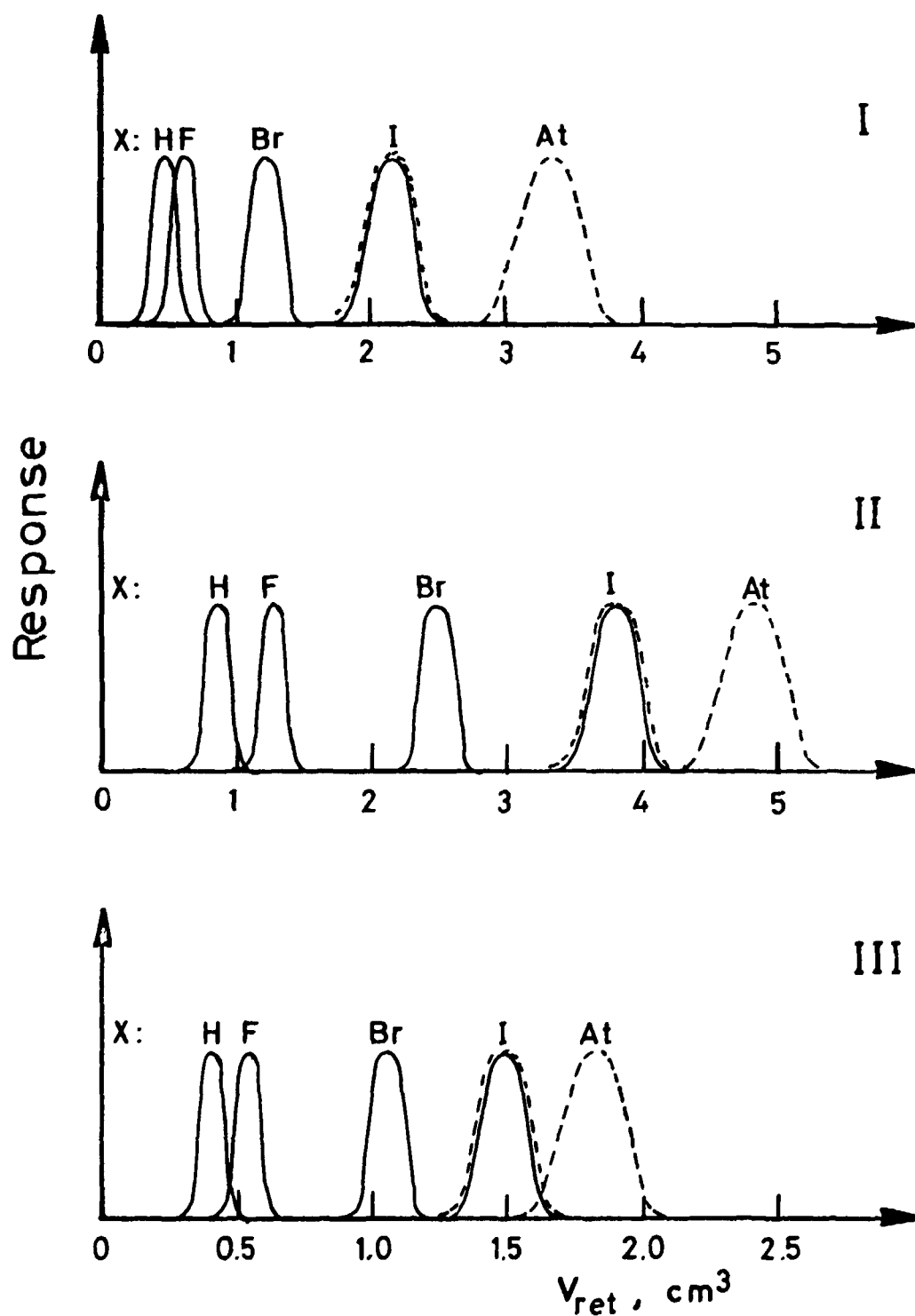


Fig. 4 Sequential analysis of uracil, 5-X-uracils/X=F,Br,I/ and carrier-free ^{125}I -uracil and ^{211}At -uracil using ion exchange HPLC. I. Aminex A7 at 25°C, 180 bar / 1.8×10^7 Pa/, with 0.05 M $KHSO_4$ eluent; II. Aminex A25 at 25°C, 50 bar / 5×10^6 Pa/, with 2 M $HCOOH$ eluent; III. Aminex A27 at 60°C, 30 bar / 3×10^6 Pa/, with 10^{-2} M $NaNO_3$ eluent.

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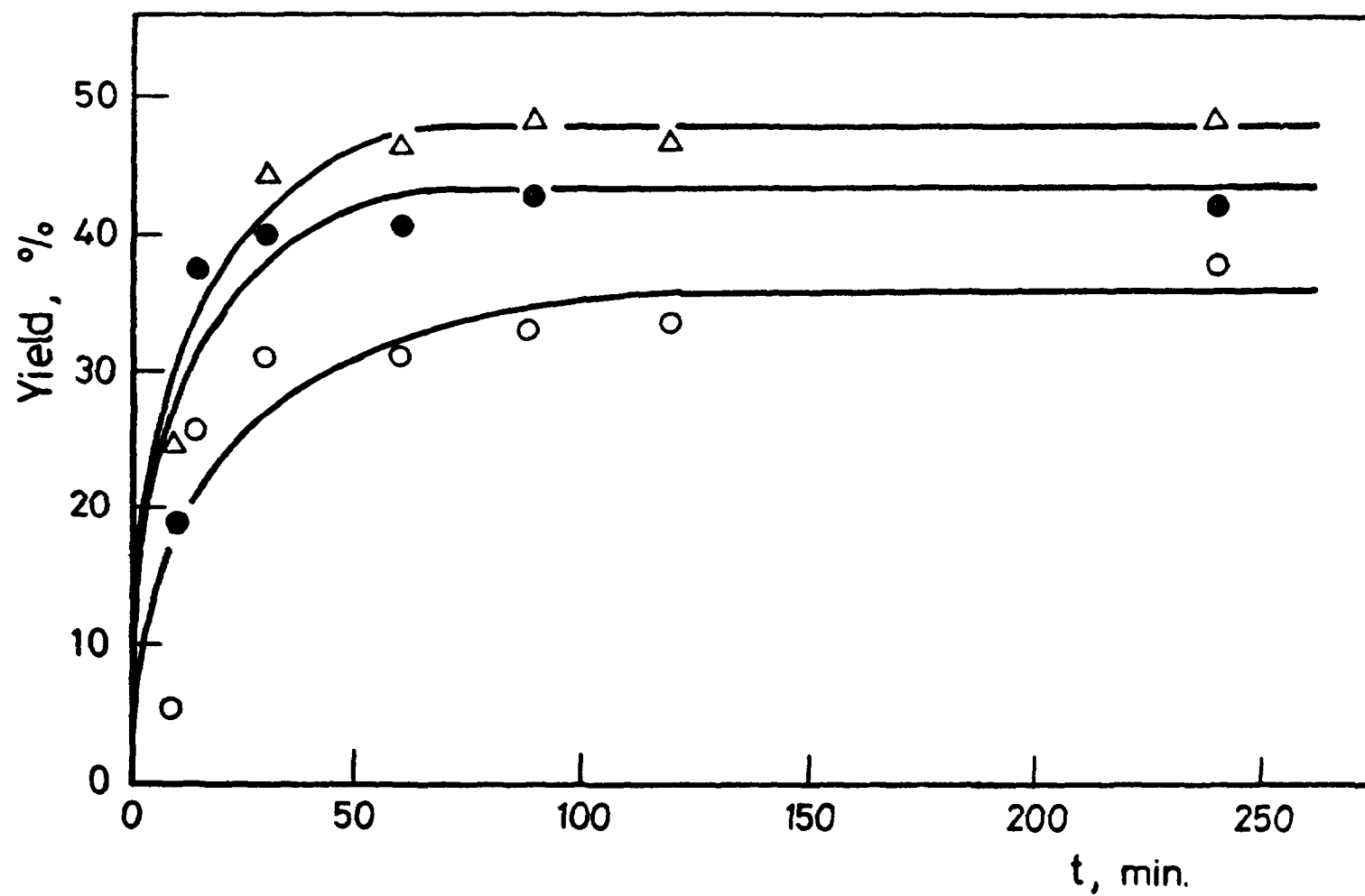


Fig. 5 Kinetic curves of electrophilic At^+ for H substitution in benzene⁸² at 80°C /○/ 100°C /●/ and 120°C /△/.

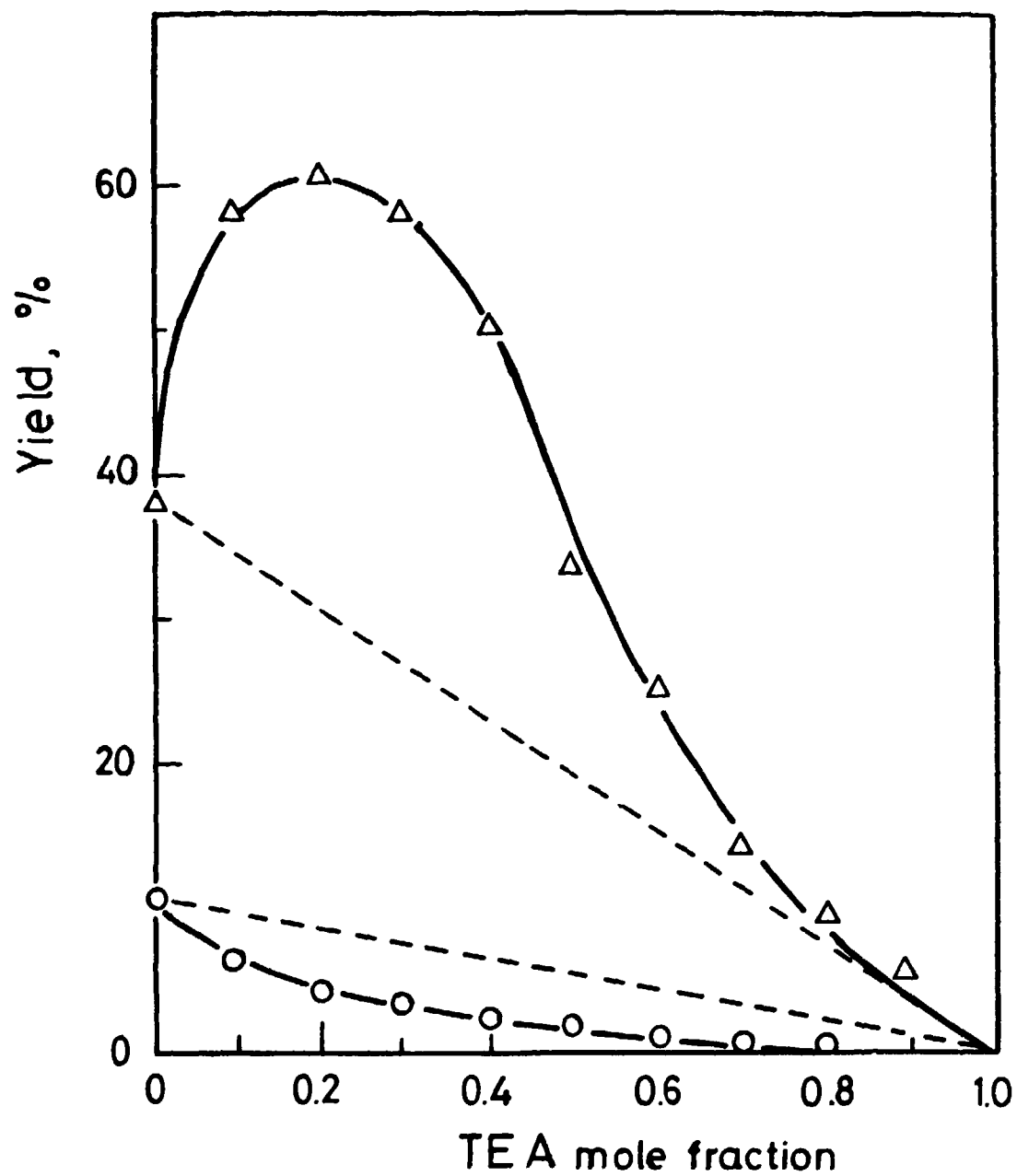


Fig. 6 Effect of dilution with triethylamine /TEA/ on ^{211}At for Cl (Δ) and ^{211}At for H ($\circ$) replacement in chlorobenzene⁹². /Dashed lines represent the theoretical dilution curves./

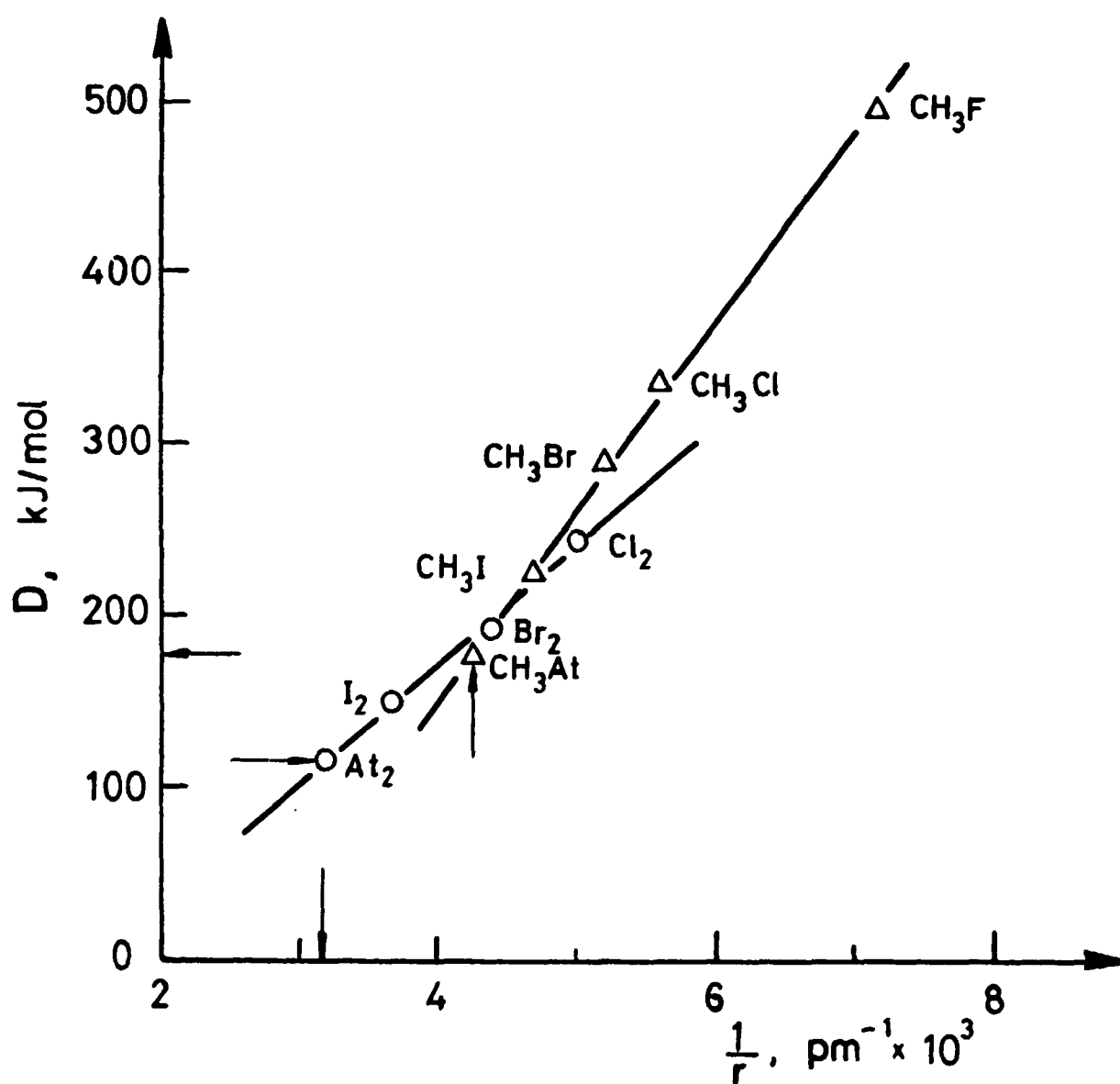


Fig. 7 Relationship between dissociation energy D and bond distance r for halogen molecules $\circ$ and methylhalogenides Δ . /Reproduced from L. Vasdros, K. Berei, Yu.V. Norseyev and V.A. Khalkin, *Magy.Kém. Folyóirat*, **80**, 487 /1974/, by permission of the Hungarian Chemical Society./

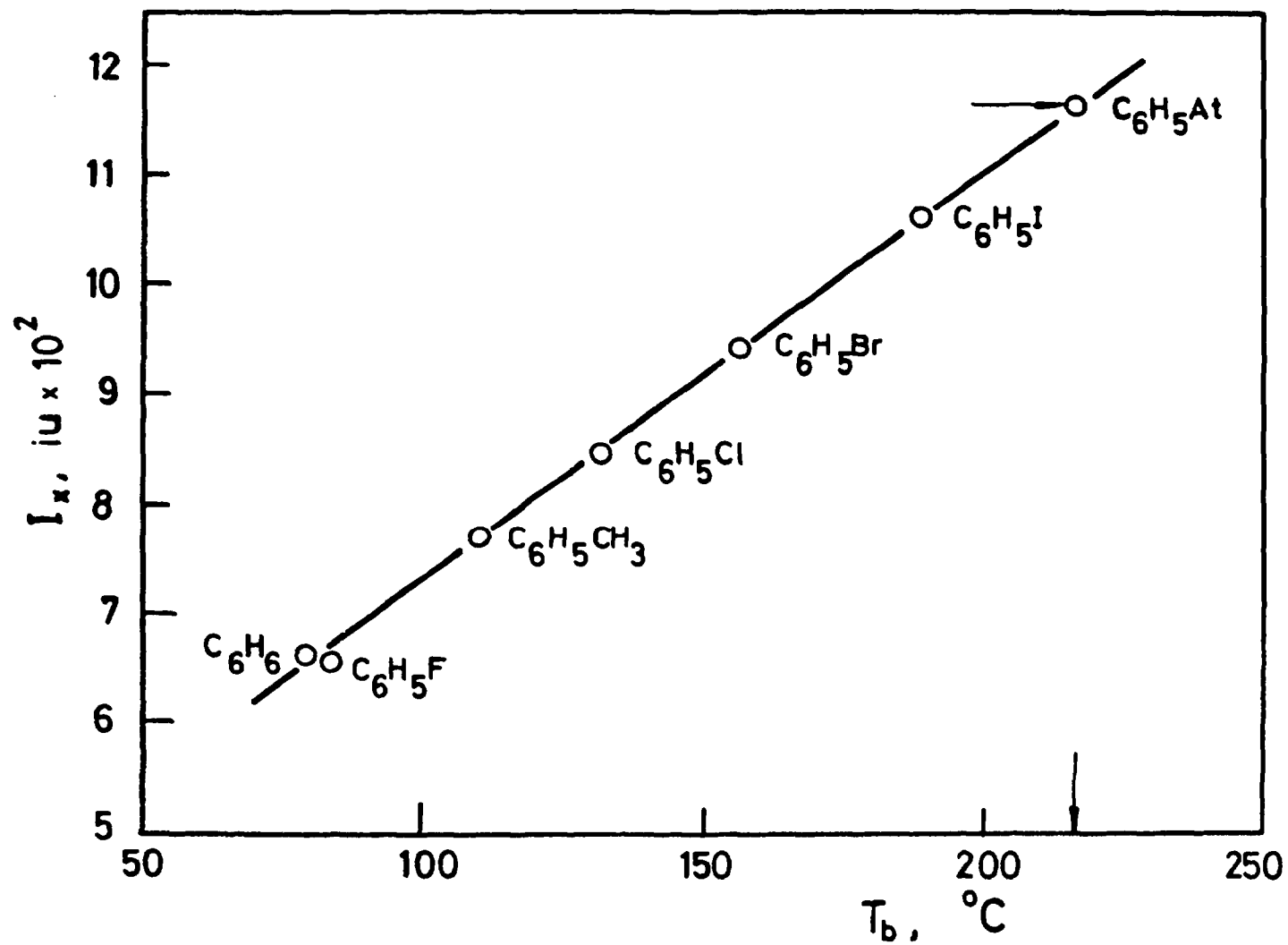


Fig. 3 Retention index values I_x measured using Squalane stationary phase vs boiling temperature of benzene, toluene and halobenzenes¹⁰³

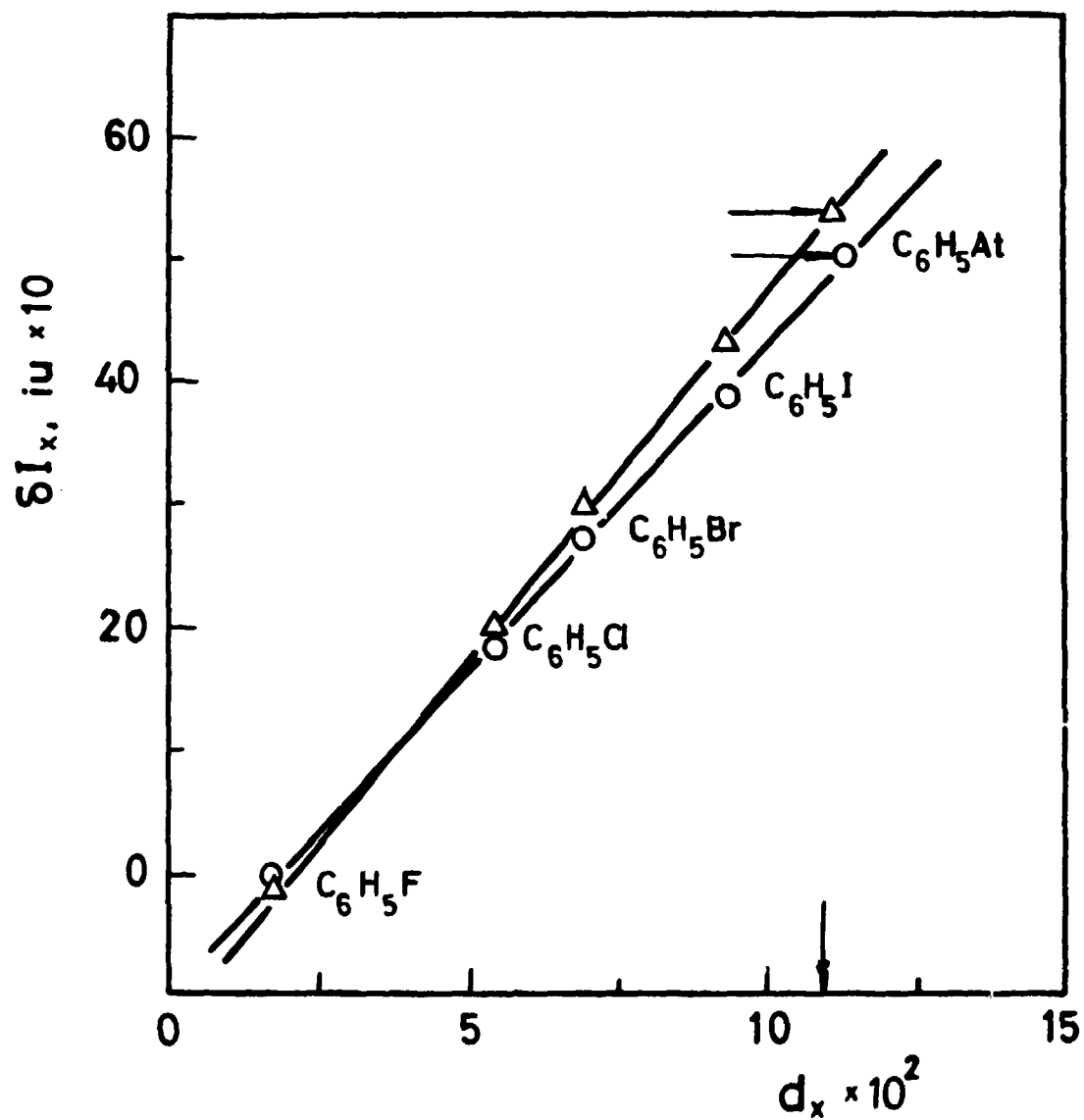


Fig. 9 Retention index increments for halobenzenes δI_x measured using Squalane /O/ and Apiezon Δ / stationary phases vs dispersity factors of corresponding halogens¹⁰³

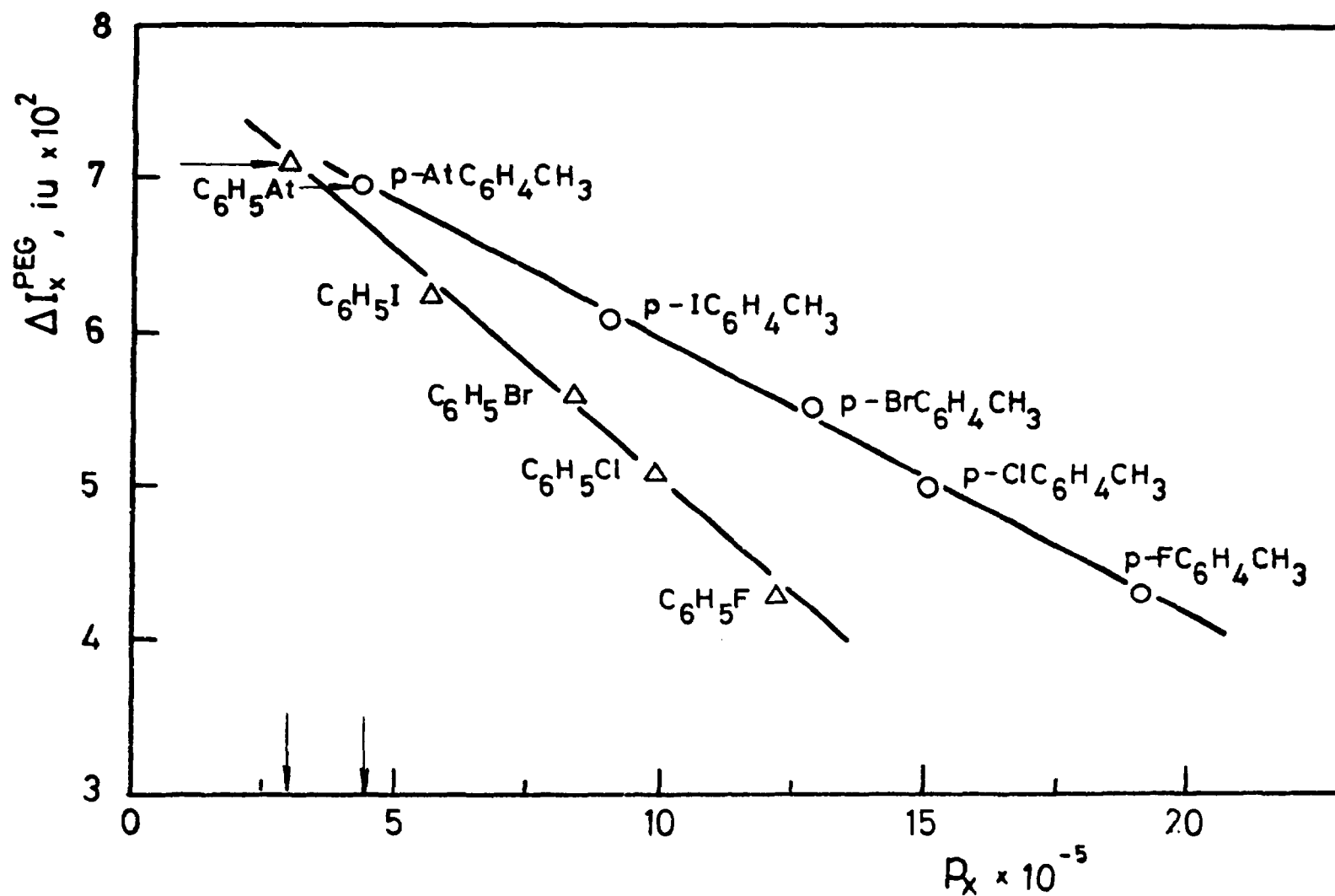


Fig. 10 Differences in retention indices for halobenzenes (Δ) and *p*-halotoluenes ($\circ$) measured using polyethylene glycol (PEG) compared with Squalane stationary phases
 ΔI_x^{PEG} as a function of polarity factors for the corresponding halogens¹⁰³

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