

Design and Synthesis of 2-Deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸FDG)

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THE FIRST SYNTHESIS of 2-deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸FDG) for human studies took place in 1976 the result of a collaboration between scientists at the National Institutes of Health, the University of Pennsylvania and Brookhaven National Laboratory which had begun three years earlier. ¹⁸FDG was developed for the specific purpose of mapping glucose metabolism in the living human brain thereby serving as a tool in the basic human neurosciences (Ido et al, 1978; Reivich et al, 1979). With ¹⁸FDG it was possible for the first time to translate the [¹⁴C]2-DG autoradiographic method (Sokoloff, 1979) to the clinical arena. Around the same time that ¹⁸FDG was developed, preclinical studies suggested the utility of ¹⁸FDG for studies of myocardial metabolism (Gallagher et al, 1977) and for tumor metabolism (Som et al, 1980).

In the first human studies and many that followed, ¹⁸FDG was synthesized at Brookhaven National Laboratory on Long Island and sent by small plane to Philadelphia Airport and then transported to the Hospital of the University of Pennsylvania where the first images of a human volunteer were made (Figure 1). In spite of the 110 minute half-life of fluorine-18 and the relatively low yields of ¹⁸FDG, this remote supply of ¹⁸FDG served to demonstrate its unique properties and its utility as a scientific tool for basic research and clinical diagnosis. In the next few years BNL supplied ¹⁸FDG to the Hospital of the University of Pennsylvania and also to the National Institutes of Health. Soon, however, most of the major institutions having a cyclotron produced ¹⁸FDG for their own use. It is remarkable that 25 years later, the production of ¹⁸FDG

at regional cyclotron-synthesis centers and its distribution to remote hospitals and other institutions for clinical use particularly in cancer is the major mode for supplying ^{18}FDG .

In this article we will highlight the major milestones in chemistry from the conceptual design through the evolution of its chemical syntheses. We note that there have been other reviews of various aspects of ^{18}FDG design and chemistry (Fowler and Wolf, 1986; Gatley et al, 1988) including a very recent article on ^{18}FDG chemistry (Beuthien-Baumann et al, 2000).

DESIGN OF ^{18}FDG : THE IMPORTANCE OF C-2

^{18}FDG was modeled after carbon-14 labeled 2-deoxy-glucose ($^{14}\text{C-2DG}$). 2-Deoxy-D-glucose (2-DG) is a derivative of glucose in which the hydroxyl group (-OH) on C-2 is replaced by a hydrogen atom (Figure 2). The biological behavior of 2-DG is remarkably similar to glucose, with a few important differences. Like glucose, 2-DG undergoes facilitated transport into the brain followed by phosphorylation by hexokinase because the hydroxyl group on C-2 is not a critical element for either of these processes. In contrast to glucose, however, metabolism does not proceed beyond phosphorylation because the hydroxyl group on C-2 is crucial in the next step, phosphohexose isomerase. As a result, 2-deoxy-D-glucose-6-phosphate is trapped in the cell providing a record of metabolism. In essence, removal of the hydroxyl on C-2 isolates the hexokinase reaction. This property of 2-DG was noted in 1954 by Sols and Crane (Sols and Crane, 1954) who remarked:

“2-deoxy-glucose possesses certain advantages over glucose as a substrate for experimental studies with crude preparations of brain and other tissue hexokinases. The phosphate ester formed from 2-deoxyglucose is not inhibitory and it is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase. Thus, the use of 2-deoxyglucose isolates the hexokinase reaction.”

The translation of the ^{14}C -2-DG method to humans required that 2-DG be labeled with an isotope which decayed by body penetrating radiation and that the chemical properties of the isotope and its position on the deoxyglucose skeleton would not significantly perturb its biochemical and transport properties. Of course, this could be achieved by isotopic substitution of stable carbon in the 2-deoxy-D-glucose structure with carbon-11, and this synthesis was accomplished shortly after the development of ^{18}FDG (MacGregor et al, 1981). However, fluorine-18 was chosen for initial studies both because the C-F bond is a strong bond and because its 110 minute half life was sufficiently long for transport from Long Island to Philadelphia where the first human studies were carried out on the Mark IV scanner (Kuhl et al, 1977).

The design of an F-18 labeled version of 2-deoxyglucose hinged on substituting the F-18 on a carbon atom which would preserve the properties of the parent molecule. The choice of C-2 for the fluorine substitution was an obvious one. C-2, unlike other carbon atoms in the molecule, can be modified without interfering with either facilitated transport required to bring the molecule across the blood brain barrier (BBB) or the hexokinase reaction. It was also reasonable to assume that 2-deoxy-2-fluoro-D-glucose (FDG) would not be a substrate for phosphohexoseisomerase. Thus it was predicted that 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG) would be a good substrate for hexokinase and that, with the absence of a hydroxyl group on C-2, the phosphorylated product would be intracellularly trapped at the site of metabolism providing a record of metabolic activity which could be imaged externally (Figure 3). The development of ^{18}FDG was further supported by the fact that FDG had been synthesized in unlabeled form and shown to be a good substrate for hexokinase (Bessell et al, 1972). The importance of

substituting the fluorine atom on C-2 is illustrated by the dramatic reduction in affinity for hexokinase with 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose (Table 1).

In order to test the hypothesis that FDG would be a good model for 2-DG, FDG was labeled with C-14 (Ido et al, 1978). Autoradiographic studies with [¹⁴C]FDG in the rat gave similar results as those obtained for [¹⁴C]2-DG and phosphorylation by hexokinase also proceeded as predicted (Reivich et al, 1979).

These studies formed the groundwork for developing a synthesis for 2-deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸FDG) for studies of brain glucose metabolism in humans. However, ¹⁸FDG's unique high uptake in rapidly growing tumors (Som et al, 1980) as a result of enhanced tumor glycolysis (Weber, 1977) coupled with its low body background resulted in a very high signal to noise ratio to detect tumors in the body. The low body background from ¹⁸FDG is due on part to the fact that ¹⁸FDG which is not phosphorylated by hexokinase is excreted (Gallagher et al, 1978). This contrasts to the behavior of glucose which is not excreted due to resorption from urine to plasma via active transport across the renal tubule. The presence of a hydroxyl group on C-2 which occurs in glucose but not ¹⁸FDG is required for active transport (Silverman, 1970). This property of low body background resulting from ¹⁸FDG excretion which was not anticipated in the initial design of ¹⁸FDG for brain studies has elevated it to the forefront as a tracer for managing the cancer patient (Coleman, 2000).

FIRST SYNTHESIS OF ¹⁸FDG FOR ANIMAL AND HUMAN STUDIES

With ¹⁸FDG as a goal, the options for rapid incorporation of F-18 in the C-2 position were assessed. Fortunately, there were two syntheses for unlabeled 2-deoxy-2-fluoro-D-glucose in the chemical literature at the time that ¹⁸FDG was being developed. One of these involved the electrophilic fluorination of 3,4,6-triacetylglucal with the electrophilic fluorination reagent

trifluoromethylhypofluorite (CF_3OF) (Adamson et al, 1970) which was used in the synthesis of [^{14}C]FDG (Ido et al, 1978). The other synthetic approach to unlabeled FDG involved the use of potassium bifluoride (KHF_2) in a nucleophilic displacement reaction (Pacak et al, 1969). Though neither CF_3OF nor KHF_2 nor the synthetic schemes was directly applicable to the synthesis of ^{18}FDG , it was likely that elemental fluorine (F_2) could be substituted for CF_3OF based on initial reports that its reactivity could be controlled in diluted form (Barton, 1976). This approach was successful and the fluorination of 3,4,6-tri-O-acetylglucal with elemental fluorine represented a new synthetic route to unlabeled FDG (Ido et al, 1977). Fortunately the methodology for producing [^{18}F] F_2 by the irradiation of a neon target containing F_2 via the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ reaction using specially prepared nickel irradiation vessel had already been developed (Lambrecht and Wolf, 1973) and applied to the first synthesis of 5-[^{18}F]fluorouracil (Fowler et al, 1973). Thus electrophilic fluorination of 3,4,6-tri-O-acetyl-D-glucal with [^{18}F] F_2 produced a 3:1 mixture of the F-18 labeled 1,2-difluoroglucose isomer and the 1,2-difluoromannose isomers which were separated by preparative gas chromatography. The 1,2-difluoroglucose isomer was hydrolyzed in HCl to give ^{18}FDG (Figure 4). The yield was about 8%, the purity was >98% and the synthesis time was about 2 hours.

Because ^{18}FDG had never been administered to a human subject either in labeled or in unlabeled form, there was no adequate safety data to support administration to humans. The literature at the time had one report of an LD_{50} for FDG of 600 mg/kg in rats (Bessell et al, 1973). This was not sufficient to support human studies. Therefore toxicity studies were performed in mice and dogs with unlabeled FDG (Som et al, 1980). Doses of FDG were 14.3 mg/kg and 0.72 mg/kg administered intravenously at weekly intervals for 3 weeks for mice and dogs respectively. There was a control group, which was injected with vehicle for each species.

Mice were weighed weekly and at the end of 3 weeks they were sacrificed and their organs examined grossly and microscopically. For dogs, baseline, 2-hour, 1-week and 2-week blood and urine samples and a few CSF samples were obtained for analysis. At the end of 3 weeks the dogs were sacrificed and their internal organs were examined grossly and microscopically. Neither mice nor dogs that received FDG showed any gross or microscopic differences with their respective control groups. These results indicated that the anticipated dose of 1 mg of ^{18}FDG (0.014 mg/kg) could be safely administered to human volunteers. This was a factor of 150 times less than that administered to dogs and 3000 times less than that administered to mice without any evidence of acute or chronic toxicity.

Radiation dosimetry was estimated based on the tissue distribution of ^{18}FDG in dogs sacrificed at 60 minutes and at 135 minutes post injection of ^{18}FDG (Gallagher et al, 1977). The target organ in these initial estimates was the bladder which received 289 mrem/mCi (Reivich et al, 1979). These estimates were later refined when human distribution and excretion data became available (Jones et al, 1982).

These developments: the design of ^{18}FDG based on a knowledge of structure-activity relationships; the synthesis of $[^{14}\text{C}]$ FDG (Ido et al, 1978); autoradiographic comparison of $[^{14}\text{C}]$ FDG and $[^{14}\text{C}]$ 2-DG (Reivich et al, 1979); the synthesis of ^{18}FDG (Ido et al, 1978) toxicological studies of FDG (Som et al, 1980); biodistribution of ^{18}FDG in mice and dogs (Gallagher et al, 1977); and dosimetry calculations (Reivich et al, 1979) all combined to support the first studies in humans.

IMPROVEMENTS AND A MAJOR MILESTONE (1976-1986)

During the next 10 years after the development of the electrophilic route to ^{18}FDG , its utility as a radiotracer in the neurosciences and in the diagnosis of heart disease and cancer grew.

This stimulated the investigations of different synthetic methods to improve yields thereby to increase availability. Other electrophilic routes were developed and nucleophilic routes were sought (Table 2). The most useful of the electrophilic routes was labeled acetylhypofluorite ($\text{CH}_3\text{CO}_2[^{18}\text{F}]$) which offered advantages over $[^{18}\text{F}]F_2$ in terms of yield and experimental simplicity. Labeled acetylhypofluorite was readily synthesized via *in situ* formation in acetic acid or via gas-solid phase synthesis using $[^{18}\text{F}]F_2$. However, it was subsequently found that the stereospecificity of acetylhypofluorite was dependent on reaction conditions and solvent with one of the most commonly used methods giving ca. 15% of 2-deoxy-2- $[^{18}\text{F}]$ fluoro-D-mannose (^{18}FDM), an isomer with the fluorine atom occupying the axial position. A re-investigation and analysis of the product distribution from other fluorination reagents derived from elemental fluorine and showed that they all produce the mannose isomer in varying amounts (Bida et al, 1984). The synthesis producing the most acceptable product purity involved the gaseous $\text{CH}_3\text{CO}_2[^{18}\text{F}]$ fluorination of 3,4,6-tri-O-acetyl-D-glucal in freon-11. In this synthesis, the ratio of ^{18}FDG : ^{18}FDM was 95:5. Though the effect of using a mixture of ^{18}FDG and ^{18}FDM on glucose metabolic rate in the human brain has been reported to be negligible, the use of a mixture was less than ideal because the rate constants and the lumped constants for these two molecules could differ in a non-predictable fashion introducing a variable in human studies. A kinetic comparison of ^{18}FDG and ^{18}FDM in the rhesus monkey indicates that there is a 20% reduction in apparent cerebral metabolic rates for glucose when ^{18}FDM is used. If this is similar in humans, it was estimated that a 15% impurity of ^{18}FDM would lead to an underestimation of 3% in glucose metabolic rate (Braun et al, 1994).

In addition to the production of the F-18 labeled mannose isomer, there were other limitations to the electrophilic route to ^{18}FDG . The nuclear reaction commonly used to produce

[¹⁸F]F₂ was the ²⁰Ne(d, α)¹⁸F in a high pressure neon gas target to which a small amount of F₂ gas was added (Casella et al, 1980). The targetry to produce [¹⁸F]F₂ and its maintenance at the time was cumbersome and handling elemental fluorine, the most reactive of all elements, required special precautions. However, the major limitation was that under the best circumstances, only 50% of the label is incorporated into the product. This is also the case in the use of CH₃CO₂[¹⁸F] because half of the label is lost in the conversion of [¹⁸F]F₂ to CH₃CO₂[¹⁸F].

In terms of F-18 yield, another nuclear reaction the ¹⁸O(p,n)¹⁸F reaction, was far superior as can be seen when the cross sections are compared (Figure 5) (Ruth and Wolf, 1979). The adaptation of the ¹⁸O(p,n)¹⁸F reaction to a practical production method which would conserve the inventory of costly and occasionally rare O-18 enriched water stimulated the development of small volume enriched water targets which produced F-18 as [¹⁸F]fluoride in high yield (Wieland et al, 1986; Kilbourn et al, 1984). Methods for recovering O-18 enriched water for re-use have been reported including the use of an anion exchange resin (Dowex 1 x 10) which permits a 95% recovery of [¹⁸F]fluoride ion and a loss of ¹⁸O-enriched water of less than 5 μ l from a volume of 3 ml (Schlyer et al, 1990). With the availability of high yields of [¹⁸F]fluoride, the development of a high yield nucleophilic route to ¹⁸FDG became even more compelling. A number of approaches were reported prior to 1986 (Table 2). All of these were plagued with difficult steps including low incorporation of F-18 and difficulty in removing protective groups. Thus the electrophilic route, with its limitations, remained the method of choice through 1985.

A major advance in the synthesis of ¹⁸FDG from [¹⁸F]fluoride was reported in 1986 when it was discovered that kryptofix [2.2.2] could be used to increase the reactivity of [¹⁸F]fluoride (Hamacher et al, 1986). In essence, kryptofix masks the potassium ion which is the counterion of the [¹⁸F]fluoride. The reaction of [¹⁸F]fluoride with 1,3,4,6-tetra-O-acetyl-2-O-

trifluoromethanesulfonyl- β -D-manno-pyranose to give 1,3,4,6-tetra-O-acetyl-2-[¹⁸F]fluoro- β -D-gluco-pyranose gives a 95% incorporation of F-18 and the overall synthesis including purification proceeds in about 60% yield. The synthesis involves 2 steps, displacement with [¹⁸F]fluoride and de-protection with HCl (Figure 6). This was an almost perfect solution to the need to produce ¹⁸FDG in high yield and in high purity. It also produced ¹⁸FDG in no-carrier-added form and later ion chromatographic analysis of various preparations from this route showed the presence of FDG in a mass of 1-40 μ g (Allexoff et al, 1992). Thus this new method served an increasing need in the nuclear medicine and the neuroscience communities which were discovering new uses for ¹⁸FDG. It is also simple and amenable to automation and in the 15 years since it was reported, a number of automated synthesis modules have become commercially available (Satyamurthy et al, 1999).

¹⁸FDG SYNTHESIS (1986-PRESENT)

No major new developments have been made following this simple, high-yield nucleophilic route. However, a number of variants have been investigated to improve the displacement and the deprotection steps and considerable effort has been put into fine-tuning the reaction and to identifying impurities and contaminants which are carried through to the final product. This has become more critical with the increasing use of ¹⁸FDG in clinical practice where a pharmaceutical quality product is required.

One of the goals has been to optimize the removal of kryptofix 2.2.2 which is used to facilitate the displacement reaction. Methods have been reported for both the removal (Moerlein et al, 1989; Alexoff et al, 1991) and the detection (Ferrieri et al, 1993; Chaly and Dahl, 1989) of kryptofix. The simplest method to remove kryptofix is the incorporation of a short cation

exchange resin in the synthesis system so that the hydrolysate (HCl) passes through the cartridge before final purification (Alexoff et al, 1991).

Alternatives to the use of kryptofix 2.2.2 have been investigated in order to avoid its appearance as a contaminant in the final product. These include the use of tetrabutylammonium as the counterion (Yuasa et al, 1997; Brodack et al, 1988) as well as the development of a resin-supported form of [¹⁸F]fluoride for on-column fluorination (Toorongian et al, 1990). The latter method is synergistic with the use of an anion exchange resin to recover O-18 enriched water for re-use. Several kinds of polymer supported quaternary ammonium and phosphonium salts such as dimethylaminopyridinium or tributylphosphonium have been systematically examined for the on-column synthesis of ¹⁸FDG (Ohsaki et al, 1998).

Alternatives to deprotection with HCl have also been investigated. The use of a cation exchange resin was investigated and reported to efficiently hydrolyze the acetylated labeled precursor in 10-15 minutes at 100 degrees thereby eliminating the need for a neutralization step in the synthesis (Mulholland, 1995) and also serving to remove kryptofix 2.2.2. The use of base hydrolysis in the deprotection step has also been investigated as an approach to reduce the need for high temperatures and to decrease the synthesis time. Though epimerization at C-2 is a known reaction of aldoses under basic conditions and in this case would produce ¹⁸FDM as a radiochemical impurity (Varelis and Barnes, 1996), a systematic study of the reaction conditions for basic hydrolysis determined that epimerization could be limited to 0.5% using 0.33 M sodium hydroxide below 40 degrees for about 5 minutes. to avoid the neutralization step in the synthesis (Meyer et al, 1999).

2-Deoxy-2-chloro-D-glucose (ClDG) was identified as an impurity during ion chromatographic determination of the specific activity of ¹⁸FDG preparations from the

nucleophilic route (Alexoff et al, 1992). ClDG is produced as a competing displacement reaction with chloride ion which comes from different sources including HCl used in the hydrolysis step. In typical ^{18}FDG preparations, ClDG is present in a total amount of $<100\text{ }\mu\text{g}$ as is determined by ion chromatography and pulsed amperometric detection. Larger amounts are produced when larger amounts of the triflate precursor are used. The amount of ClDG can be reduced by using sulfuric acid instead of HCl for hydrolysis. The reduction of the amount of ClDG has also been an impetus for avoiding HCl in the hydrolysis step. Though ClDG does not present a toxicity problem, its presence is not desirable from the standpoint of pharmaceutical quality.

OUTLOOK

Advances in chemistry and the remarkable properties of ^{18}FDG have largely overcome the limitations of the 110 minute half-life of fluorine-18 so that ^{18}FDG is now available to most regions of the US from a number of central production sites. This avoids the need for an on-site cyclotron and chemistry laboratory and has opened up the use of ^{18}FDG to institutions which have a PET scanner (or other imaging device) but no cyclotron or chemistry infrastructure. Currently ^{18}FDG is used by many hospitals as an “off the shelf” radiopharmaceutical for clinical diagnosis in heart disease, in seizure disorders and in oncology, the area of most rapid growth. However, its ready availability has opened the possibility to also use it in more widespread applications in the human neurosciences including drug research and development (Fowler et al, 1999). This is an important application because with ^{18}FDG it is possible to determine which brain regions are most sensitive to the effects of a given drug. Because glucose metabolism reflects, in part, the energy involved in restoration of membrane potentials, regional patterns may be used to generate hypotheses as to which molecular targets are mediating the effects of the

drug. Also a baseline study can be run allowing intra-subject comparison before and after the drug. Since subjects are awake and alert at the time of the study, the behavioral and therapeutic effects of the drug and their association with metabolic effects can be measured. Though the use of a functional tracer like ¹⁸FDG is not as precise as the use of a radiotracer which is more specific for a given neurotransmitter system, it nonetheless provides a measure of the final consequences of the effects of the drug on the human brain. This is important because even though a drug may interact with a particular neurotransmitter, it may be the downstream consequences of that interaction which are of relevance to its pharmacological effects. When radiotracer availability permits, the ideal situation is to pair an ¹⁸FDG measurement with a neurotransmitter specific measurement and in that way to correlate neurotransmitter-specific effects with regional metabolic effects. ¹⁸FDG has many advantages as a scientific tool for preclinical studies in small animals when it is coupled with small animal imaging devices. Because the ¹⁸FDG method requires a ~30 minute uptake period before the imaging is actually done the animals can be awake during this period and anesthetized immediately before imaging, thus avoiding the effect of anesthesia on the behavior of the tracer.

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Figure Captions:

Figure 1. (clockwise from upper left) Synthesis of ^{18}FDG for the first human study (left to right, Tatsuo Ido, C-N Wan and Alfred P. Wolf); Delivery of ^{18}FDG to Philadelphia Airport (Tatsuo Ido and Vito Casella); ^{18}FDG injection and imaging in Mark IV scanner (Martin Reivich and Joel Greenberg); Brain images.

Figure 2. Structure of glucose, 2-deoxy-D-glucose (2-DG) and 2-deoxy-2-fluoro-D-glucose (FDG) showing modifications at C-2.

Figure 3. ^{18}FDG model compared to glucose and 2-DG. Note that replacement of the hydroxyl ($-\text{OH}$) group at C-2 does not alter facilitated transport or phosphorylation by hexokinase (HK) but does prevent metabolism beyond the phosphorylation step.

Figure 4. Synthesis of ^{18}FDG via fluorination with $[^{18}\text{F}]$ labeled elemental fluorine (Ido et al, 1978).

Figure 5. Comparison of fluorine-18 yields from the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ reaction and the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction (Casella et al, 1980; Ruth and Wolf, 1979).

Figure 6. Synthesis of ^{18}FDG via fluorination with $[^{18}\text{F}]$ fluoride ion (Hamacher et al, 1986).

Table 1. Substrate specificities for hexokinase. Note that substitutions at C-2 retain specificity for hexokinase while substitutions on C-3 and C-4 result in increases of more than 100 in Km.

Substrate	Hexokinase source	Km (mmol)	reference
D-glucose	Yeast	0.17	Bessell et al, 1973
2-deoxy-D-glucose	Yeast	0.59±0.11	Bessell et al, 1973
2-deoxy-2-fluoro-D-glucose	Yeast	0.19±0.03	Bessell et al, 1973
2-deoxy-2-fluoro-D-glucose	Bovine brain	0.2	Machado De Domenech and Sols, 1980
2-deoxy-2-fluoro-D-mannose	Yeast	0.41±0.05	Bessell et al, 1973
3-deoxy-3-fluoro-D-glucose	Yeast	70±30	Bessell et al, 1973
4-deoxy-4-fluoro-D-glucose	Yeast	84	Bessell et al, 1973

Table 2. Synthetic routes to ^{18}FDG (1976-1986).

[^{18}F]Labeled Precursor	Substrate	Reference
Electrophilic Methods		
$[^{18}\text{F}]F_2$	3,4,6-tri-O-acetyl-D-glucal	Ido et al, 1978
$[^{18}\text{F}]F_2 \rightarrow \text{CH}_3\text{CO}_2[^{18}\text{F}]$	"	Shiue et al, 1982; Adam, 1982; Diksic and Jolly, 1983
$[^{18}\text{F}]F_2 \rightarrow \text{CH}_3\text{CO}_2[^{18}\text{F}]$	D-glucal	Ehrenkaufer et al, 1984; Jewett et al, 1984
$[^{18}\text{F}]F_2 \rightarrow [^{18}\text{F}]XeF_2$	3,4,6-tri-O-acetyl-D-glucal	Shiue et al, 1983; Sood et al, 1983
Nucleophilic Methods		
$\text{H}[^{18}\text{F}] \rightarrow \text{Cs}[^{18}\text{F}]$	Methyl-4,6-O-benzylidene-3-O-methyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranoside	Levy et al, 1982; Levy et al, 1982
$\text{H}[^{18}\text{F}] \rightarrow \text{Et}_4\text{N}[^{18}\text{F}]$	Methyl or vinyl 4,6-O-benzylidene- α -D-mannopyranoside-2,3-cyclic sulfate	Tewson, 1983; Tewson and Soderlind, 1985
$\text{H}[^{18}\text{F}] \rightarrow \text{KH}[^{18}\text{F}]F_2$	1,2-anhydro-3,4:5,6-di-isopropylidene-1-C-nitro-D-mannitol	Szarek et al, 1982; Beeley et al, 1984
$\text{H}[^{18}\text{F}] \rightarrow \text{K}[^{18}\text{F}]$ Kryptofix 2.2.2	1,2,4,6-tetra-O-acetyl-2-trifluoromethanesulfonyl- β -D-mannopyranose	Hamacher et al, 1986

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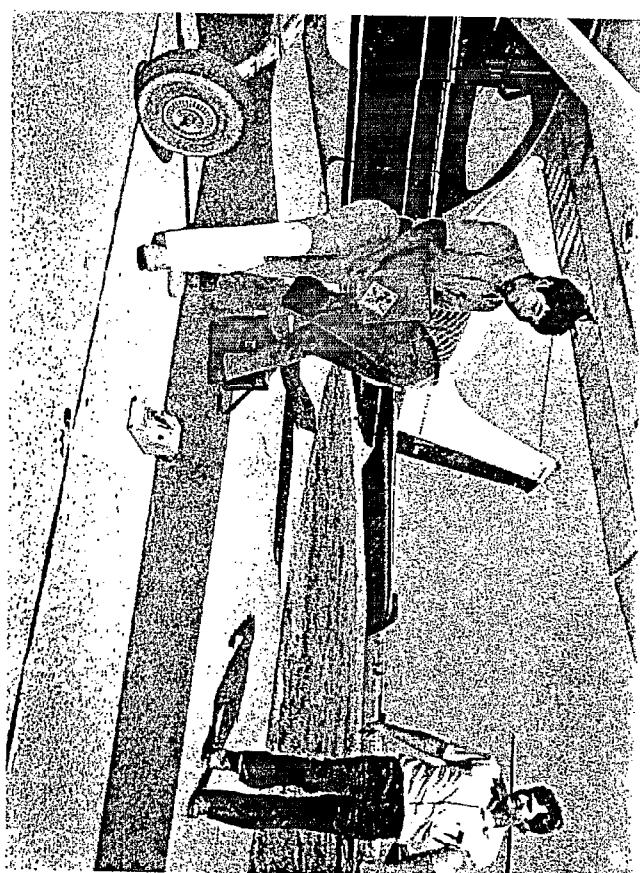
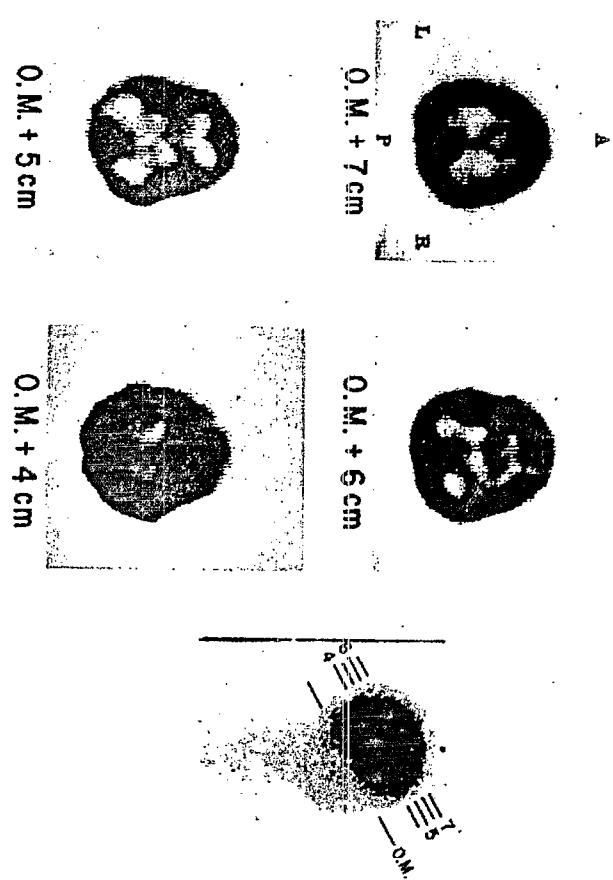
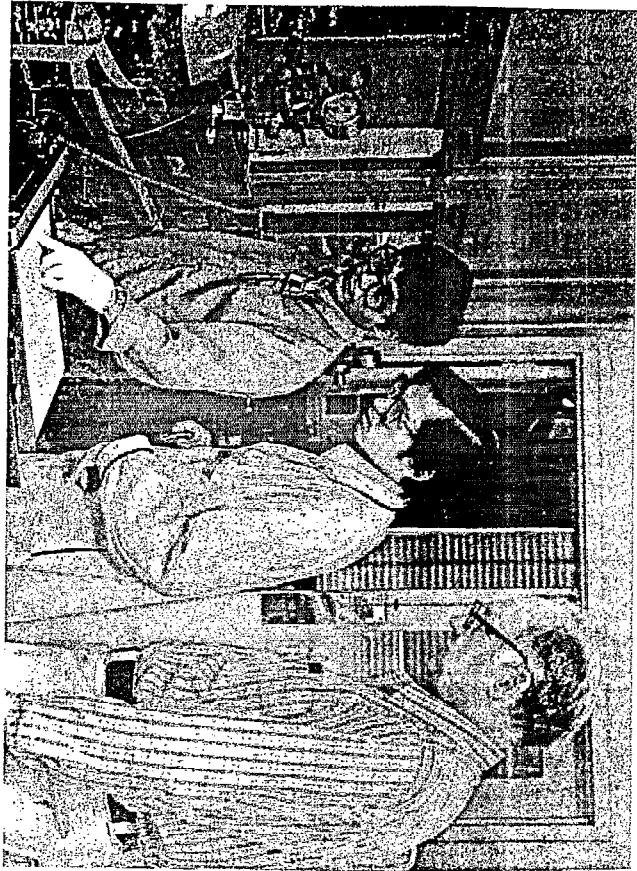
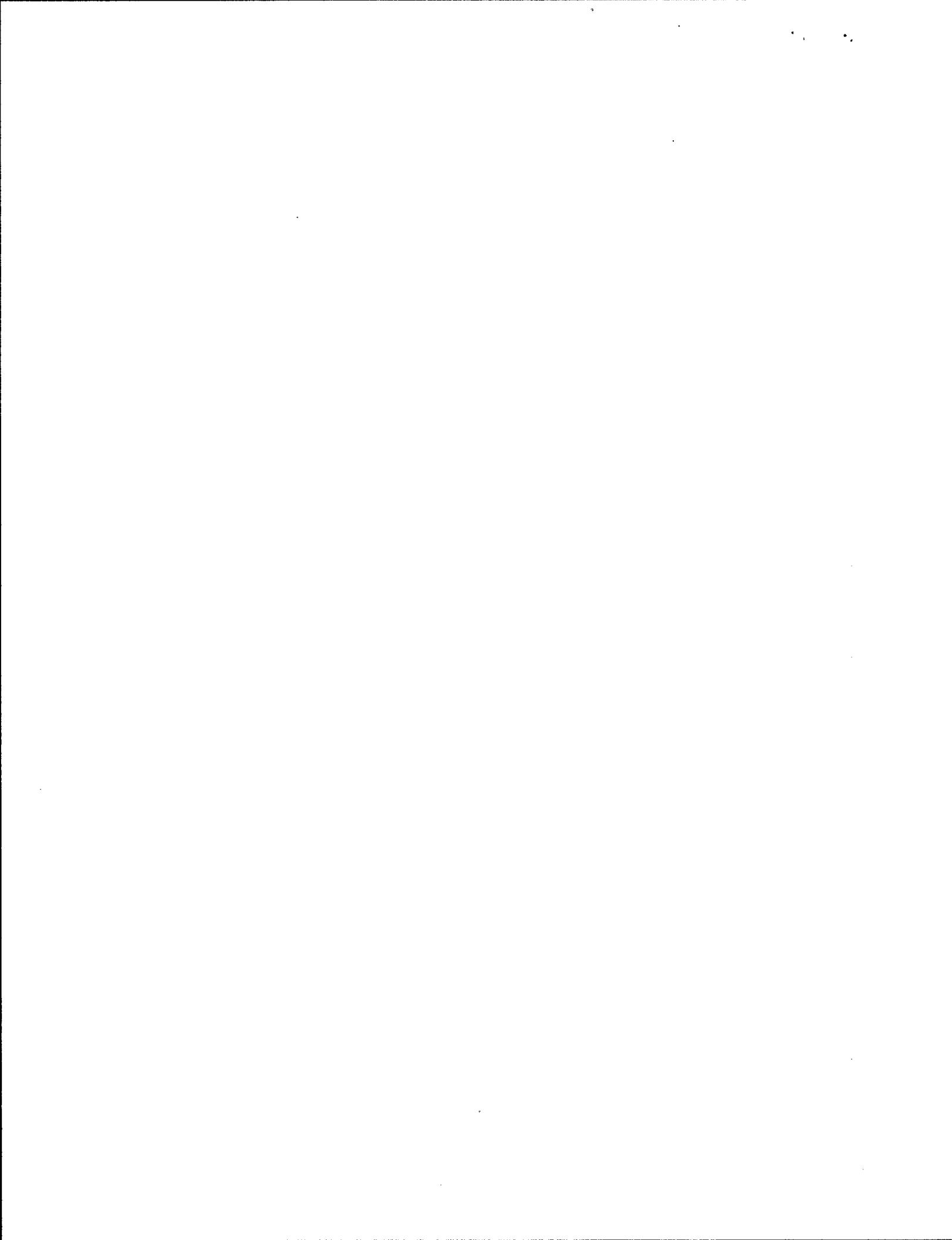


Figure 1



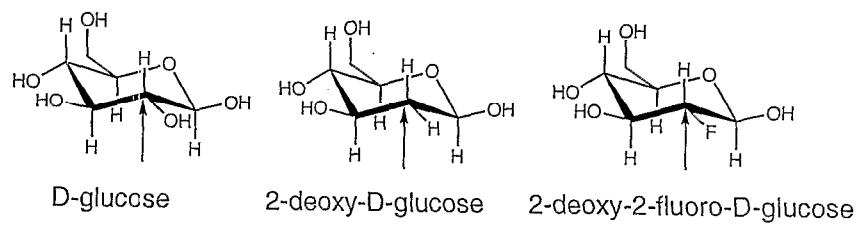
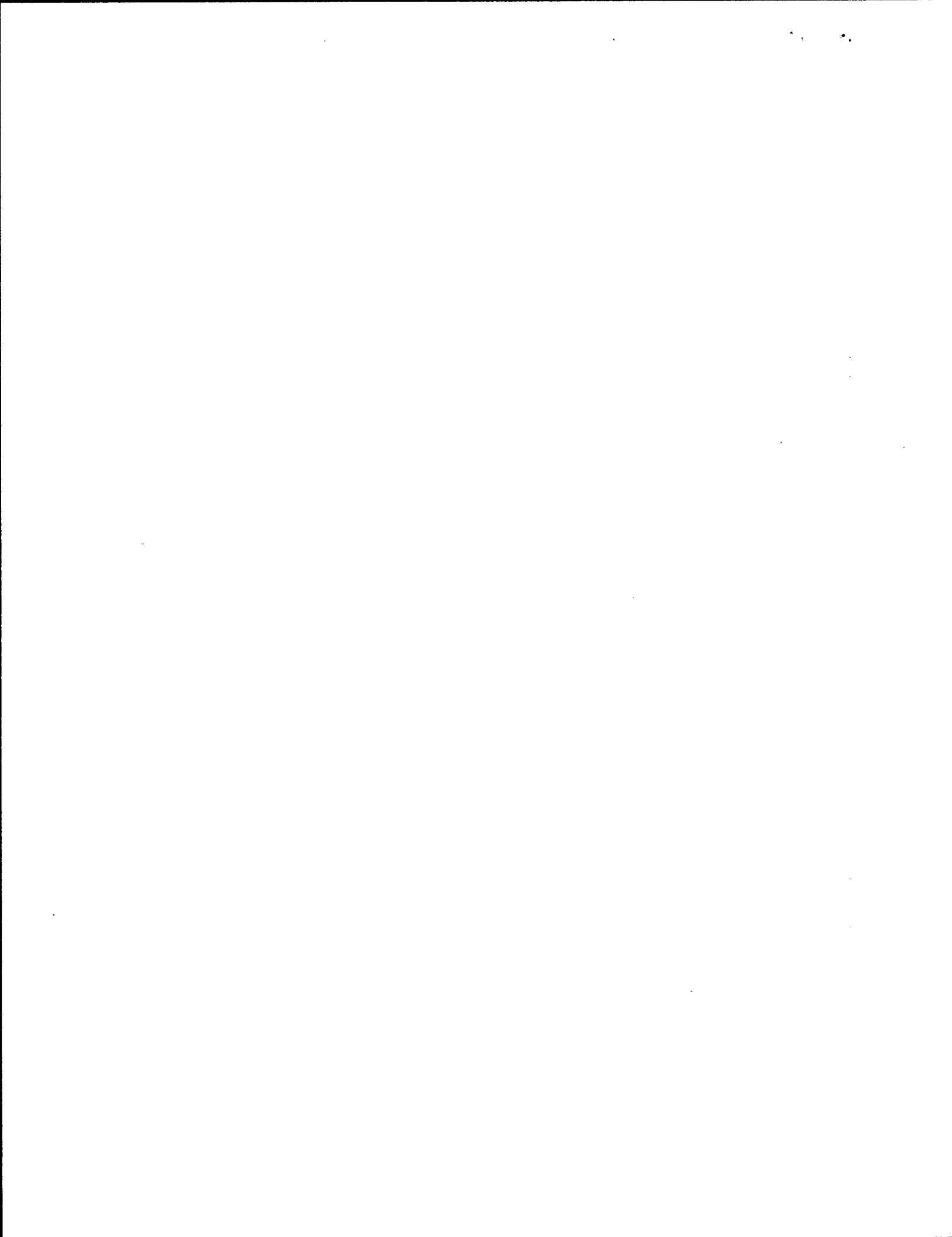


Figure 2



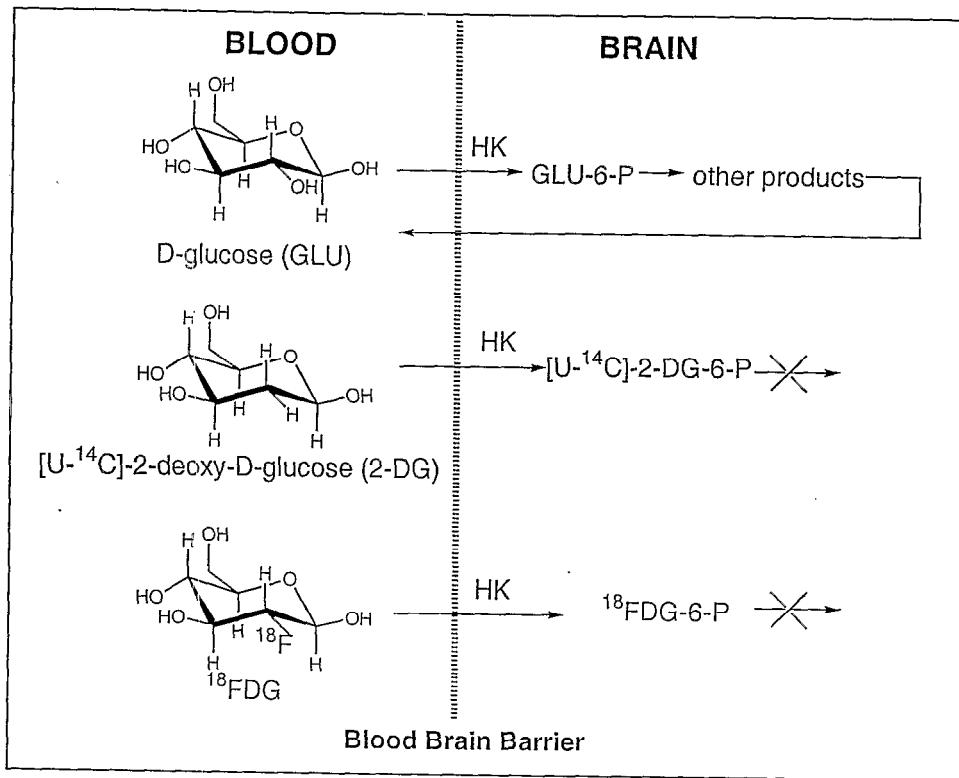
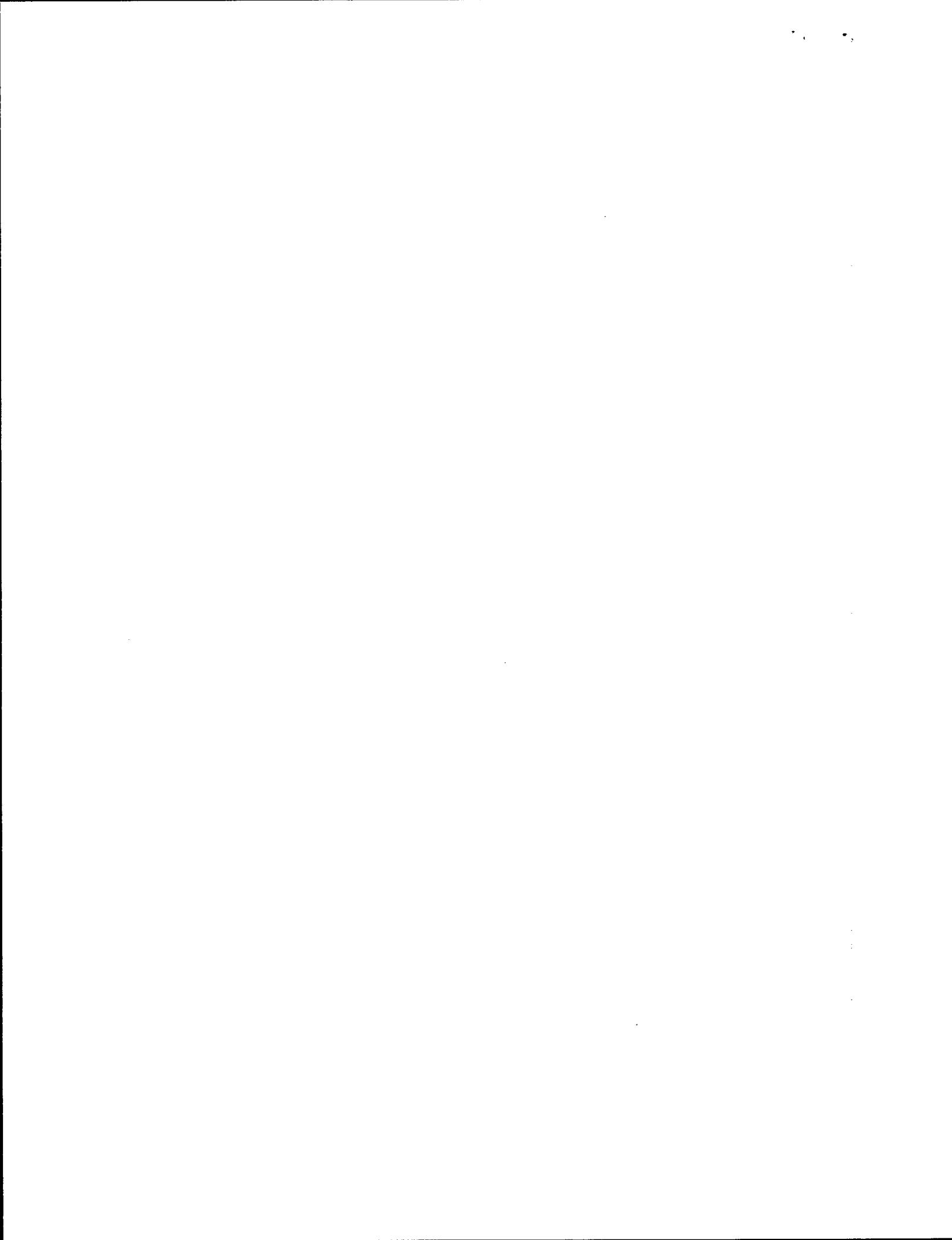


Figure 3



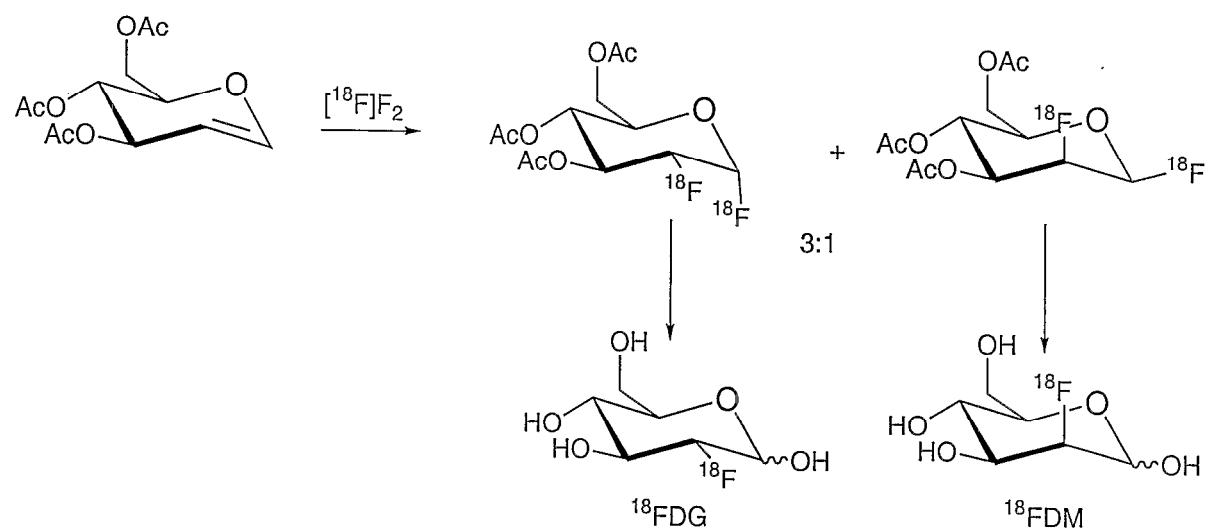
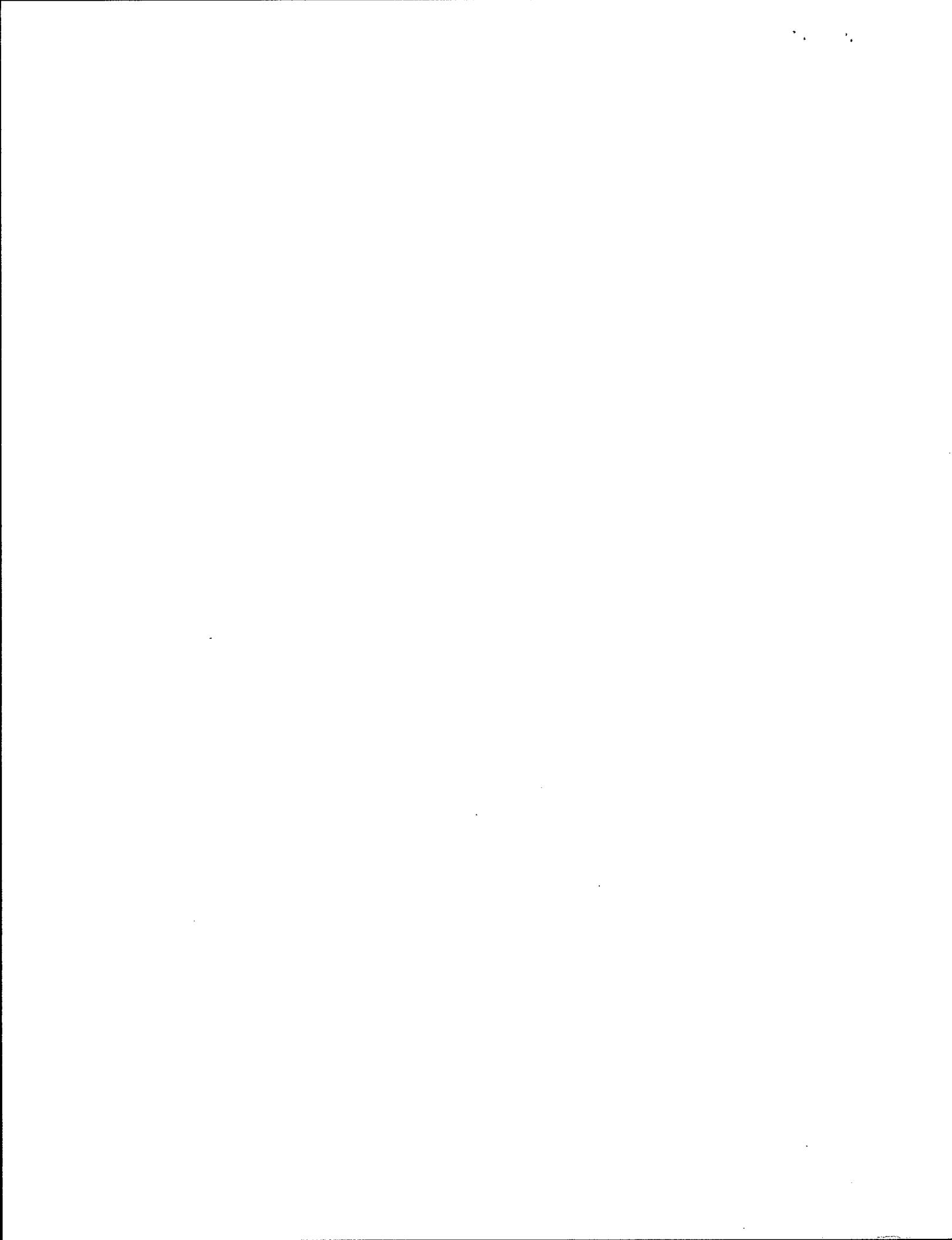


Figure 4



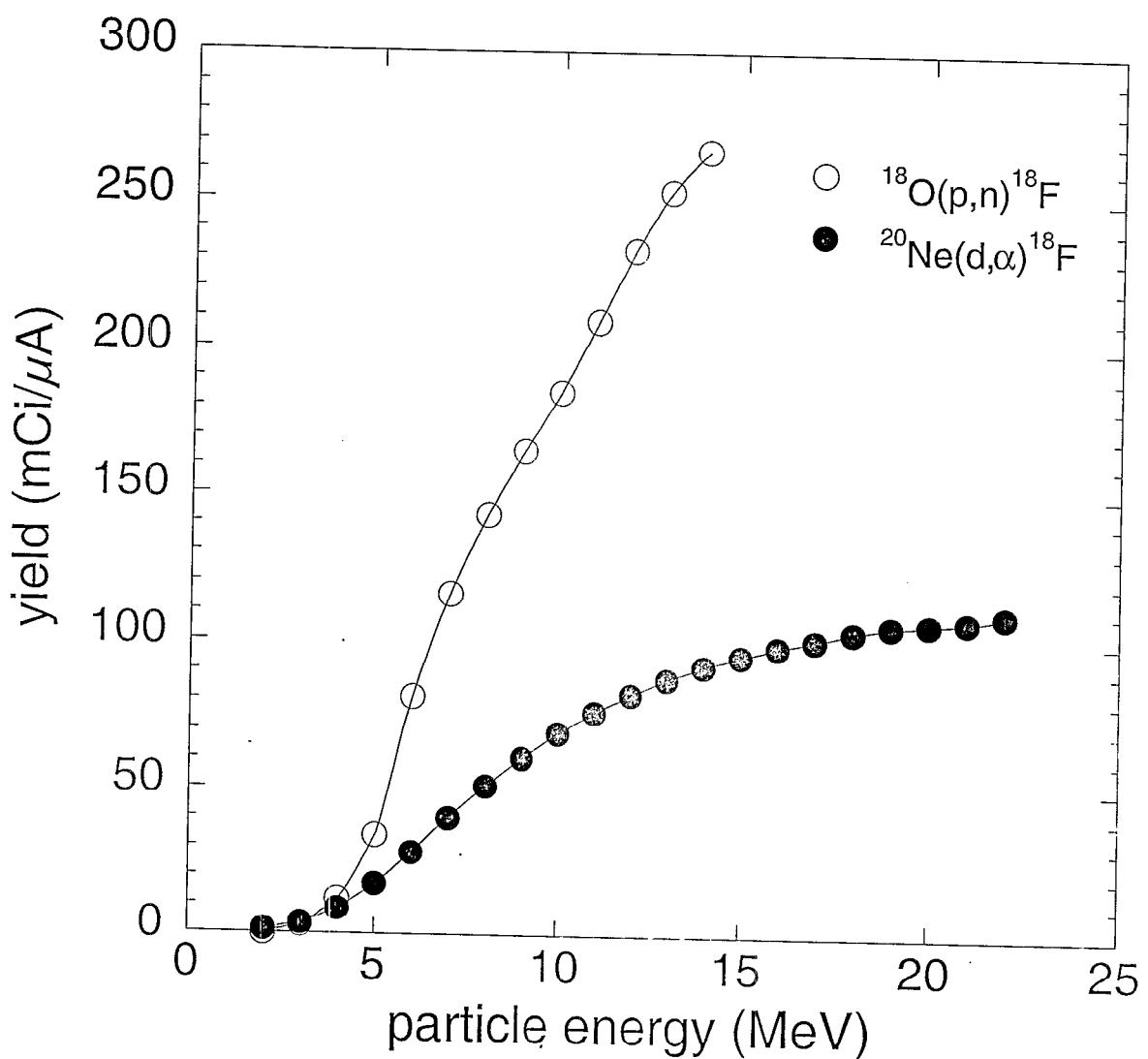
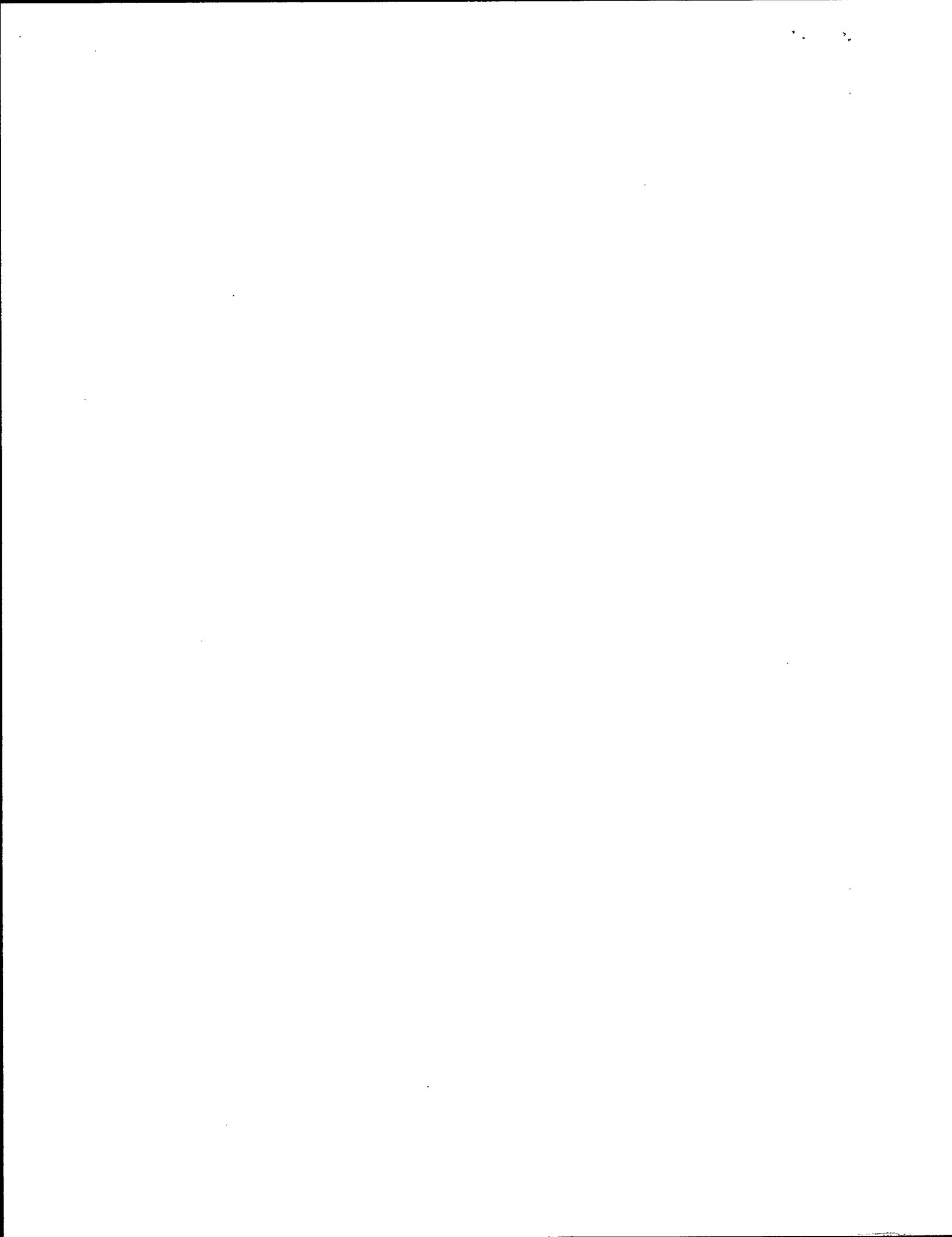


Figure 5



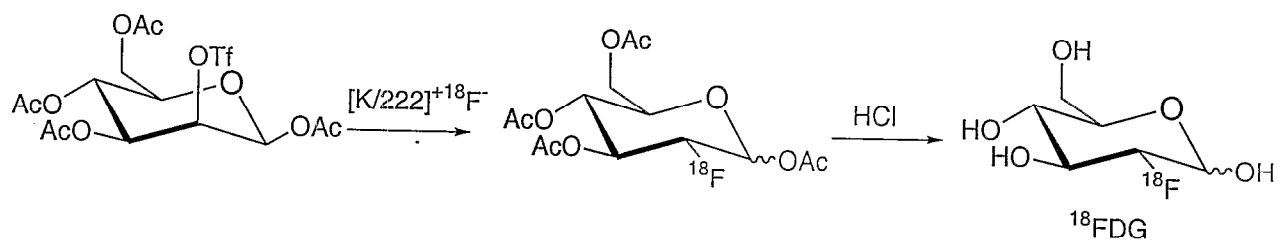


Figure 6

