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THE N.C.A. NUCLEOPHILIC ^{18}F-FLUORINATION OF 1,N-DISUBSTITUTED ALKANES AS FLUOROALKYLATION AGENTS

Dirk Block, Heinz Hubert Coenen, Gerhard Stöcklin

Institut für Chemie 1 (Nuklearchemie)
Kernforschungsanlage Jülich GmbH
Postfach 1913, D-5170 Jülich, FRG

SUMMARY

This systematic study describes the preparation of bifunctional n.c.a. ^{18}F-fluoroalkanes using aminopolyether (APE) supported nucleophilic substitution. With the APE (Kryptofix® 2.2.2.) potassium carbonate complex in acetonitrile n.c.a. $^{18}F^-$ is introduced into disubstituted alkanes ($X(CH_2)_nX$, n = 1-3, X = Br, OMes, OTos) in high yields within 10-15 min. The substitution yield increases in the sequence of leaving groups Br < OMes < OTos and with increasing alkyl chain length. At substrate concentrations of 0.025 M of bistosyloxyethane a radiochemical yield of 82 ± 8% of [1-^{18}F]-fluoroethyltosylate is obtained. This compound appears optimal as fluoroalkylation agent with respect to size, stability and ease of its preparation.

Key words: aminopolyether 2.2.2., nucleophilic n.c.a. ^{18}F-fluorination, bifunctional ^{18}F-fluoroalkanes, fluoroalkylation agents

INTRODUCTION

So far, nucleophilic substitution is the only efficient method to achieve no-carrier-added (n.c.a.) radiofluorination

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with fluorine-18 ($T_{1/2}$ = 110 min). A high specific activity is often needed for in-vivo radiotracer application using positron emission tomography (PET). This is especially true for receptor binding studies in man where ligands with specific activities of some 10 TBq/mmol are needed. Direct nucleophilic substitution with n.c.a. $^{18}F^-$ is often difficult in more complex molecules. An alternative method is the introduction of [^{18}F]-fluorinated prosthetic groups, for example via bifunctional alkanes which are prepared by nucleophilic exchange with n.c.a. $^{18}F^-$. An example is [^{18}F]-bromofluoromethane which was prepared by us using an aminopolyether (Kryptofix® 2.2.2.) activated fluorination system (1). First results on higher homologues of bifunctional alkanes as fluoroalkylation agents have recently been reported by us (2). Other examples have also been reported at the same meeting using triflate replacement in the presence of tetrabutylammonium hydroxide (3) or halogen replacement in the presence of the aminopolyether (APE) 2.2.2. system (4).

Earlier, systematic studies on the n.c.a. radiofluorination with APE/K^{18}F in aprotic dipolar solvents had been performed with monosubstituted aliphatic (4,5) and activated aromatic (6) model compounds. The method proved to be very fast and effective for high yield preparations of radiopharmaceuticals such as [17-^{18}F]-fluoroheptadecanoic acid (7) and [2-^{18}F]-fluorodeoxyglucose (8).

A systematic extention to the ^{18}F-exchange in 1,n-disubstituted alkanes of the form $X(CH_2)_nX$, where n = 1-3, was meant to elucidate the sterical and electronic neighbouring effects of nucleofugic substituents. In nucleophilic substitution reactions of geminal substituted compounds steric and electronic effects are known to play an important role (9,10). Alkanes with $n \geq 4$ are rather large prosthetic groups which would not

be attractive in pharmaceutical design because of steric reasons and have therefore not been examined. It was the goal of this study to find the optimal fluoroalkylation agent, both with respect to the ease of preparation and stability. Optimization of the reaction time, solvent and substrate concentration for fast labelling purposes had to be performed.

RESULTS AND DISCUSSION

Chain length and substituent effects. The previously determined optimal reaction conditions for an effective nucleophilic exchange with n.c.a. $^{18}F^-$, activated by a solution of the aminopolyether 2.2.2./K_2CO_3 complex in acetonitrile (> 10 mM) (5,7,11), were also used for the radiofluorination of disubstituted alkanes according to eq. 1:

$$\text{n.c.a. } {}^{18}F^- + X\text{-}(CH_2)_n\text{-}X \xrightarrow[MeCN]{(2.2.2./K)^+} {}^{18}F\text{-}(CH_2)_n\text{-}X + X^- \qquad (1)$$

In a first set of experiments the influence of the chain length in various disubstituted alkanes $X(CH_2)_nX$ was systematically studied. The results obtained with differently substituted alkanes (X = Br, OMes, OTos) under identical reaction conditions are listed in Table 1.

An increase of the radiochemical yield of the bifunctional [^{18}F]-fluoroalkanes is found with increasing chain length for all the three substituents. The increase is especially drastic when going from methyl- to ethyl derivatives. This is opposite to the reactivity of monosubstituted alkanes in S_N2 reactions (12). As expected, with n = 3 the bromine substitution is almost as efficient as in monosubstituted bromoheptane. The electronic activation by the -I substituent at the carbon where the exchange takes place, decreases when going from n = 1 to n = 3,

Table 1: Radiochemical yields of the n.c.a. ^{18}F-fluorination of disubstituted alkanes $X(CH_2)_nX$

X	% Radiochemical Yield n = 1	n = 2	n = 3
Br	0.1	16.4 ± 4	55.7 ± 8
TosO-	0.9	82.0 ± 8	89 ± 4
MesO-	1.1	77 ± 5	79 ± 3
for comparison: n-bromoheptane[a)]			65 ± 6

[a)] from ref. 5

(reaction conditions: 0.024 mmol substrate/ml acetonitrile
0.02 mmol APE 2.2.2./K_2CO_3; 82 °C,
10 min reaction time)

opposite to the large increase in fluorination yield. Obviously, the steric hindrance of substituents, especially effective in the pentavalent transition state of a S_N2 reaction on disubstituted methanes, decreases with chain length and appears to be the most important factor determining the nucleophilic reactivity.

The second important parameter influencing the fluorination yield is the nucleofugicity of the leaving group. The disubstituted alkyl iodides and triflates were not investigated in view of their poor stability and that of their fluorinated products, especially of the methylene derivatives (13). Even the preparation of symmetrical bistriflyloxyethane and -methane as starting material is not possible without complications (14). On the other hand, the effect of nucleofugicity with compounds of longer chain length is negligible as was observed in the case of monosubstituted alkanes (7,11). This can be understood considering the high reactivity of fluoride in the anion activated system with APE in acetonitrile. Thus mesomeric effects or the polarizability of the leaving group are only

of minor importance. With n = 3 all the three substituents exhibit similar reactivity considering the short reaction time of 10 min (cf. Tab. 1). The tosyloxy group does not show the highest nucleofugicity in the series of methylene derivatives as for n = 2 and 3. Apparently the smaller steric hindrance of the mesyloxy group compensates for the commonly lower nucleofugicity when compared to the tosylate. However, with the smallest substituent bromine, this effect does not balance its poor leaving ability in methylene bromide as shown in Table 1. Aiming at a small prosthetic group, further investigations were done with bistosyloxyethane since it exhibits a high stability and reactivity.

Effect of solvent polarity. The negative effect of increasing solvent polarity on the reaction rate in S_N2 substitution is well known (15). On the other hand, the APE has to be used in as high concentrations as possible to achieve a homogeneous solution rather than in trace amounts as phase transfer catalyst. Correlations of solvent parameters such as donor or acceptor number (DN, AN) or dielectric constant (ε) with the nucleophilic substitution yield of $^{18}F^-$ in monosubstituted alkanes have been examined (5,11). No correlation was found with the solvent polarity in heterogeneous systems (solid/liquid) with phase transfer catalysis (16). Considering the relatively low reactivity of disubstituted methanes and ethanes, high reagent concentrations and therefore solubilities and polarities of solvents were of special interest. Formation- and dissociation rates of APE potassium salt complexes are functions of solvent polarity (17) which therefore will also determine the reaction rate of n.c.a. radiofluorination with APE/K^{18}F.

The radiochemical yield of [^{18}F]-fluoroethyltosylate from the exchange of the ethylbistosylate with n.c.a. $^{18}F^-$ in five

different solvents are listed in Table 2 together with the empirical solvent polarity E_T (18) and the corresponding solubility of K^+ in the presence of APE 2.2.2. For direct comparison the amount of substrate, APE complex, solvent and the reaction time were kept constant. The reaction temperature was 82 °C, except for CH_2Cl_2 (65 °C). Table 2 clearly demonstrates the correlation between solvent polarity E_t at 30 °C, the solubility of the aminopolyether complex, and the radiochemical yield. Since high yields are found with high polarities, the expected solubility effect on the anion-activating APE complex is apparently much stronger than the interaction of the solvent molecules in the substitution step itself.

Table 2: Radiochemical yield of [^{18}F]-fluorotosyloxyethane and solubility of K^+ in the presence of APE 2.2.2. in solvents with various polarity $E_{T(30)}$

Solvent	Empirical Polarity [$E_{T(30)}$] [a)]	Solubility of K^+ [mmol/ml]	Radiochemical Yield [%]
Acetonitrile	46.0	0.068±0.004	82±8
Acetone	42.2	0.045±0.002	28±9
Dichloromethane [b)]	41.1	0.030±0.003	52±5
Chloroform	39.1	0.010±0.001	9±5
1,4-Dioxane	36.0	< 0.005	4±1

a) from ref. 18; b) at 65 °C

(reaction conditions: 0.024 mmol $TosOCH_2CH_2OTos$/ml acetonitrile; 0.02 mmol APE 2.2.2./K_2CO_3; 82 °C; 10 min)

In the solvents of low polarity the poor solubility of the salt complex causes heterogeneous reaction conditions, considering the constant amount at 0.04 mmol K^+ used in all solvents. The low reactivity of n.c.a. $^{18}F^-$ in the more nonpolar systems must

be attributed to partially undissolved 2.2.2./K^{18}F complex considering the even lower solubility of K^+ in the presence of 2.2.2./KF in acetonitrile of 0.040±0.004 mmol/ml. Previous considerations of wall losses by $^{18}F^-$ adsorption might therefore very well be a problem of solubilities.

An exception is acetone, where only small substitution yields were found in spite of the rather high polarity and solubility. Formation of unidentified side products observed here is probably due to the basicity of 2.2.2./K_2CO_3 in dipolar aprotic solvents ($pK_a \leq 19$) (19,20) which leads to deprotonation in acetone ($pK_a = 20$).

Effect of reaction time. While the anion activated fluorination of monosubstituted alkanes proceeds rather fast (5,7,8,11), the reaction rate in geminal substituted compounds is relatively slow. Decomposition was also observed for various substrates under the basic conditions employed here. The dependence of the radiochemical yield of the n.c.a. $^{18}F^-$-exchange in bistosyloxyethane and bistosyloxypropane on the time of reaction is shown in Fig. 1. Saturation yields of [^{18}F]-fluoroethyl- and [^{18}F]-fluoropropyltosylate are already obtained after 10-15 min with low substrate concentrations of 0.015 mmol/ml in acetonitrile at reflux. The exchange in the propyl derivative is somewhat higher in agreement with the above discussion on the effect of chain length. The radioactivity in form of $^{18}F^-$ exhibits a concommitant decrease, indicating activity balance and no formation of side products. Both the compounds are stable under reflux in acetonitrile up to 45 min as shown in Fig. 1. The relatively strong basic conditions in the presence of APE 2.2.2./K_2CO_3 (19,20) does not cause dehydrotosylation or dehydrofluorination. This favours the tosyloxy compounds as fluoroalkylation reagents for H-acidic compounds in the presence of

bases. Considering the decay rate of fluorine-18, however, the optimal reaction period is about 10 min, at which time the maximal uncorrected yields are formed.

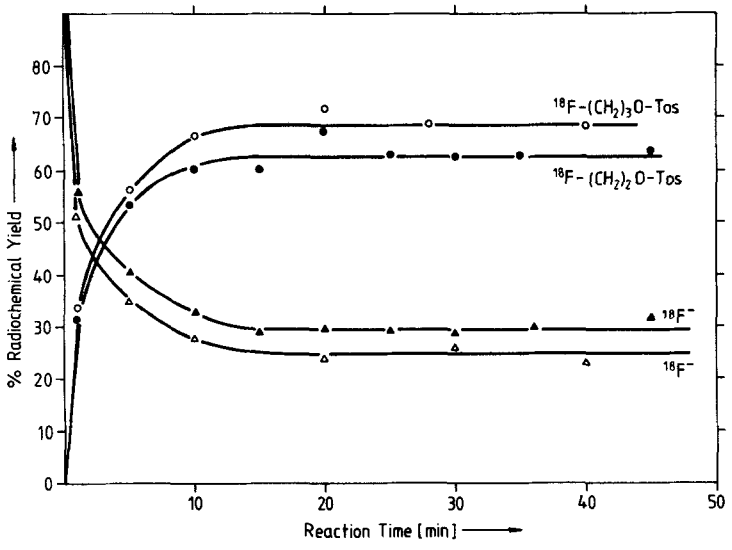

Fig. 1 Dependence of the n.c.a. radiofluorination yield of [^{18}F]-fluorotosyloxyethane and -propane on the reaction time.
(reaction conditions: 0.015 mmol substrate/ml acetonitrile; 0.02 mmol APE 2.2.2./K_2CO_3/ml; 82 °C)

Effect of substrate concentration. In agreement with a bimolecular reaction mechanism a dependence of the labelling yield on the concentration of the substrate was found. The effect of the concentration of disubstituted alkanes from 0.01 to 0.3 mmol/ml in acetonitrile at reflux is presented in Fig. 2 for bistosyloxyethane and -methane and bismesyloxymethane.

The [^{18}F]-fluoroethyltosylate reaches a maximum radiochemical yield of > 80% at precursor concentrations of > 0.025 mmol/ml. [^{18}F]-fluoromethylmesylate asymptotically approaches the same value only at 10 times higher concentrations. A maximum radiochemical yield of about 45% cannot be exceeded for [^{18}F]-fluoromethyltosylate since the solubility limit of

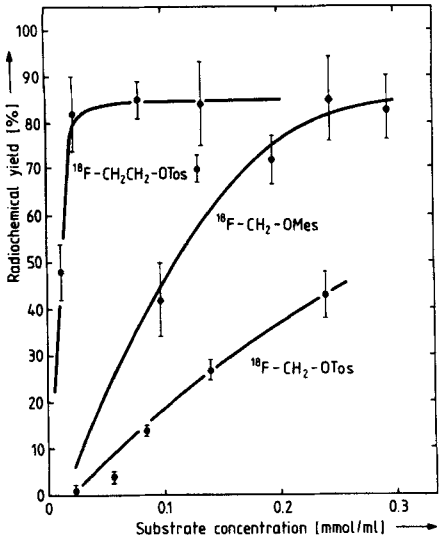

Fig. 2 Dependence of the n.c.a. radiofluorination yield of [^{18}F]-fluorotosyloxy- and -mesyloxy-methane and -tosyloxyethane on the substrate concentration.
(reaction conditions: 0.02 mmol APE 2.2.2./ K_2CO_3/ml acetonitrile; 82 °C; 10 min)

bistosyloxymethane in acetonitrile is reached at 0.25 mmol/ml. Fig. 2 clearly indicates that the yields in APE supported n.c.a. fluorination are strongly dependent on the substrate concentration. High absolute concentrations are often necessary in spite of the low amount of [^{18}F]-fluoride present (1 nM), i.e. the already high excess of substrate. A comparison with Tab. 1 demonstrates that a determination of the optimal concentration is mandatory for each individual substrate. Its solubility and the effect on the solubility of the APE salt complex are yield determining factors.

CONCLUSION

The aminopolyether supported nucleophilic n.c.a. fluorination can be successfully employed for the preparation of bi-

functional [^{18}F]-fluoroalkanes which are useful fluoroalkylation agents (21). The choice of the starting material with $n \geq 3$ is rather independent of the leaving substituent and can be made on the basis of economic or availability criteria. Symmetrical bistosyloxyalkanes, however, are advantageous with respect to the stability of educts and the corresponding monofluorinated products when compared to halides or triflates. Besides the lower fluorination yield of dihaloalkanes observed by us and others (4), the [^{18}F]-1-fluoro-n-bromoalkanes prepared from dibromoalkanes, 1-bromo-n-triflyloxyalkanes (3) or 1-bromo-n-tosyloxyalkanes (22) are less reactive alkylation agents. In contrast, bistosyloxyalkanes exhibit a high reactivity both in the fluorination and the alkylation reaction (21). This is especially true for ethane derivatives. Due to its small size [^{18}F]-fluoroethyltosylate appears to be the agent of choice as alkylating group. It can be produced in high radiochemical yields of > 80% within 10 min in refluxing acetonitrile at substrate concentrations of 0.025 mmol/ml. For different substrates and solvents optimal concentrations and the solubility of the APE 2.2.2./potassium salt complex have to be determined in order to avoid heterogeneous reactions with n.c.a. $^{18}F^-$.

EXPERIMENTAL

Materials. The aminopolyether Kryptofix® 2.2.2. (4,7,13,16,21,24-hexaoxa-1,10-diazobicyclo-8,8,8-hexacosan), the reagents and solvents were purchased from Merck (Darmstadt, FRG). The solvents used in the radiofluorination reactions were appropriately dried. The substrates for fluorination and the monofluorinated standard compounds were prepared when commercially not available.

Bistosyloxymethane, -ethane, and -propane were prepared from the corresponding diiodoalkane with a twofold molar ratio of p-toluolsulfonic acid silver salt in dry acetonitrile at reflux

for 24 hrs (23). Correspondingly, the bismesyloxymethane, -ethane, and -propane are synthesized from freshly prepared silver mesylate using a 10% excess with respect to the diiodoalkanes in dry acetonitrile at reflux for 12 hrs (23).

For the preparation of 1,n-fluorotosyloxy- and -mesyloxy-alkanes 1 mmol of the starting compound, 1.5 mmol KF and 10 mmol APE 2.2.2. were kept under reflux in dry acetonitrile for 2 hrs. After cooling the solution is concentrated in vacuo and the products were separated by column chromatography on silica gel Si-60 (Merck) and ether-hexane mixtures as eluant. The yield was 20-50% of the theory.

The identity of the prepared compounds was checked by comparison with ^{1}H-NMR literature data. The ^{1}H-NMR data for the new compounds are: fluorotosyloxymethane ($CDCl_3$): δ(ppm) = 7.75-7.25 (4H); 5.7 (d 2H, 50.4 Hz); 2.45 (s 3H) and fluoro-mesyloxymethane ($CDCl_3$): δ(ppm) = 5.86 (d 2H, 51 Hz); 3.3 (s 3H).

Radionuclide production and preparation of reactive fluoride. Fluorine-18 was produced via the $^{18}Ne(d,\alpha)^{18}F$ reaction in a Ne/H_2 gas target at the Jülich CV 28 compact cyclotron (24). The desired amount of aminopolyether 2.2.2. and K_2CO_3 was added to the aqueous solution of $^{18}F^-$. This mixture is evaporated to dryness in the reaction vessel under a stream of dry helium gas as described previously (1,5,7).

N.c.a. radiofluorination of 1,n-disubstituted alkanes. 0.01 to 0.3 mmol of the 1,n-disubstituted alkanes in 1 ml of dry (typically) acetonitrile was added to the cooled reaction vessel containing the dry APE 2.2.2./K_2CO_3 with typically 10 MBq n.c.a. $^{18}F^-$. The mixture was refluxed for a desired amount of time while magnetically stirred. Closing the reaction vessel with a septum allowed a reaction at higher temperatures than the boiling point and sample taking with exclusion of moisture. The radiochemical yields were determined by comparison

Table 3: HPLC conditions and k'-values of disubstituted 1,n-fluoroalkanes

Compound	Eluant	Column Material	k'-Value
Fluorotosyloxymethane	MeOH:H_2O 6:4 0.1% HAc	RP-18	3.4
Fluorotosyloxyethane	Hexane:1.2.Dichlorethane 2:1	Si60	1.4
Fluorotosyloxypropane	MeOH:H_2O 1:1 0.1% HAc	RP-18	5.1
Fluoromesyloxymethane	$CHCl_3$	Si60	1.0
Fluoromesyloxyethane	MeOH:H_2O 1:1 0.1% TEA	RP-18	1.5
Fluoromesyloxypropane	MeOH:H_2O 1:1 0.1% TEA	RP-18	4.5
Fluorobromoethane	MeOH:H_2O 6:4 0.1% TEA	RP-18	3.5
Fluorobromopropane	MeOH:H_2O 1:1 0.1% HAc	RP-18	7.0

of aliquots measured directly in a Packard Auto-Gamma scintillation counter and of discontinuously taken eluant fractions from a HPLC separation of a second aliquot. The HPLC separation of the individual radiofluorinated bifunctional alkanes was performed on 250 x 4 mm LiChrosorb Si60 or LiChrosorb RP-18 columns from Merck (Darmstadt). The corresponding eluants and k'-values of the reference compounds are listed in Tab. 3.

Solubility of APE 2.2.2./K_2CO_3. Identical to the drying procedure of n.c.a. $^{18}F^-$, 0.1 mmol of the aminopolyether K_2CO_3 complex were dried for 15 min in a stream of helium at 120 °C. 1 ml of the absolute solvent of interest was added and the solution heated to 82-85 °C for 10 min under vigorous stirring. The solution was filtered hot over a Millex HV (0.45 µm) filter (Millipore). The filtered solution was determined gravimetrically.

After evaporation the residue was dissolved in water and the content of potassium determined by atomic absorption spectroscopy (AAS). Identical solubilities within the experimental error were obtained by a radiochemical method using ^{42}K as a tracer.

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