FINAL DEGREE THESIS

SYNTHESIS AND CHARACTERIZATION OF TETRAPHENYLMETHANE DERIVATIVES

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TITLE: ***"SYNTHESIS AND CHARACTERIZATION OF TETRAPHENYLMETHANE DERIVATIVES"***

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RESUMEN:

En el presente Trabajo de Fin de Grado se ha llevado a cabo la preparación de compuestos derivados de tetrafenilmetano mediante métodos eficientes y que os permitan obtener nuestros productos sin hacer uso de purificaciones cromatográficas. Además de realizarse la síntesis de nuevos compuestos, se incluye la síntesis de todos los compuestos intermedios entre los que encontramos el tetraquis(4-nitrofenil)metano, tetraquis(4-aminofenil)metano y tetraquis(4-bromofenil)metano . El compuesto precursor de los nuevos compuestos sintetizados es el tetraquis(4-azidofenil)metano. Este compuesto es precursor para la construcción de complejos moleculares con geometrías tetraédricas. Gracias a la presencia del grupo azido en nuestro producto, se puedo llevar a cabo la síntesis de dos compuestos nuevos mediante el uso de la química click. De esta forma, dos nuevos compuestos con cargas positivas permanentes fueron sintetizados, uno con cuatro y otro con ocho cargas positivas. Ambos presentan además contraiones diferentes que influyen en la solubilidad del producto final.Parte de este trabajo también consta la parte dedicada a la caracterización de los compuestos, tanto intermedios como nuevos.

SUMMARY:

In this investigation, the preparation of compounds derived from tetraphenylmethane has been carried out using efficient methods allowing to obtain the products in sufficient chemical yield. In addition to the synthesis of new compounds, the synthesis of all intermediates is described, including tetrakis(4-nitrophenyl)methane, tetrakis(4-aminophenyl)methane, and tetrakis(4-bromophenyl)methane. The direct precursor for the new compounds is tetrakis(4-azidophenyl)methane. This compound is a precursor for the construction of molecular complexes with tetrahedral geometries. In addition, thanks to the presence of the azido group in the intermediate, it was possible to carry out the synthesis of two new compounds through the use of click chemistry. This way, new products containing permanent positive charges, one with four and the other with eight charges, were prepared. Both have counterions that, depending on their structure, influence the solubility of the product. This work also includes the part dedicated to the characterization of the compounds, both intermediates and new.

ABBREVIATIONS, ACRONYMS AND SYMBOLS USED:

Ac	Acetyl
Ar	Aromatic
cat.	Catalyst
Et	Ethyl
FC	Friedel-Craft reaction
HRMS	High resolution mass spectrometry
Me	Methyl
DMF	Dimethyl formamide
R_F	Retardation factor
RT	Room temperature
t	Time
THF	Tetrahydrofuran
TLC	Thin layer chromtography
Ts	Tosyl

Nuclear Magnetic Resonance (NMR)

b	Wide signal
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
J	Coupling constant
m	Multiplet
s	Singlet
t	Triplet
td	Triplet of doublets
tt	Triplet of triplets
δ	Themical shift
APT13C	^{13}C test subject to proton
COSY	Correlation spectroscopy
HMBC	Heteronuclear multiple bonds correlation
HSQC	Heteronuclear simple quantum correlation
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy

Infrared (IR)

a	Wide
d	Weak
f	Strong
m	Medium

Table of content

INTRODUCTION AND BACKGROUND

1. INTRODUCTION

A. TETRAPHENYLMETHANE AND DERIVATIVES

Tetraphenylmethane (Figure 1) is an organic compound consisting of a methane core with four phenyl substituents. Tetraphenylmethane derivatives are very important subunits in molecular construction. Such tetrahedral building blocks have been successfully incorporated in supramolecular networks and have also found use as precursors of click-based porous organic framework[1,2]. Few syntheses of different functionalized derivatives of tetraphenylmethane have already been reported. Currently known simple **tetraphenylmethane** derivatives (Figure 1) that are fully substituted in the *para* positions include the compounds **3, 4,** and **5**. Newly characterized derivatives, presented in the thesis, are click-based positively charged compounds synthesized by click reaction (see the next chapter) of the compound **5** with the appropriate negatively charged anchor.

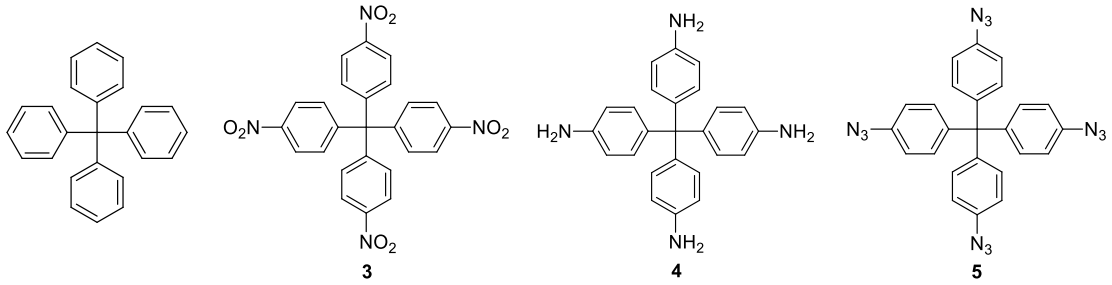


Figure 1: Synthesised already published compounds. Tetraphenylmethane, tetrakis(4-nitrophenyl)methane (3) , tetrakis(4-aminophenyl)methane (4) and tetrakis(4-azidophenyl)methane (5) from left to right.

B. CLICK CHEMISTRY

"Click chemistry" is a term to describe reactions that are high yielding, fast, simple to use, easy to purify, versatile and regiospecific, but not necessarily enantioselective[3]. The required process characteristics include the ability to occur in one pot, being not disturbed by water, generating the minimum and inoffensive products, or even it should be insensitive to oxygen. In addition, these kinds of reactions are available by using no solvent or a solvent that is benign or easily removed. Purification, if required, must be done by non-chromatographic methods, such as crystallization or distillation, and the product should be stable under physiological conditions [3].

Several reactions have been identified that fit the concept better than others. However, the reaction we are interested in is the one that involves [3+2]

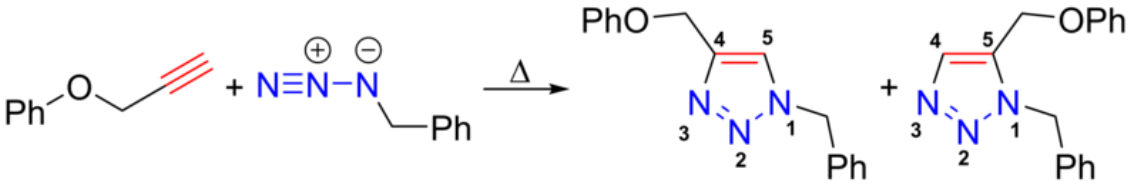


Figure 2: Click reaction thermally induced..

cycloadditions between azide and alkyne to afford the triazole product as a mixture of 1,4-adduct and 1,5-adduct under thermal conditions (Figure 2).

This reaction has been ignored for so long due to the low reactivity of azides as 1,3-dipole compounds. It is for that reason that a catalyst should be added. One of the options that we can use is the Cu^{I}-catalyzed cycloaddition of azides (**¡Error! No se encuentra el origen de la referencia.**) and terminal alkynes to form 1,2,3-triazoles. Moreover, this reaction exclusively forms the 1,4-substituted product, making it regiospecific. It typically does not require an elevated temperature but can be performed from 0 °C to 160 °C. The pH of the reaction is also not a problem because you can use a wide range between 5 through 12. In addition, the catalyst makes the reaction even 10^{7} times faster than the uncatalyzed one and the purification is based only on filtration. For these reasons, this reaction is excellent and very popular to bind covalently two components [4].

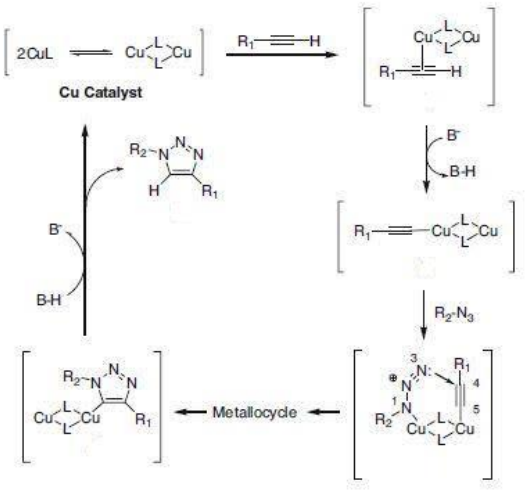


Figure 3: Mechanism of click reaction with copper as catalyst[(6)].

The Cu^{I} present as a catalyst is inserted into terminal alkynes (Figure 3). These alkynes will be deprotonated with a base, added in non-basic solvents, or not added if the solvent is water. After this step, the azido group is added to one of the copper atoms. Due to the proximity, nitrogen atom easily attacks the other carbon atom generating a metallocycle. Finally, the following protonation releases the Cu^{I} catalyst from the triazole product, recuperates the catalyst, and yields the 1,2,3-triazole compound[4, 5].

C. CHARGED ANCHORS

A charged anchor is a molecule or substance which is composed by charged groups, positively or negatively, allowing strong electrostatic binding to a solid support and a reactive ("clickable") group that allows covalent binding of active molecules to the anchor[6].

The general structure of these compounds contain quaternary ammonium groups chosen as the positively charged groups. Triple bond is chosen as binding part of the molecule. The "clickable group" (triple bond) allows the formation of covalent bonds with azido groups by means of so-called "click" reactions[4].

In our case (Figure 4), positively monocharged and double-charged anchors have been chosen to react with the **tetrakis(4-azidophenyl)methane** and generate multiply charged compounds[7].

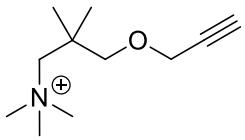
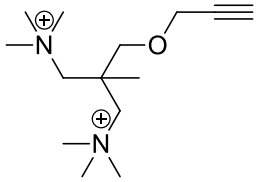
(a)  (b) 

Figure 4: Anchors that have been used to perform click reactions - (a) monocharged anchor, (b) double-charged anchor.

We worked with two anchors with one (Figure 4, compound (a)) or two (Figure 4, compound (b)) positive charges that also influence their properties. The higher number of charges will mean a stronger ionic bond of the anchor to surfaces or other negatively charged substrates[7].

2. BACKGROUND

One of this research group's objectives is to synthesize a new type of modifiers of solid phases used for chromatographic separations. The modifiers contain multiple permanently positively charged groups (anchors), allowing strong electrostatic binding to the negatively charged solid phases[8,9]. For this, charged compounds derived from neopentane and cyclodextrin units were designed that can be used to prepare chromatography columns for enantiomer separations. Influenced by the idea of an article based on the synthesis of microporous covalent organic frameworks (COFs)[10], which have great potential for the separation of small molecules, the synthesis of compounds that can be used to generate ionic organic frameworks (IOFs) is proposed. Following these lines, **tetraphenylmethane** was initially prepared, being the base compound of all subsequent syntheses. This compound evolved until it became **tetrakis(4-azidophenyl)methane** and later, through the use of catalysts and click chemistry, the synthesis **of charged derivatives from tetraphenylmethane** with **four** and **eight charges** were prepared. These new charged compounds present the possibility of being assembled with negatively charged compounds to produce IOFs and that could be used for the separation of molecules depending on the pore size created.

OBJETIVES AND WORKING PLAN

3. OBJECTIVES AND WORKING PLAN

In accordance with the competences included in the teaching guide for the Final Research Project in Chemistry at the University of Zaragoza (UZ), when the project is carried out in a research laboratory, the following general ACADEMIC OBJECTIVES are set:

- Know and use the usual working methods in a research laboratory, following the basic safety rules: use of a vacuum / argon line; work at variable temperatures, use of anhydrous solvents, etc.

- Characterize the prepared compounds through different appropriate techniques, interpreting and relating the results obtained. Where possible, use the permitted instrumentation.

- Develop critical capacity and initiative to solve scientific problems. Adapt yourself to cooperative work, interact with colleagues, and participate in common tasks in a chemical research laboratory.

- Prepare a scientific report that collects the specific research results and the discussion of them in a concise and rigorous way, as well as the bibliography that frames the work carried out in their area, acquiring knowledge of the current state of it.

To achieve these objectives, considering the precedents discussed in the Introduction, the following WORK PLAN was proposed.

I. Develop and synthesize the **tetrakis(4-azidophenyl)methane** through easy and cheap reactions and complete their characterization by analytic and spectrometric methods. Optimize procedures to achieve the organic synthesis with the highest possible yield.

II. Synthesize and develop clicked-compounds as a result of the click reaction between **tetrakis(4-azidophenyl)methane** and charged anchors.

III. Carry out studies on the properties of the synthesized compounds and evaluate their properties experimentally.

RESULTS DISCUSSION

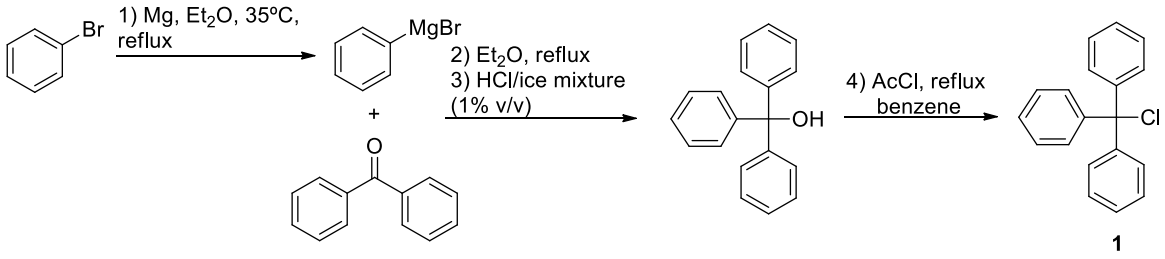
4. RESULTS DISCUSSION

A. Synthesis and Characterization

a. Synthesis and characterization of tetrakis(4-azidophenyl)methane

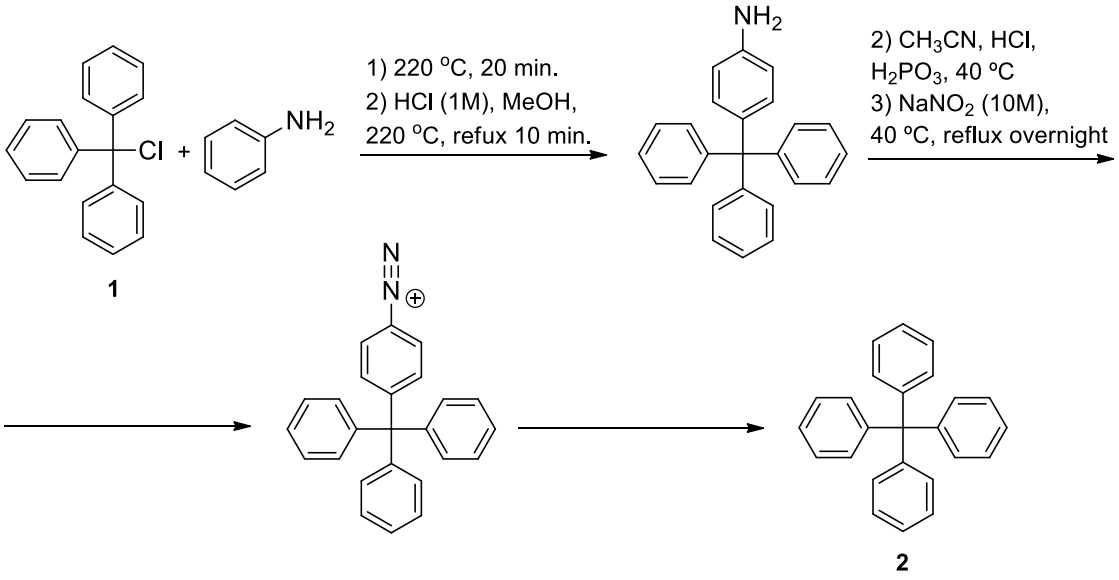
Tetrakis(4-azidophenyl)methane **(5),** has been synthesized by following the appropriate literature.

In first place, triphenylmethyl chloride **(1)** was synthesised (Scheme 1) in two separated steps[11]. Although the Grignard reagent could be bought, for training reasons its synthesis was carried out and then used to obtain a triphenylmethyl alcohol that reacted with AcCl to replace the OH with Cl group and obtain our first synthesised product.



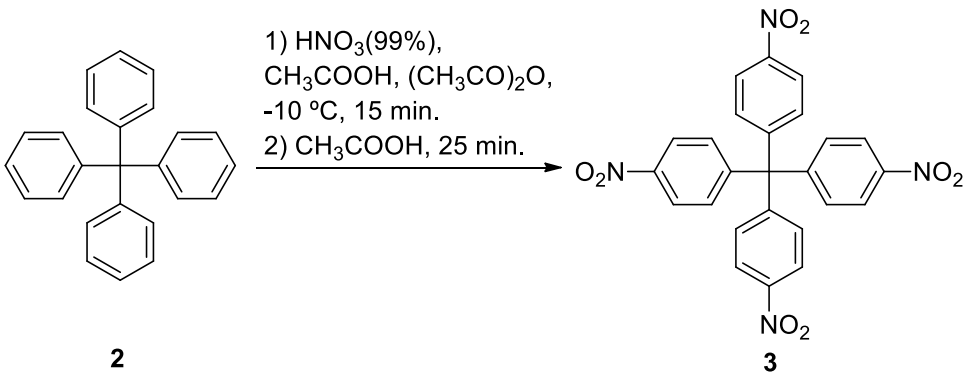
Scheme 1: Synthesis of triphenylmethyl chloride from bromobenzene[10].

The tetraphenylmethane **(2)** was obtained by the reaction (Scheme 2) of triphenyl methyl chloride with aniline in two steps[12,13]. Initially, we obtained the 4-tritylaniline and after the removal of the amino group, we obtained the target product.



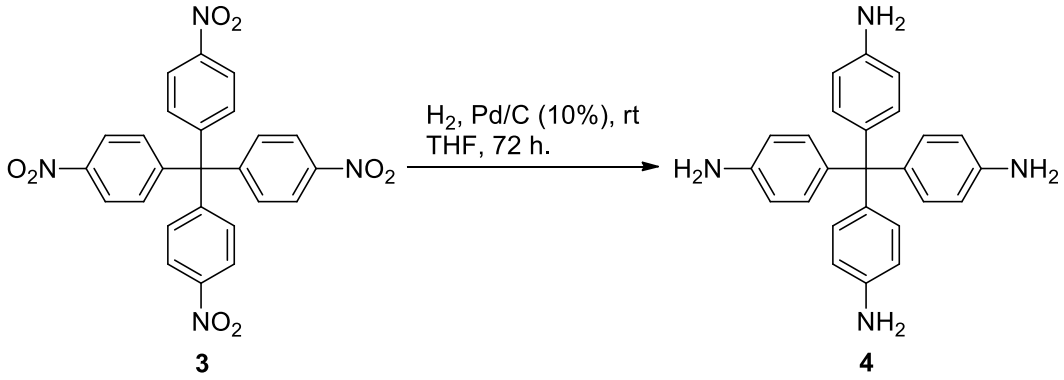
Scheme 2: Synthesis of tetraphenylmethane[12].

Tetrakis(4-nitrophenyl)methane **(3)** was obtained (Scheme 3) by nitration of tetraphenyl methane[14]. Full nitration happens when, in our case, four of the hydrogen atoms in para-positions on the benzene ring are replaced by a nitro group, NO_2. It is important to keep the reaction mixture to -10ºC to avoid multiple substitutions onto the rings.



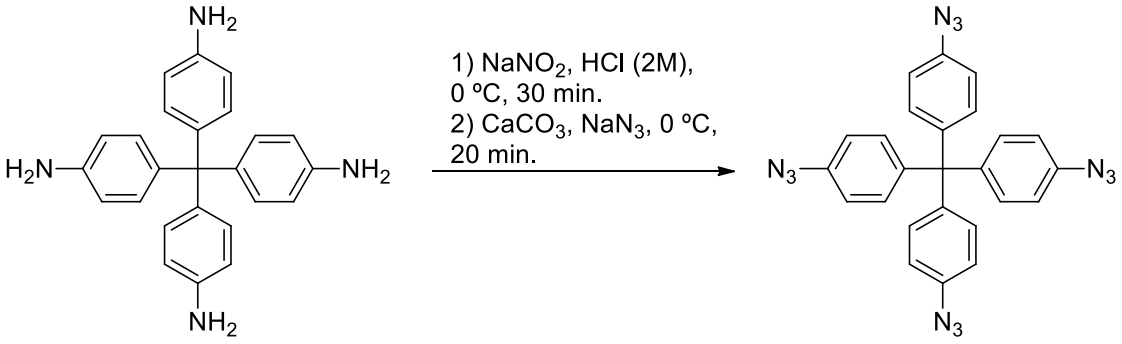
Scheme 3: Synthesis of tetrakis(4-nitrophenyl)methane[13].

Tetrakis(4-amino)phenyl methane (**4**) has been synthesized, performing (Scheme 4Scheme 4) the hydrogenation of tetrakis(4-nitrophenyl)methane with Pd/C(10%) catalyst for 72 h. at room temperature[14]. Initially, this synthesis was tried by using only 1 equivalent of the catalyst. However, the reaction had not proceeded, and we had to use more equivalents of the catalyst for the reaction to proceed. Finally, we used four equivalents of catalyst to perform the reaction and obtain a quantitative yield.



Scheme 4: Synthesis of tetrakis(4-aminophenyl)methane[13].

In this step, a reduction with Raney-Ni[15] was also performed. However, the reagent was not active enough, and the NMR showed a mixture of products. It was the result of a partial reduction of the starting material. Probably, it could be possible to obtain full conversion if we would optimize the method by increasing the temperature, changing the solvent, or waiting more time to perform the reaction.



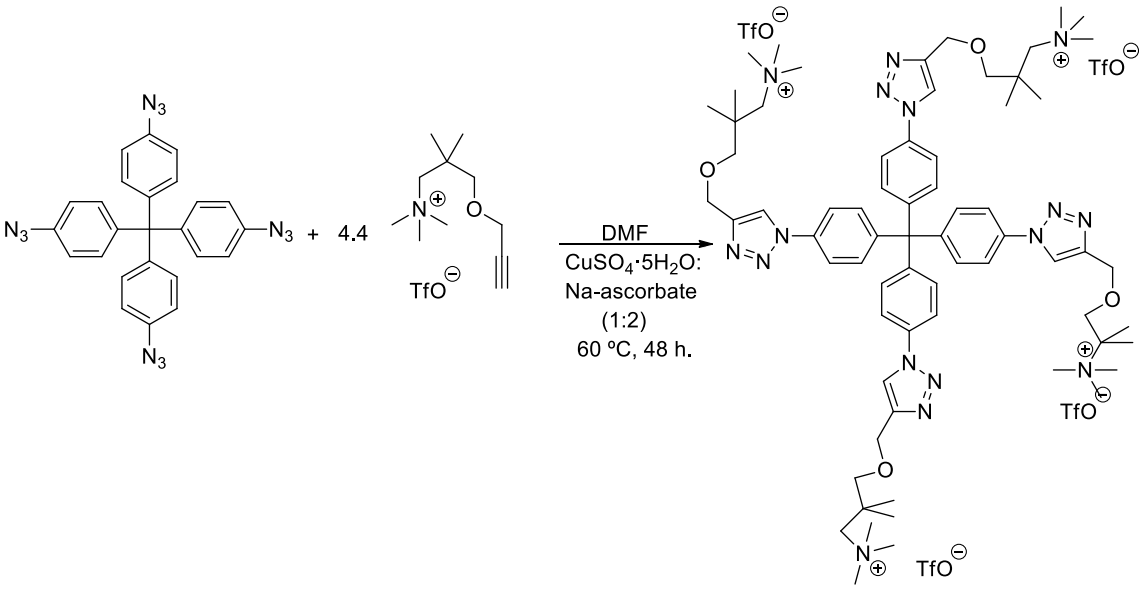
Scheme 5: Synthesis of tetrakis(4-azidophenyl)methane[13].

Tetrakis(4-azidophenyl)methane **(5)** has been obtained (Scheme 5) from primary amines by the way of diazonium ion formation followed by azidation in acid solution[14]. This reaction has been performed by keeping the temperature to 0 °C to avoid the risk of using NaN_3 as a reagent.

b. Synthesis and characterization of new tetraphenylmethane derivatives

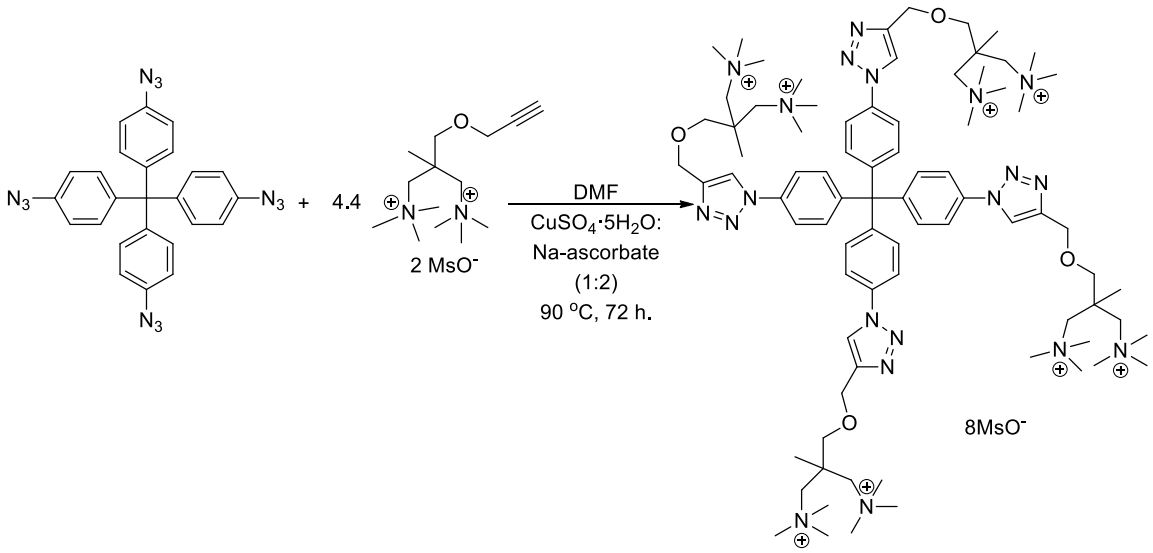
Two novel charged compounds derived from tetrakis(4-azidophenyl)methane have been synthesized. The preparation of the new compounds obtained by click chemistry has been carried out in both cases by the reaction of tetrakis(4-azidophenyl)methane **(2)** and positively charged anchors[8], that had been previously synthesized by the laboratory colleague Petr Kasal.

In first place, the synthesis of compound **7** was performed following a "click reaction" with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as reagents[16] and the final compound four times charged was synthesised (Scheme 6).



Scheme 6: Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium monocharged anchor[15].

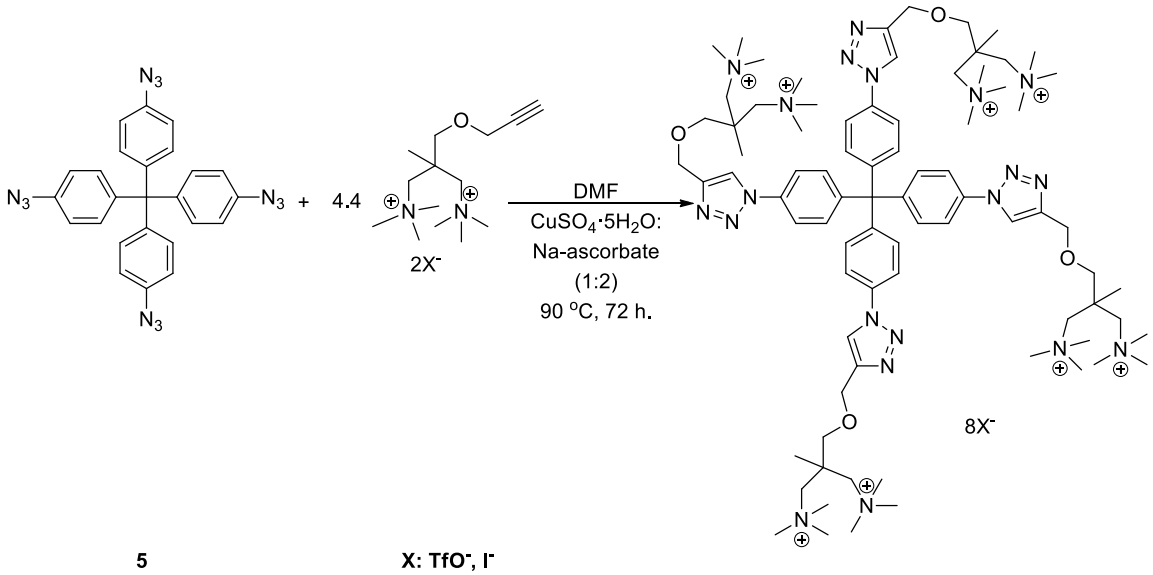
Secondly, the synthesis of compound **8** (Scheme 7) was performed following the same scheme as compound **7**. However, temperature and time of reaction had to be optimized to complete achieve fully conversion.



5 **B** **8**

Scheme 7: Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium double-charged anchor[15].

In addition, when the second click reaction (Scheme 8) was performed for first time, a problem with the solubility appeared.



5 **X: TfO^-, I^-**

Scheme 8: Click reaction[15] between tetrakis(4-zidopheyl)methane and trimethylammonium double-charged anchor with triflate and iodide as counterions.

When we performed the reaction[16] with the double charged anchor with triflate as a counter ion, it was impossible to determine if we obtained any product because the final solid was insoluble in any available solvent. After that, the performance of the click reaction was done with the double charged anchor having iodide as a counterion.

However, we had the same problem, the final product was insoluble in any solvent, and we could not determine if we had the wanted product.

We concluded that the final product has such a complicated solubility due to its composition. The aromatic core of the compound was soluble in organic solvents, whereas the anchor was soluble in water and polar solvents. This gave the compound an amphoteric behavior, and we had to study if the exchange of counterions used could make our product soluble in some solvent and thus be able to characterize it. For this reason, we needed to study how the reaction changes when the counterion is switched [(13)].
The size of the anchors contributes to the control of the stoichiometry of the reaction and influences the speed of the reaction. We had to increase the temperature to speed up the reaction, whose rate decreases with the increasing number of the triazole rings and the decreasing number of unreacted azido groups.

B. Study of solubility of charged tetraphenyl methane derivatives

An ion exchange resin is a resin or polymer that acts as a medium for ion exchange. It is an organic polymer substrate in which the compounds are retained due to their charge, and then the exchange of ions is performed[17,18].

In our case, anion exchanger resin was used. Its function is based on the retention of the positively charged molecules and then the exchange of the counterions[19]. It was used to switch the counterions of our double-charged anchors and study how the solubility of the final product changes with the different ions.

Once we obtained the double-charged anchor with all the different counterions, we performed the click reactions[14]. We had to consider that in the other cases, after the click reaction, we obtained a precipitate that was not soluble in DMF (it was the solvent of our reaction).
We decided to set the experiments, and after 72 h, the results are shown in Table 2.

Determination of finished reactions between anchors and triphenylmethane and the solubility of the final reaction mixture in DMF

Table 1: Determination of finished reactions between anchors and triphenylmethane and the solubility of the final reaction mixture in DMF.

COUNTER-ION	FINISHED REACTION?	DMF SOLUBILITY (mg/mL)
Chloride (Cl^-)	yes	<0.01
Bromide (Br^-)	no	<0.01
Methane sulphonate (MsO^-)	yes	0.1
p-Toluenesulphonate (TsO^-)	yes	0.11

Hexafluorophosphate (PF_6^-)	yes	<0.001
Acetate (AcO^-)	-	-
Trifluoroacetate (CF_3COO^-)	yes	<0.01
Tetrafluoroborate (BF_4^-)	no	<0.01
Sulphate (SO_4^{-2})	-	-

In the case of the anchors with sulphate and acetate counterions, we can't see any product spot in TLC, which means both compounds decompose at the reaction temperature and the click reaction was not taking place.

When bromide and tetrafluoroborate are used as counterions of our anchor, there is almost the same amount of free anchor that we had initially and a small product spot on TLC. The reaction rates were too slow, and we declined to use both counterions to perform our synthesis.

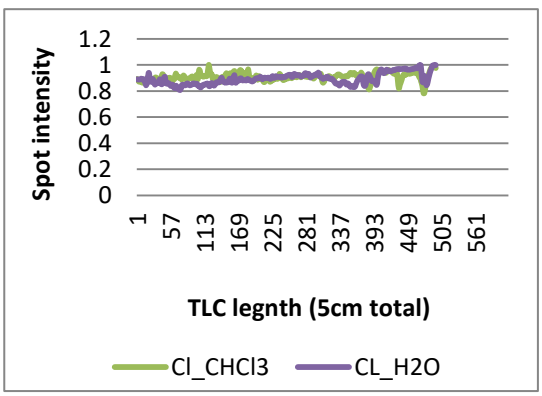
When chloride, hexafluorophosphate, and trifluoroacetate were used as counterions, the whole anchor reacted, but a solid precipitate appeared in the vial. They brought us precipitates insoluble in organic solvents.

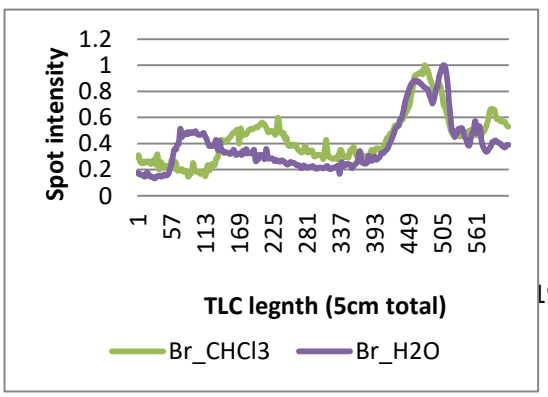
In the case of p-toulenesulphonate and methylsulphate as counterions of our anchor, the free anchor disappeared, and the product was soluble. We decided that they could be good options for our synthesis.

C. Purification of the final product

Before transferring our results to the final reaction, we decided to try to find a way to isolate the products from the reaction mixture. The extraction was performed between water and chloroform. In all cases, the extraction was done using 0.10 µL of the reaction mixture, 0.1 mL of water and 0.1 mL of chloroform. The mixture was separated, evaporated, and measured by TLC. All TLCs had 5 cm lentgth.
All the reaction mixtures were evaluated in MeOH:AcOH:NH_4OAc (10:10:9) as elution mixture. Then, the spots were observed by using manganese as visualizer. All TLCs were evaluated with imageJ to see into which layer and what amount of our compound was extracted.

Solubility of final product of "click reactions" in $CHCl_3$ and H_2O.





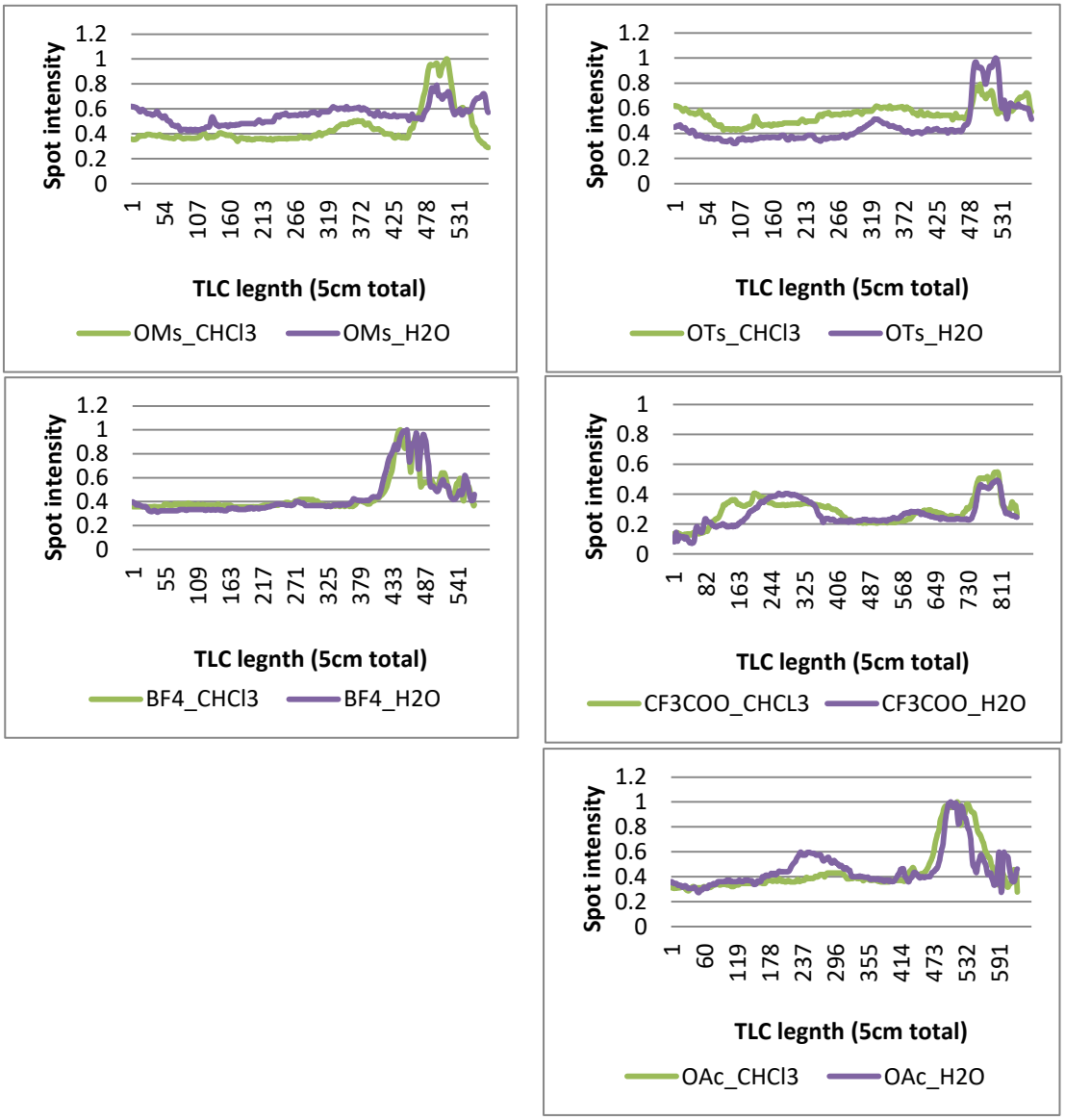


Figure 6: These plots represent how intense the final product's TLC spots were, after the extraction of the reaction products. The click reaction was performed using Cl^-, Br^-, MsO^-, TsO^-, CF_3COO^-, $BF4^-$ and AcO^- as counterions (from left to right and up to down plots) of the charged anchors. In the "X" axis it is the position of the signal in pixels. In the "Y" axe it is the relative intensity of the spot in each point.

After checking the solubility in both solvents, we realized that only for anchor, which has the methyl sulphate as counterion, the solubility in chloroform was higher than for the water phase. It means that we could separate our product from the catalyst easily.

Unfortunately, after performing the reaction on a large scale and extracting, the product appeared in the water phase. However, the solubility of our final product had changed entirely, and we checked that it was soluble in MeOH. On the other hand, the catalyst's solubility was so low that we could finally perform the purification of our product by washing the solid with MeOH.

Nevertheless, the yield over 104% means that the catalyst has not been completely separated, and we had at least 4% of impurity into our final product.

EXPERIMENTAL PART

5. EXPERIMENTAL PART

A. Instrumentation

Nuclear magnetic resonance (NMR).

The 1H and 13C {1H} nuclear magnetic resonance (NMR) spectra were performed on the Varian NMR System 300 MHz, Varian Inova 400 MHz, and Bruker Avance III 600 MHz spectrophotometers.. The chemical shifts (δ) are expressed in ppm referenced with respect to $CDCl_3$ (1H, 13C) or DMSO (1H, 13C). COZY, NOESY and 1H-13C heterocorrelation experiments (HSQC and HMBC) have been performed using standard Bruker programs.

Mass spectrometry

Low resolution mass spectra were measured with a Shimadzu LCMS-2020. Samples were ionized by electrospray technique (ESI) and detected by quadrupole or TOF. Drying and nebulizer gas was nitrogen.

High resolution mass spectra were measured with a Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS Samples were ionized by electrospray technique (ESI) and detected by quadrupole or TOF. Drying and nebulizer gas was nitrogen.

Infrared (IR) spectroscopy.

Infrared spectroscopy spectra were measured with a Nicolet Avatar 370 FTIR. The method used for measuring was a diffuse reflectance (DRIFT) in KBr or Attenuated Total Reflectance (ATR) with Ge crystal. IR absorptions are given in wavenumbers as cm^{-1}.

Thin Layer Chromatography analysis

Thin layer chromatography (TLC) was performed in all the cases using TLC Silica gel 60 plates for normal phase chromatography. The material was a pkg of 25 plates, plate L x W 20 cm x 20 cm. The plate was cut to use in each experiment pieces of 5 cm x 2 cm.

The retardation factor (R_f) is used to measure the movement of compounds along the TLC plate and it is defined as the rate between distance travelled by a component and the total distance travelled by the solvent.

For each experiment a different elution mixture was used and it will be explained in the experimental data of each compound.

B. Exchange of anchor counterions with ion exchange resins

In our case, anion exchanger resin was used to exchange the counterions of our anchors. It function is based on the retention of the positively charged molecules and then the exchange of the counterions. By this method, we switched the counterions of our double-charged anchors and studied how the solubility of the final product changes with the different ions.

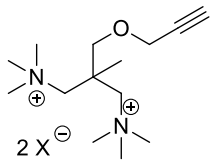
The exchange was performed following the next same steps:

1) To set the resin inside a column.
2) To wash the column with 1M HCl (60 mL) until we obtain acid pH (red pH paper).
3) To wash the column with water (120 mL) until neutral pH was obtained (green pH paper).
4) To wash the column with 5% NaOH (60 mL) until we obtain basic pH (dark blue pH paper).
5) To wash the column with water (120 mL) until we obtain neutral pH.

At this moment, the resin was filled with OH^- ions. We have to introduce our anchor in the resin to switch their counterions to the OH^- ions.

6) To dissolve the anchor in water (10 mL) and pour it into the column.
7) To wash the column with water (55 mL) until we obtain neutral pH (during the exchange, I^- ions are switched to OH^- in the resin, and our product was eluted. It brings us basic pH).

After the elution of the whole anchor, we have to neutralize the mixture with the appropriate 1M acids (in MeOH) until we obtain neutral pH (all the OH groups have been switched to the acid anions, and water was produced).



X=Br^-, Cl^-, MsO^-, TsO^-, PF_6^-, BF_4^-, AcO^-, $TFAO^-$, SO_4^-

Figure 7: It is the double-charged anchor derivate from trimethylamine used for the click reaction. In this figure there are all the counterions that were tried in order to change the solubility of the final product.

In our case, we performed the reaction for nine different acids.

Table 2: Information about the molar masses of each anchor after switch the iodine to other acids as counterions. In addition, it is also shown the amount of anchor obtained after neutralization of the anchor and evaporation of the solvent.

1M ACID (in MeOH)	ANCHOR OBTAINED MASS (mg)	ANCHOR MOLAR MASS (g/mol)
Hydrochloric acid (HCl)	17.5	313.30
Hydrobromic acid (HBr)	22.5	402.22

Methanesulphonic acid (MsOH)	24.3	432.62
p-Toluenesulphonic acid (TsOH)	30.7	584.8
Hexafluorophosphate acid (HPF_6)	29.9	534.34
Acetic acid (AcOH)	20.2	360.50
Trifluoroacetic acid (CF_3COOH)	26.2	468.44
Tetrafluoroboric acid (HBF_4)	23.3	416.1
Sufphuric acid (H_2SO_4)	20.2	338.4

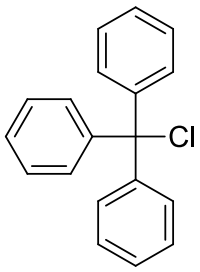
C. General information

Some preparations have been done under inert argon atmosphere, using Schlenk line and techniques. The anhydrous solvents have been prepared in situ by distillation over active metals (Na), under vacuum or even with 3Å sieves.

All the intermediates has been prepared following the bibliography to finally achieve **tetrakis(4-azidophenyl)methane** compound.

a. Synthesis and characterization of tetraphenylmethane derivatives

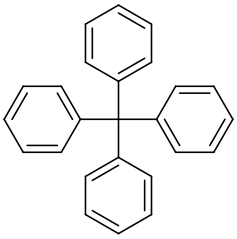
Triphenyl chloride (1).



Add bromobenzene (4.083 g, 26 mmol) to a suspension of magnesium (0.6319 g, 26 mmol) in diethyl ether (100 mL). Reflux the resultant solution for 2 hour to generate the Grignard reagent at 35 °C. Dissolve benzophenone (3.682 g, 20 mmol) in diethyl ether (30 mL) and reflux the mixture overnight. Quench with a chloride acid/ ice mixture (approximately 1% v/v, 100 mL). Two layers were separated and the organic one was washed with water (3 x 10mL) and dried with $MgSO_4$. After filtration, you have triphenylmethyl alcohol. The triphenylmethyl alcohol (20 mmol, 4.8001g) was refluxed with acetyl chloride (2 mL, 30.4 mmol) in benzene (10 mL) for 5 min and add acetyl chloride (2.5 mL) and reflux 40 min. Cooling down the mixture to get the chloride compound. It was dried and we got yellow/orange grease (5.4349 g, 19.49 mmol).

Yield: 86%. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.22 (m, 12H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 145.28, 129.70, 127.74, 127.29, 77.04 **TLC** Hexane:EtOAc (10:1) R_f 0.79.

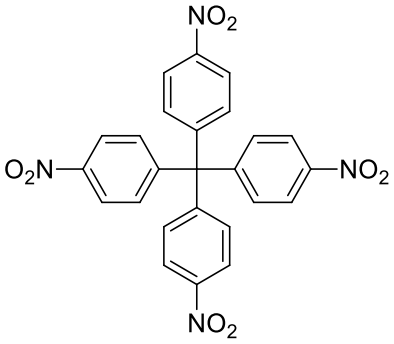
Tetraphenylmethane (2).



In a 250 mL flask, a mixture of triphenylmethyl chloride **(1)** (5.434g, 19.49 mmol) and aniline (30 mL, 210.54 mmol) was heated at 220 °C during 20 minutes getting a purple solid which was cooled to room temperature (rt.). During the stirring, 20 mL of hydrochloric acid 1M and 10 mL of methanol were added to it. The suspension was heated under reflux for 10 minutes and let it cool down to rt. The purple solid was filtered, washed with water (3 x 2 mL) and finally dried. Acetonitrile (50 mL) was added to the solid. HCl (30 mL) and hypophosphite (21 mL) were added upon stirring. The mixture was heated to 40 °C and the solid started solubilizing. Sodium nitrite aqueous solution (10 M - 8.206 g in 21 mL) was slowly dropped upon vigorous stirring. After the reaction was stirred overnight, the mixture was filtered, and washed by water (3 x 7 mL) and ethanol (3 x 2 mL). Dissolve it in $CHCl_3$ and finally white solid was obtained after vacuum drying (6.420 g, 19.40 mmol).

Yield: Quantitative yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42 – 7.13 (m, 16H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 146.81, 131.17 (d, *J* = 4.5 Hz), 127.47, 125.92 (d, *J* = 4.0 Hz), 65.01 **TLC** Hexan:EtOAc(10:1) R_r 0.24.

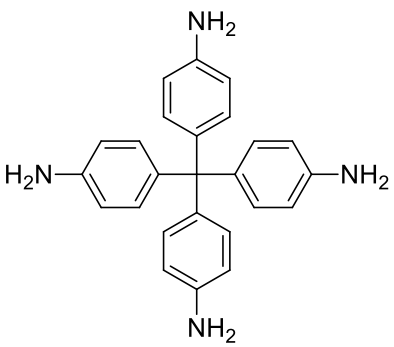
Tetrakis(4-nitrophenyl)methane (3).



Tetraphenylmethane **(2)** (5.0001g; 15.60 mmol) was added in portions to 25 mL of fuming nitric acid (96%) at -10 °C with vigorous stirring. To this mixture 8.5 mL of acetic anhydride and 16.5 mL of acetic acid (99%) was slowly added and stirred for 15 min. Finally, the reaction mixture was diluted with 80 mL of acetic acid (99%) and the resulting yellow solid was filtered on a glass frit, washed with acetic acid and MeOH and dried under dynamic vacuum to obtain it as a pale brown crystalline solid (6.6359 g, 13.26 mmol).

Yield: 85% **^{1}H NMR** (300 MHz, DMSO) δ 8.23 (d, *J* = 8.6 Hz, 6H), 8.19 (s, 1H), 8.09 (s, 2H), 7.61 (d, *J* = 8.5 Hz, 4H), 1.24 (s, 2H), 0.86 (s, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 151.51, 146.57, 131.96, 124.29, 65.76 **TLC** $CHCl_3$:MeOH(20:1) R_f 0.68.

Tetrakis(4-aminophenyl)methane (4).

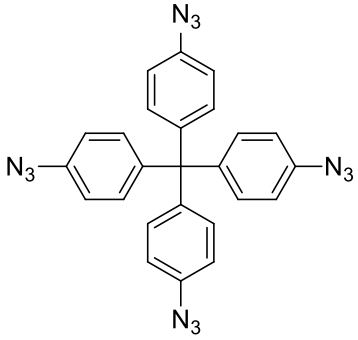


In a two-necked round-bottomed flask, tetra-(4-nitrophenyl)-methane **(3)** (2.0022g, 4.00 mmol) and Pd/C (10 %, 1.9998 g) were suspended in degassed THF (80 mL) under nitrogen. The reaction mixture was degassed and backfilled with hydrogen for five times.

The resulting reaction mixture was vigorous stirred under hydrogen atmosphere for 48 h at room temperature. Then, the resulting mixture was filtered on a glass frit, washed with methanol and THF. Then the mixture was neutralized with MeOH until neutral pH and evaporated to afford pure compound as a light brown solid (1.5308 g, 4.00 mmol).

Yield: Quantitative yield. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 6.89 – 6.86 (m, 8H), 6.62 – 6.58 (m, 8H), 4.37 (s, 4H). **^{13}C NMR** (101 MHz, Methanol-d_4) δ 144.21, 138.41, 131.54 (d, J = 8.6 Hz), 114.14, 29.49 **TLC** $CHCl_3$:MeOH:NH_3(10:1:0.25) $\boldsymbol{R_f}$ 0.76.

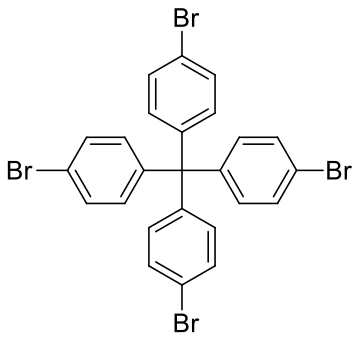
Tetrakis(4-azidophenyl)methane (5).



Tetrakis(4-aminophenyl)methane **(4)** (0.7989g, 2.10mmol) was dissolved in 2M aqueous HCl (42 mL) into a 1L rounded-bottomed flask and cooling down to 0 °C. A solution of $NaNO_2$ (0.9 g) in H_2O (4 mL) was then added drop-wise into the cooled reaction flask with vigorous stirring. The reaction mixture was kept at 0 °C for 30 min. before being neutralized with $CaCO_3$ (1.3002 g). A solution of NaN_3 (0.9903 g) in H_2O (4 mL) was then added to the reaction mixture at 0 °C. The resulting mixture was allowed to stir for an additional 20 min. and then filtered. The collected solid was washed with H_2O and dried under dynamic vacuum to obtain it as a crude white solid (0.7230 g, 1.23 mmol)

Yield: 71% **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.18 – 7.10 (m, 8H), 6.98 – 6.91 (m, 8H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 142.89, 138.21, 132.09 (q, J = 3.2, 0.0 Hz), 118.44 (dd, J = 2.7, 0.0 Hz) **TLC** Reaction followed by desaparition of purple spot.

Tetrakis(4-bromophenyl)methane (6).

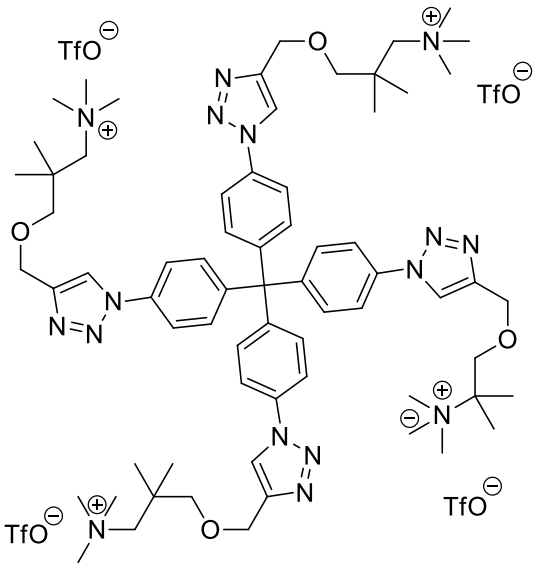


In a 4 mL vial containing tetraphenylmethane **(2)** (0.102 g, 0.319 mmol), bromine (0.16 mL, 3.19 mmol) was added drop by drop under vigorous stirring at room temperature. The mixture turns from a light brown solid to a brown-yellow suspension. After the addition was completed, the resulting solution was stirred for 5 hours and then cooled down to –78 °C. At this temperature, ethanol (4 x 10 mL) was added slowly and formed a suspension which was separated from the solvent by centrifugal. In each washing, the yellow colour of the solvent was disappearing. After drying in the rotary evaporator we obtained the unpurified solid. It was purified by column adsorption chromatography and dried the samples that contained the compound to obtain a white solid (0.0182 g, 0.0286 mmol).

Yield: 58% **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.47 – 7.38 (m, 8H), 7.07 – 7.00 (m, 8H).

b. Synthesis and characterization of charged tetraphenyl methane derivatives

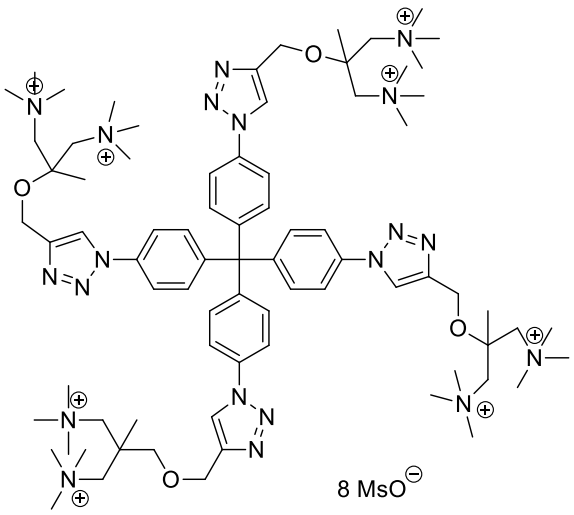
Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium monocharged anchor (7).



Tetrakis(4-azidophenyl)methane **(5)** (0.1022 g, 0.206 mmol), monocharged anchor (0.3040 g, 0.911 mmol) and 10mL of DMF were added into a 50 mL flask and set under nitrogen for 20 minutes. $CuSO_4 \cdot 5H_2O$ (0.0591 g) and Na-ascorbate (0.0859 g) were added to the mixture with continuous stirring. The temperature was set to 60 ºC and 48 h. of reaction were waited. Once the reaction finished, the product was dried under vacuum at 90 °C in order to eliminate the DMF solvent. The brown solid obtained was washed with H_2O and THF and dried under rotary to obtain a light brown solid (0.3335 g, 0.185 mmol).

Yield: 89% **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.92 (s, 1H), 7.94 (d, *J* = 0.0 Hz, 2H), 7.60 (dd, *J* = 8.2, 0.0 Hz, 2H), 4.69 – 4.55 (m, 2H), 3.48 (d, *J* = 9.6 Hz, 2H), 3.28 – 3.14 (m, 12H), 0.97 (s, 6H) **^{13}C NMR** (101 MHz, Methanol-d_4) δ 55.24 (d, *J* = 12.2 Hz), 47.81 (dt, *J* = 42.9, 21.4 Hz), 47.17, 46.96 **TLC** MeOH:AcCN:NH_4OAc(10:10:9) ***Rf*** 0.40.

Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium double-charged anchor (8).



Tetrakis(4-azidophenyl)methane **(5)** (0.0430 g, 0.092 mmol), double positively charged anchor (0.1706 g, 0.405 mmol) and 4mL of DMF were added into a 25 mL flask and set under nitrogen for 20 minutes. $CuSO_4 \cdot 5H_2O$ (0.0224 g) and Na-ascorbate (0.0341 g) were added to the mixture with continuous stirring. The temperature was set to 90 ºC and 72 h. of reaction were waited. Once the reaction has finished, the product is extracted between water and $CHCl_3$. The water phase was collected and evaporated until obtain a dark-brown solid. The solid was washed with MeOH to eliminate the catalyst and then lyophilised to obtain a dark brown solid (0.1904 g, 0.0952 mmol)

Yield: 104% **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.92 (s, 1H), 7.94 (s, 3H), 7.60 (d, *J* = 8.3 Hz, 3H), 4.12 (s, 1H), 3.81 (s, 4H), 3.34 (s, 42H), 3.19 (s, 7H), 1.44 (s, 3H). **^{13}C NMR** (101 MHz, Methanol-d_4) δ 131.99, 73.19 – 71.47 (m), 63.64, 55.24 (d, *J* = 12.2 Hz), 54.62 – 54.20 (m), 45.90, 43.42, 38.65, 34.01, 20.62, 20.36 **TLC** MeOH:AcCN:NH_4OAc(10:10:9) $\boldsymbol{R_f}$ Product In the baseline and desaparition of the anchor spot at 0.49.

CONCLUSIONS

6. CONCLUSIONS

After the development of this project and the consequent results we have obtained the following conclusions:

- To develop a method for the synthesis of tetrakis(4-azidophenyl)methane through easy and cheap reactions.
- To develop and synthesize the charged tetraphenylmethane derivatives through easy and cheap reactions.
- To study how the solubility of the charged tetraphenylmethane derivatives changes when we exchange the counterions.

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7. BIBLIOGRAPHY

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FINAL DEGREE THESIS

SYNTHESIS AND CHARACTERIZATION OF TETRAPHENYLMETHANE DERIVATIVES

Supporting information

AINHOA PORROCHE ROMERO

Directors:

Assoc. Prof. RNDr. JindřichJindřich, CSc.

Mgr. Petr Kasal

Department of Organic Chemistry
Department of Supramolecular Chemistry
Charles University, Prague, June 2022

Contenido

1. EXPERIMENTAL PART

9. EXPERIMENTAL PART

D. Instrumentation

Nuclear magnetic resonance (NMR).

The 1H and 13C {1H} nuclear magnetic resonance (NMR) spectra were performed on the Varian NMR System 300 MHz, Varian Inova 400 MHz, and Bruker Avance III 600 MHz spectrophotometers.. The chemical shifts (δ) are expressed in ppm referenced with respect to $CDCl_3$ (1H, 13C) or DMSO (1H, 13C). COZY, NOESY and 1H-13C heterocorrelation experiments (HSQC and HMBC) have been performed using standard Bruker programs.

Mass spectrometry

Low resolution mass spectra were measured with a Shimadzu LCMS-2020. Samples were ionized by electrospray technique (ESI) and detected by quadrupole or TOF. Drying and nebulizer gas was nitrogen.

High resolution mass spectra were measured with a Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS Samples were ionized by electrospray technique (ESI) and detected by quadrupole or TOF. Drying and nebulizer gas was nitrogen.

Infrared (IR) spectroscopy.

Infrared spectroscopy spectra were measured with a Nicolet Avatar 370 FTIR. The method used for measuring was a diffuse reflectance (DRIFT) in KBr or Attenuated Total Reflectance (ATR) with Ge crystal. IR absorptions are given in wavenumbers as cm^{-1}.

E. General information

Some preparations have been done under inert argon atmosphere, using Schlenk line and techniques. The anhydrous solvents have been prepared in situ by distillation over active metals (Na), under vacuum or even with 3Å sieves.

All the intermediates has been prepared following the bibliography to finally achieve **tetrakis(4-azidophenyl)methane** compound.

2. NMR SPECTRA

10. NMR SPECTRA

F. Tetrakis(4-azidophenyl)methane (5)

^{1}H-RMN

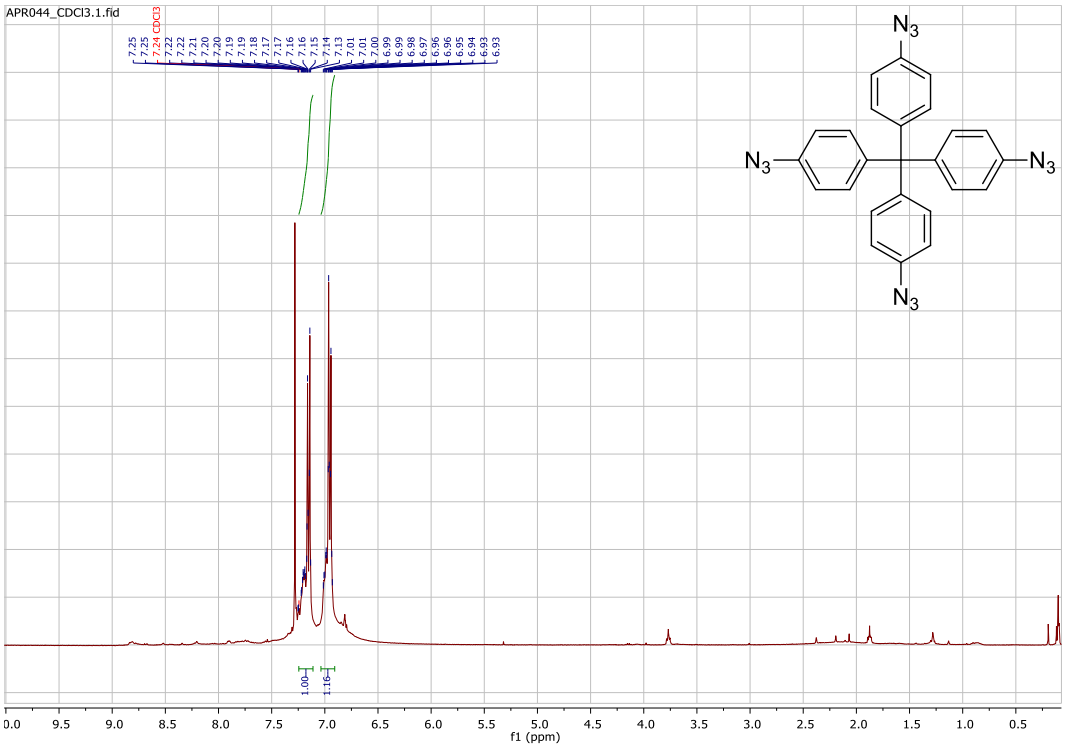

Figure 8: ^{1}H-RMN of tetrakis(4-azidophenyl)methane in $CDCl_3$.

^{13}C-RMN

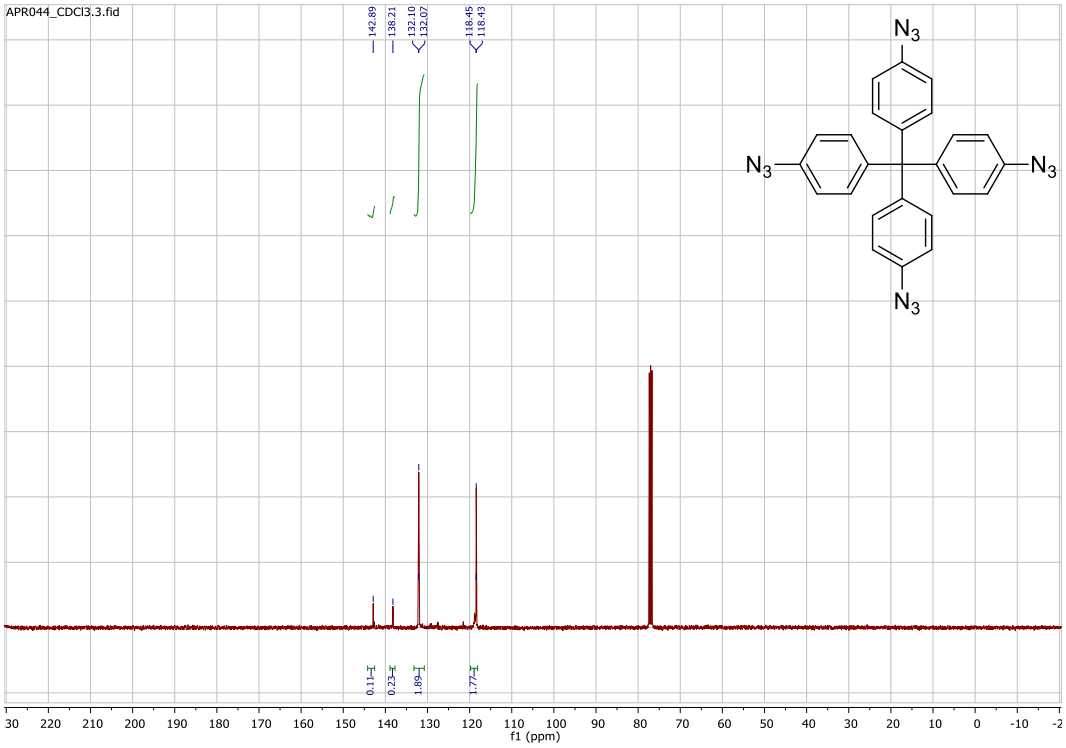

Figure 9: ^{13}C-RMN of tetrakis(4-azidophenyl)methane in $CDCl_3$.

G. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium (7)

^{1}H-RMN

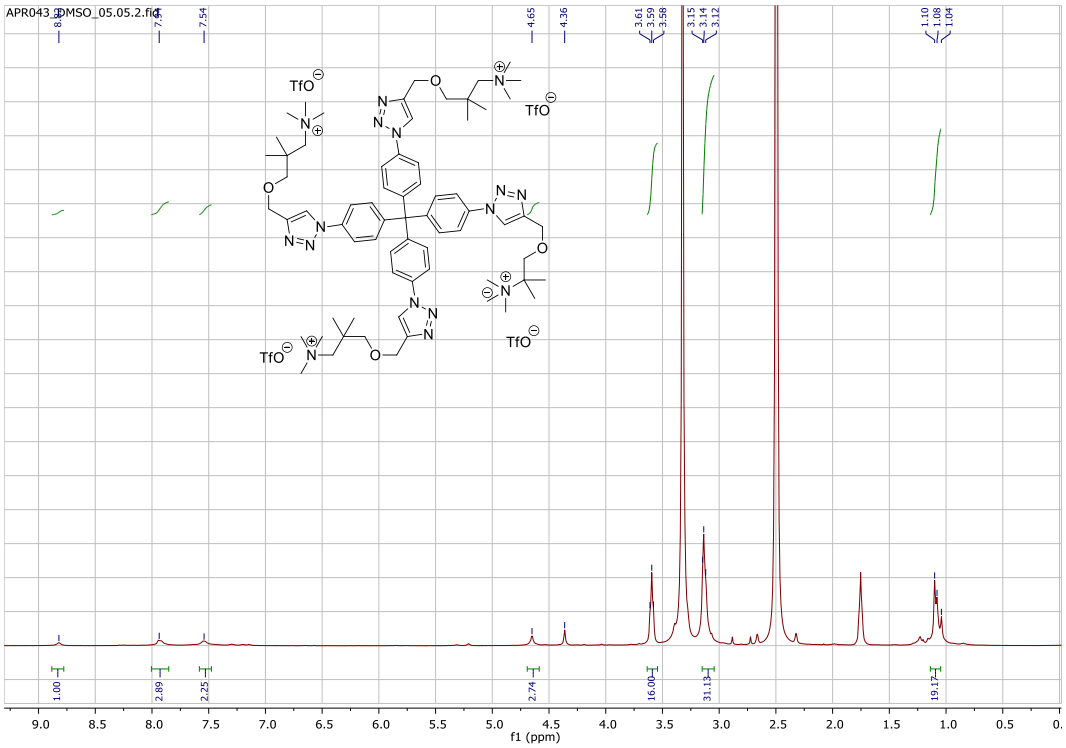

Figure 10: ^{1}H-RMN of clicked compound in DMSO. Product four times charged.

^{13}C-RMN

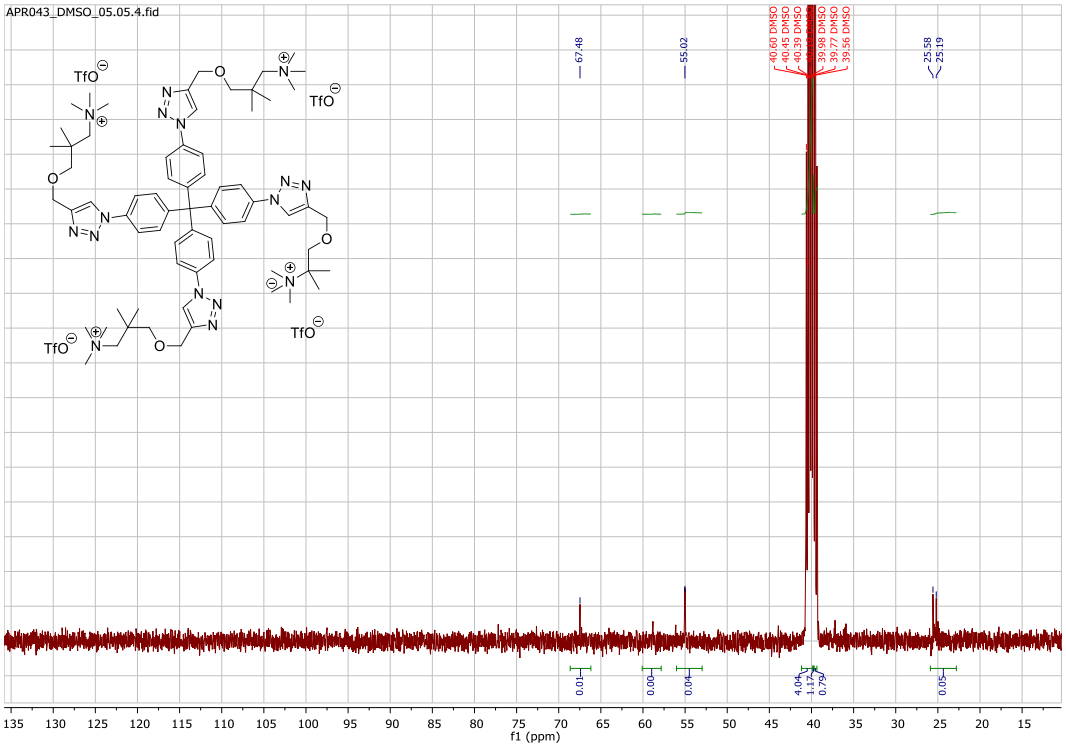

Figure 11: ^{13}C-RMN of clicked compound in DMSO. Product four times charged.

H. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium double-charged anchor (8).

^{1}H-RMN

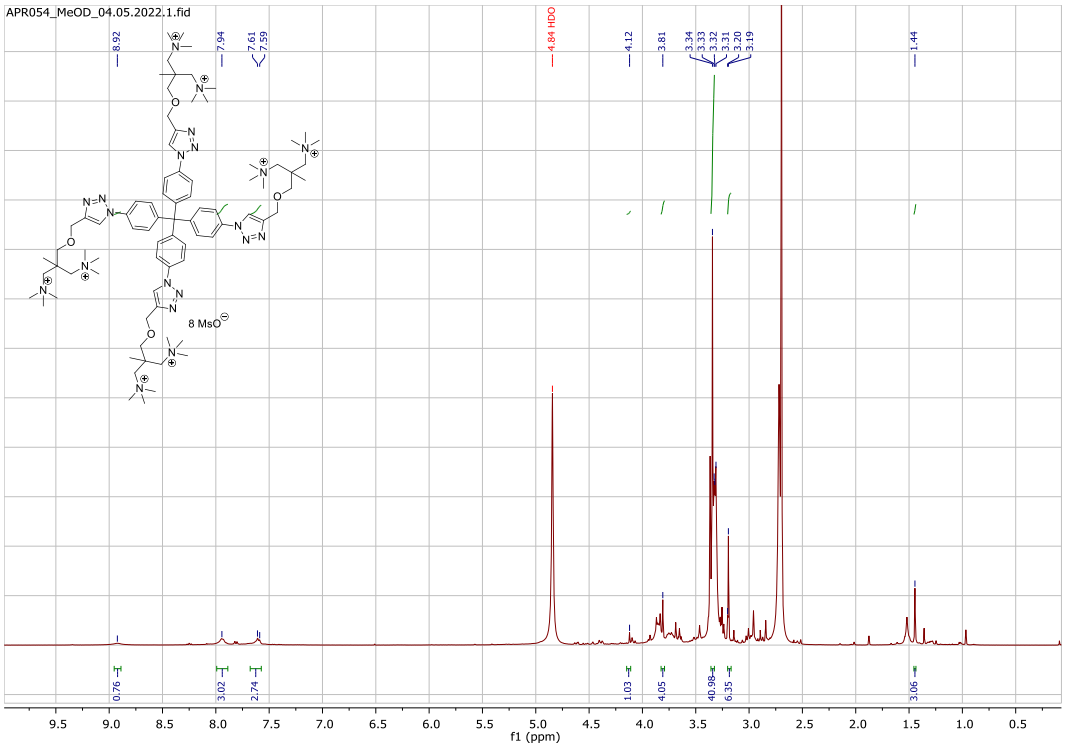

Figure 12: ^{1}H-RMN of clicked compound in MeOD. Product eight times charged.

^{13}C-RMN

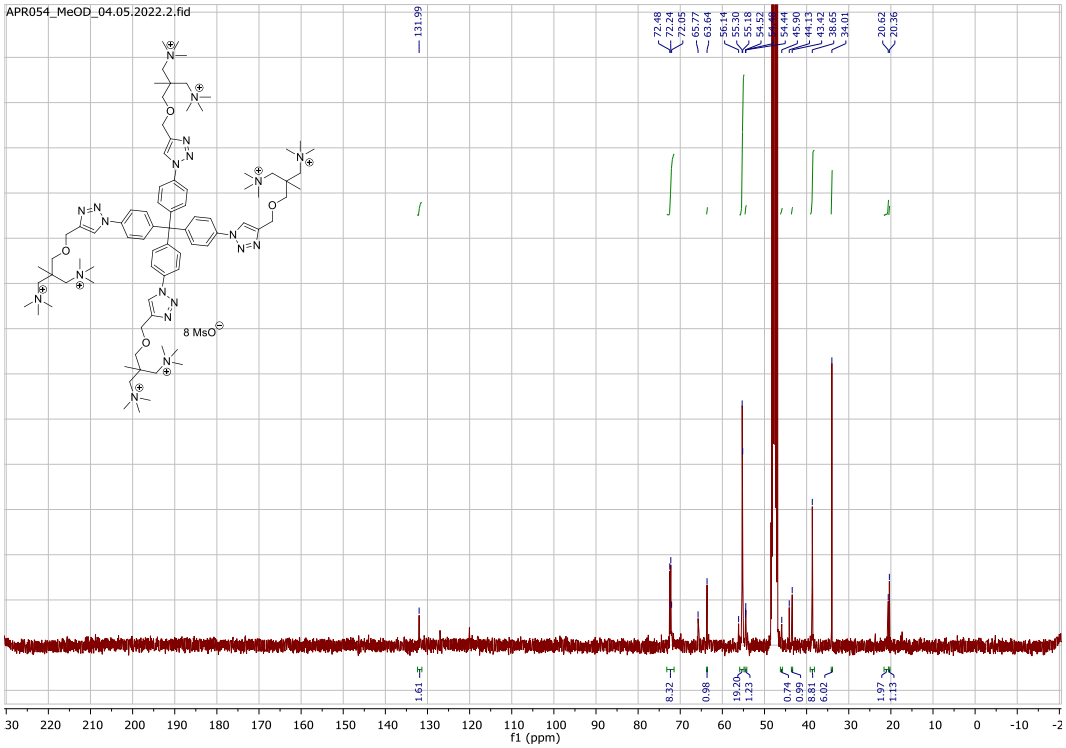

Figure 13: ^{13}C-RMN of clicked compound in MeOD. Product eight times charged.

3. IR SPECTRA

11. IR SPECTRA

I. Tetrakis(4-azidophenyl)methane (5)

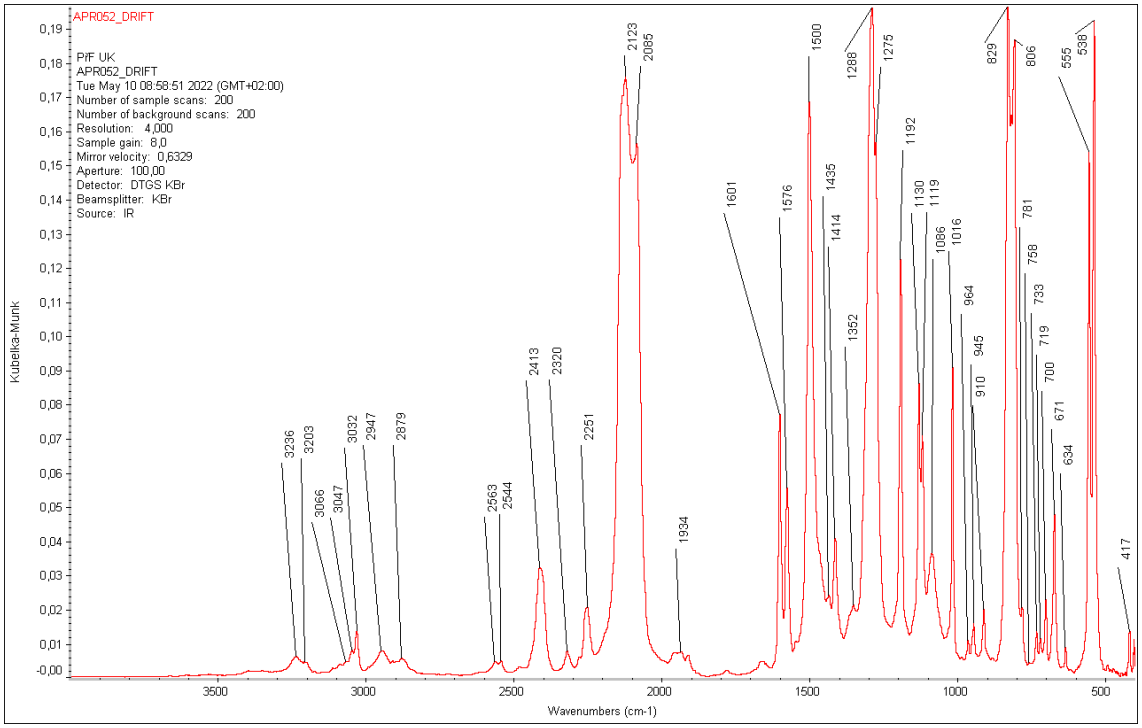

Figure 14: DRFT spectra of tetrakis(4-azidophenyl)methane.

J. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium monocharged anchor (7)

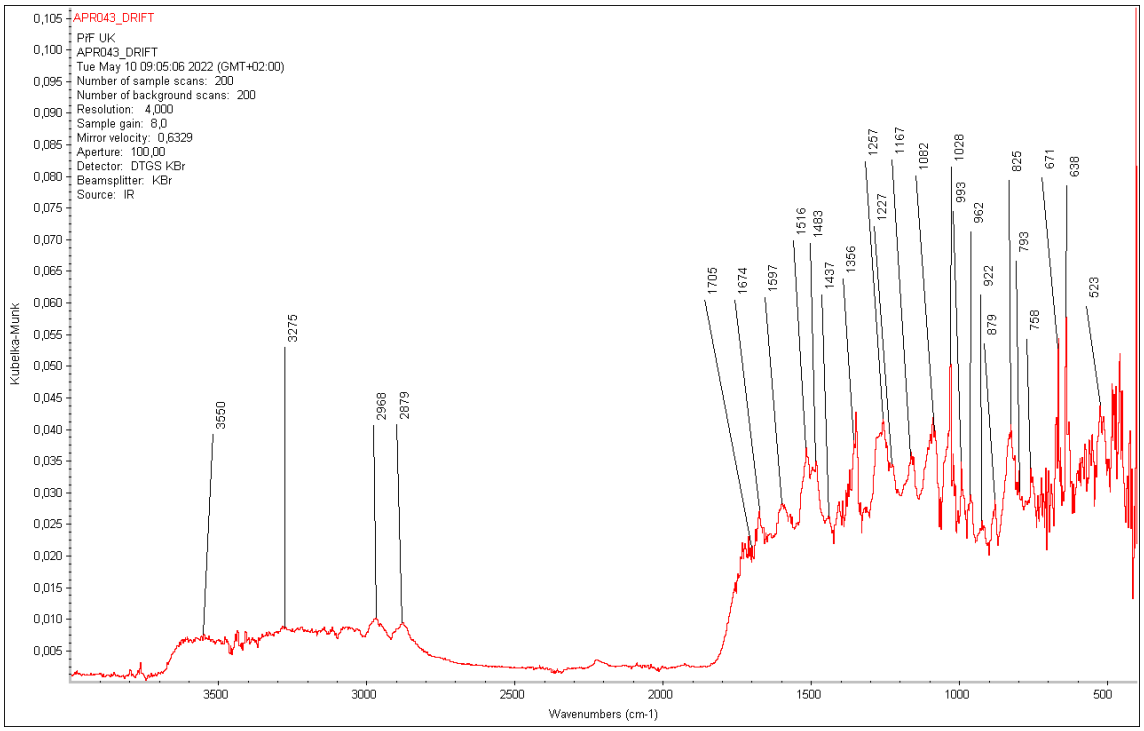

Figure 15: DRFT spectra of click reaction between tetrakis(4-azidophenyl)methane and monocharged anchor.

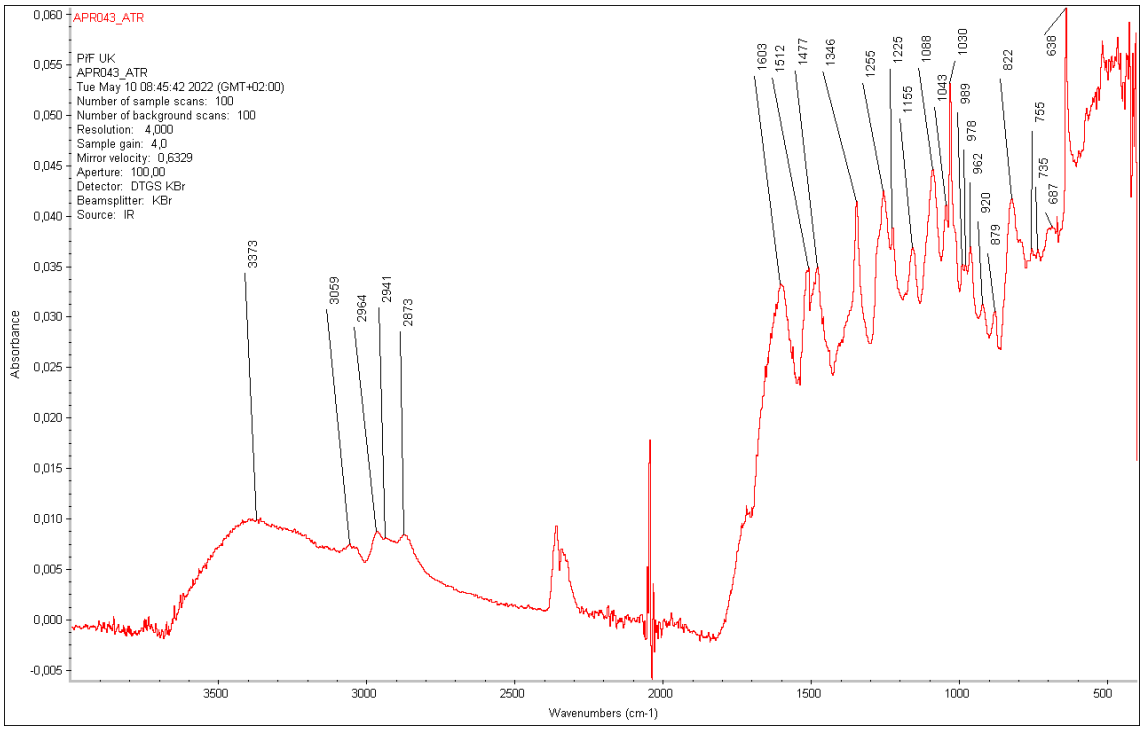

Figure 16: ATR spectra of click reaction between tetrakis(4-azidophenyl)methane and monocharged anchor.

K. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium double-charged anchor (8).

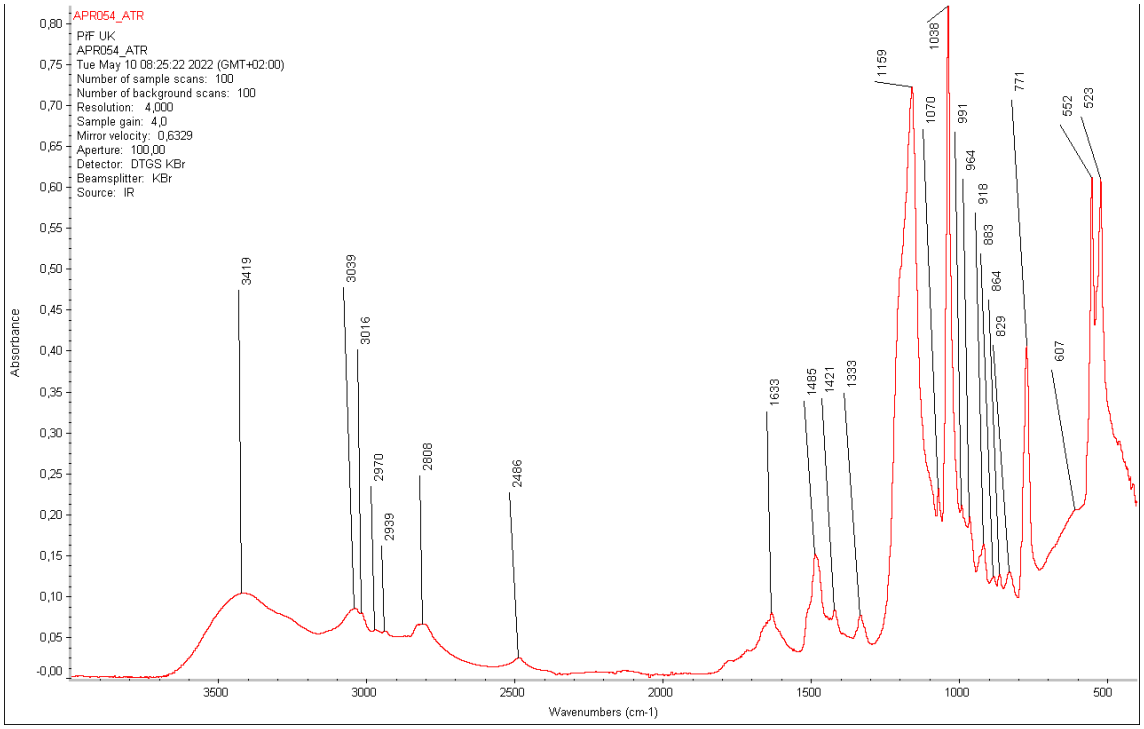

Figure 17: ATR spectra of click reaction between tetrakis(4-azidophenyl)methane and double-charged anchor.

4. MS SPECTRA

12. MS SPECTRA

L. Triphenylmethyl chloride (1).

Display Report

Analysis Info

Analysis Name	054-0701.D	Acquisition Date	5.5.2022 12:00:25
Method	LOW_MEOH_POS_.M	Operator	Martin
Sample Name	APR_048_	Instrument	esquire3000
Comment			

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive	Alternating Ion Polarity	off
Mass Range Mode	Std/Enhanced	Scan Begin	50 m/z	Scan End	1100 m/z
Capillary Exit	110.0 Volt	Skim 1	36.2 Volt	Trap Drive	40.4
Accumulation Time	22629 Ss	Averages	4 Spectra	Auto MS/MS	off

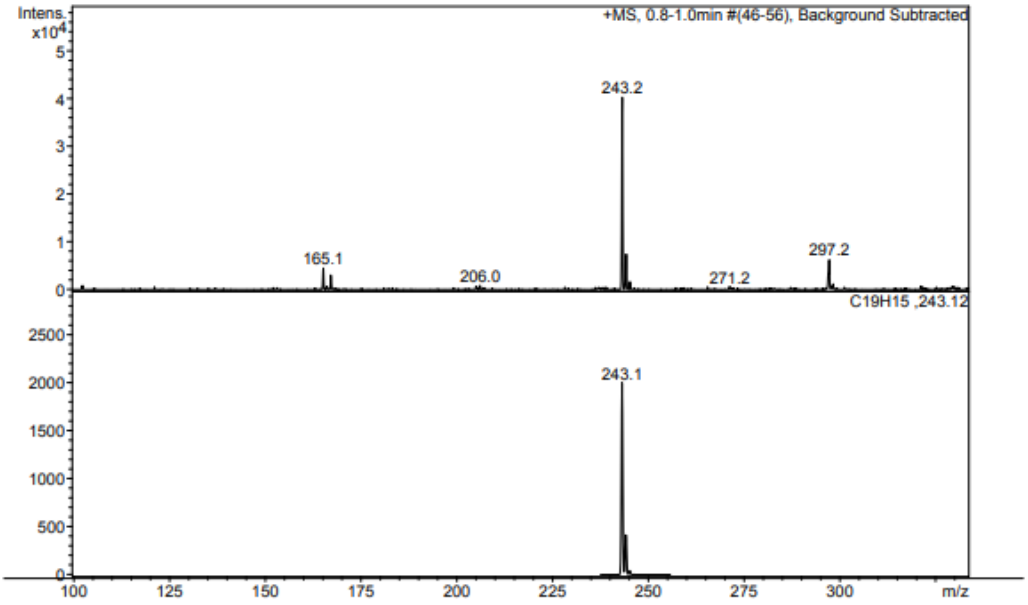

Figure 18: MS of triphenylmethyl chloride.

M. Tetrapheylmethane (2).

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\HRMS\APR_049a_000001.d	Acquisition Date	06-May-22 15:30:53
Method	APCI_low1.m	Operator	Demo User
Sample Name	APR_049a_	Instrument	compact 8255754.20121
Comment	MeOH		

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.7 Bar
Focus	Not active	Set Capillary	1500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-700 V	Set Dry Gas	5.0 l/min
Scan End	1100 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	2000 nA	Set APCI Heater	450 °C

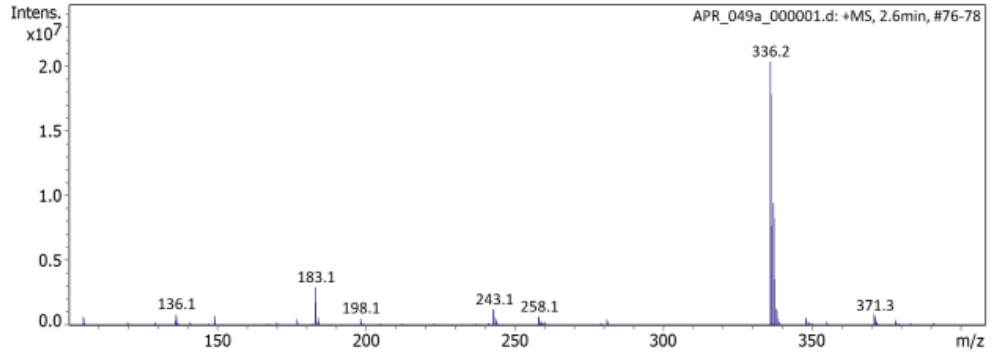

Figure 19: High resolution MS of tetraphenylmethane.

N. Tetrakis(4-nitrophenyl)methane (3).

Display Report

Analysis Info

Analysis Name	057-0301.D	Acquisition Date	5.5.2022 13:10:14
Method	LOW_MEOH_NEG_.M	Operator	Martin
Sample Name	APR_050_	Instrument	esquire3000
Comment			

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Negative	Alternating Ion Polarity	off
Mass Range Mode	Std/Enhanced	Scan Begin	50 m/z	Scan End	1000 m/z
Capillary Exit	-113.0 Volt	Skim 1	-38.3 Volt	Trap Drive	47.2
Accumulation Time	19457 Šs	Averages	4 Spectra	Auto MS/MS	off

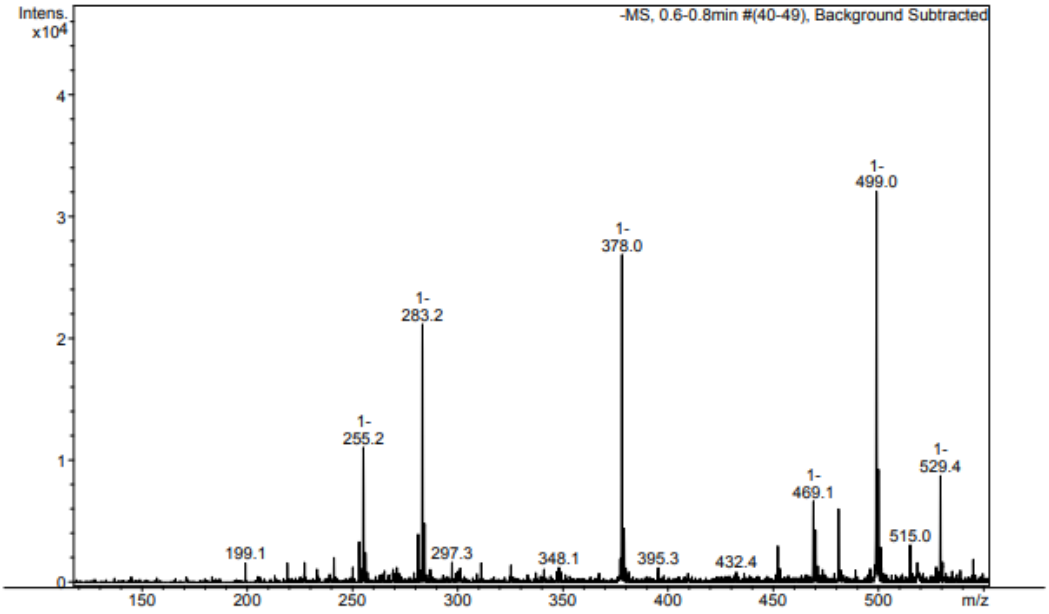

Figure 20: High resolution MS of tetraphenylmethane.

O. Tetrakis(4-aminophenyl)methane (4).

Display Report

Analysis Info

Analysis Name	050-0301.D	Acquisition Date	5.5.2022 11:40:25
Method	LOW_MEOH_POS_.M	Operator	Martin
Sample Name	APR_051_	Instrument	esquire3000
Comment			

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive	Alternating Ion Polarity	off
Mass Range Mode	Std/Enhanced	Scan Begin	50 m/z	Scan End	1100 m/z
Capillary Exit	110.0 Volt	Skim 1	36.2 Volt	Trap Drive	40.4
Accumulation Time	21851 Šs	Averages	4 Spectra	Auto MS/MS	off

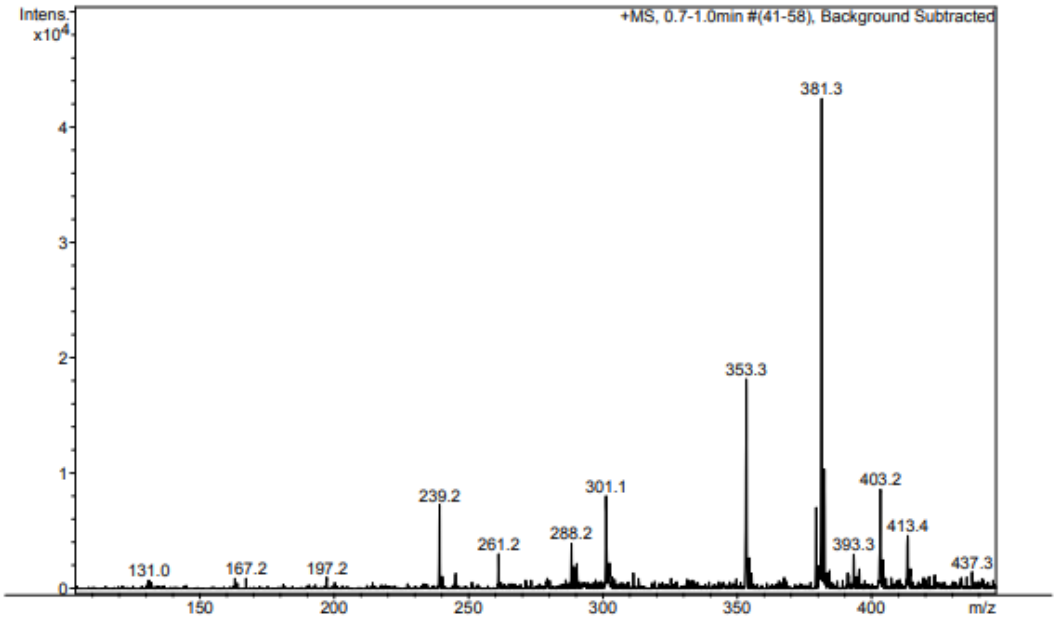

Figure 21: MS of tetrakis(4-aminophenyl)methane.

P. Tetrakis(4-azidophenyl)methane (5).

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\HRMS\APR_044_000001.d	Acquisition Date	06-May-22 15:50:33
Method	APCI_low1.m	Operator	Demo User
Sample Name	APR_044_	Instrument	compact 8255754.20121
Comment	MeOH		

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.7 Bar
Focus	Not active	Set Capillary	1500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-700 V	Set Dry Gas	5.0 l/min
Scan End	1100 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	2000 nA	Set APCI Heater	450 °C

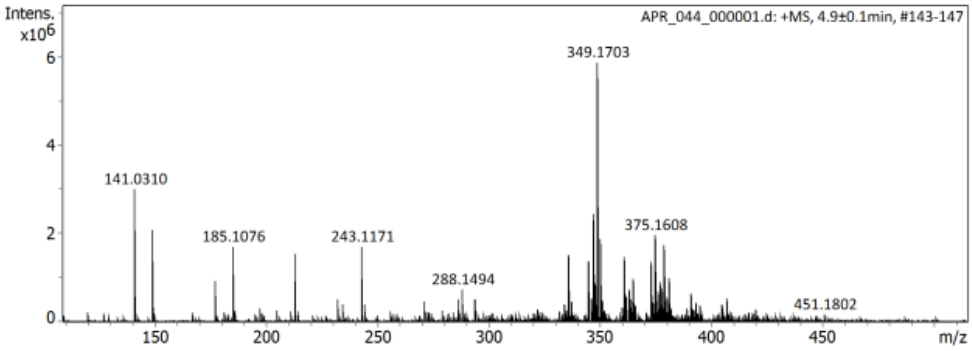

Figure 22: High resolution MS of tetrakis(4-azidophenyl)methane.

Q. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium (7).

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\HRMS\APR_043_000001.d	Acquisition Date	5/6/2022 2:36:25 PM
Method	JJCD.m	Operator	Demo User
Sample Name	APR_043_	Instrument	compact 8255754.20121
Comment	MeOH		

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	3000 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C

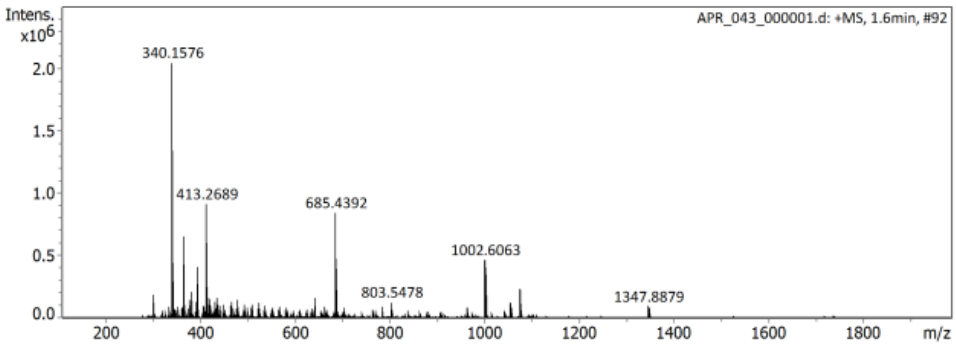

Figure 23: High resolution MS of clicked compound with four positive charges.

R. Click reaction between tetrakis(4-azidophenyl)methane and trimethylammonium double-charged anchor (8).

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\HRMS\APR_054_000002.d	Acquisition Date	5/6/2022 3:01:46 PM
Method	JJCD.m		
Sample Name	APR_054_	Operator	Demo User
Comment	MeOH	Instrument	compact 8255754.20121

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	3500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	3000 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C

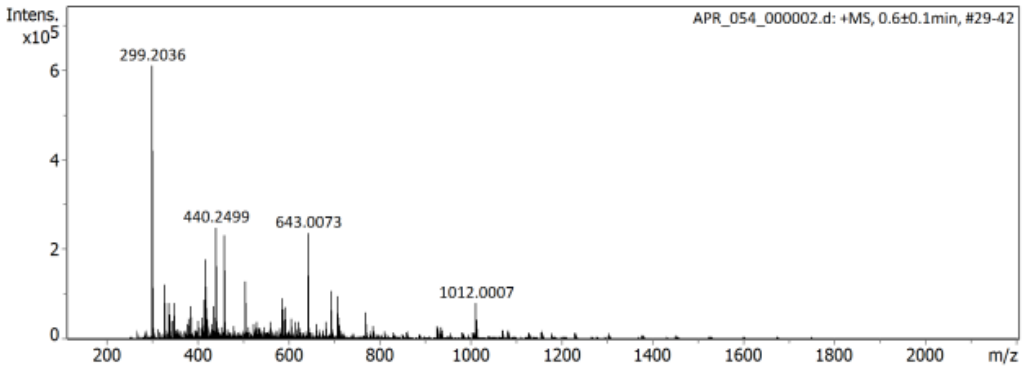

Figure 24: High resolution MS of clicked compound with eight charges.