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Analysis of Polar Precursors of 1,3,5,7-Tetranitro-1,3,5,7-tetrazocine (HMX) Using Hydrophilic Interaction Chromatography

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Abstract: Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) is currently one of the most widely used explosives. 1,3,5,7-Tetraacetyl-1,3,5,7-tetraazacyclooctane (TAT) is an attractive precursor for the synthesis of HMX; the nitration of this key precursor results in both high yield and purity under mild condition. TAT can be prepared either by acetylation of 2,6-diacetyl-pentamethylenetetramine (DAPT) or by the condensation of ACN and 1,3,5-trioxane. However, TAT and DAPT are polar compounds, and are difficult to analyze using reverse phase liquid chromatography. Herein, a chromatography method for the direct separation of these polar compounds was developed using hydrophilic interaction chromatography (HILIC) using a Venusil HILIC column, with ACN/water (95/5, v/v) as the mobile phase. The chromatographic analysis and identification of these polar compounds provide valuable information for the optimization of the synthetic process of TAT.

Keywords: 1,3,5,7-Tetraacetyl-1,3,5,7-tetraazacyclooctane · 1,3,5,7-Tetranitro-1,3,5,7-tetrazocine · Hydrophilic interaction chromatography

1 Introduction

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) is one of most powerful explosives, but its usage has been limited by high production cost. Currently, it is produced according to a modified Bachmann process, a process that possesses several undesirable features, including usage of expensive acetic anhydride, slow production rate, and poor yield [1]. Thus, researchers have been exploring alternatives that are both feasible in economy and efficiency [2]. Among various improved methods, the nitration of 1,3,5,7-tetraacetyl-1,3,5,7-tetraazacyclooctane (TAT) attracts a great deal of attention due to its high yield and product purity [2c, 3]. As an extremely valuable precursor of HMX, TAT can be prepared by acetylating of 2,6-diacetyl-pentamethylenetetramine (DAPT) or by condensation of small molecules (Scheme 1) [3a, 4]. However, the yields of these processes are still in need of improvement.

In continuing our interest and efforts on the optimization of TAT synthesis, we recently reported the a method to synthesize TAT. Based on these investigations [5], there are four key compounds in the synthesis of TAT (Scheme 1): TAT, DAPT, *N*,*N*′-methylenebisacetamide (MBA), 1,3,5-triacetyl-1,3,5-triazacyclohexane (TRAT), which are all polar compounds and can be detected by UV/Vis spectroscopy. DAPT is the starting material for TAT (Scheme 1 a). MBA is not only the starting material (Scheme 1 b), but also an important intermediate for TAT synthesized according to Scheme 1 c. TRAT is the main byproduct of the reaction Scheme 1 c, and also the nitration precursor for 1,3,5-trinitroperhydro-1,3,5-triazine (RDX). Thus, analysis of TAT and the related compounds during its synthesis is crucial to elucidate the synthetic mechanism, and thus to optimize the synthetic process. Nevertheless, it remains a key challenge to develop an efficient and simple method to separate and detect these compounds, and further to control the synthetic process of TAT.

Chromatographic separation is a rapid and sensitive technique, but there are currently no reports regarding chromatographic separation of TAT and related compounds. Reverse phase liquid chromatography (RPLC) is the most commonly used chromatographic method; however, RPLC does not retain polar analytes; separation of polar analytes

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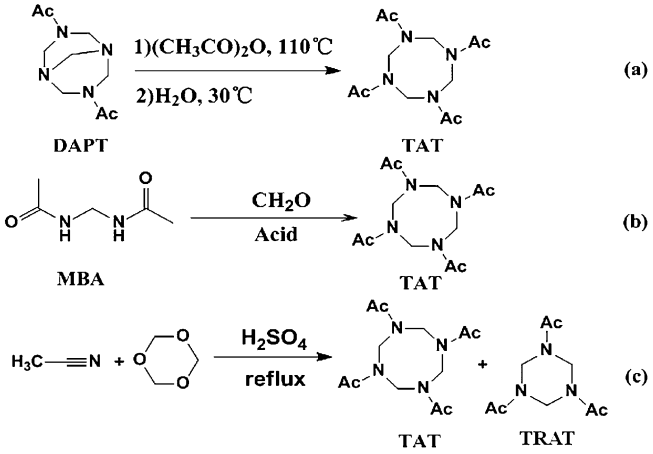


Scheme 1. Synthetic routes of TAT.

is a significant challenge for RPLC, i.e., using a C18 column. Kaiser investigated the separation of RDX and HMX on a CN column, and HMX appears shortly after void time [6]. Normal phase liquid chromatography (NPLC), including SiO_2 and NH_2 columns, were demonstrated to be used for the separation of polar analytes [7]. However, the reaction mixture of TAT and HMX usually contain large amount of acetic acid or acetic anhydride; these chemicals can react irreversibly with NH_2 group. Silica columns can be used with a pH in the range of 2 to 8, however when a hexane/2-propanol system was used as mobile phase. The retention of polar analytes was too strong, and only poor resolution was achieved. Instead, hydrophilic interaction chromatography (HILIC) has been proved to be a solid alternative approach in terms of the analysis of polar analytes [8]. HILIC takes advantage of polar stationary phases and a high-organic mobile phase in order to achieve remarkable retention for very polar analytes, which are difficult to be retained by RPLC. The mobile phase in HILIC largely addressed the solubility issue of polar analytes in NPLC. Due to the high polarity of TAT, TRAT, DAPT, and MBA, herein, we developed a separation method for these analytes based on HILIC.

2 Results and Discussion

2.1 Retention of TAT and other Analytes with HILIC

HPLC is a fast, efficient detection method that can provide a lot of information to optimize the synthesis of TAT. In order to set up a HPLC method to separate and detect TAT, TRAT, and other analytes, we investigated five columns, and the exposed functional entities on these stationary phases are shown in Figure 1.

Sample solutions containing TAT, TRAT, DAPT, and MBA (0.1 mg mL^{-1}, 10 μL) were applied to these columns and eluted with ACN/water mobile phase, respectively. The effect of water content in the mobile phase to the retention factors of analytes are shown in Figure 2.

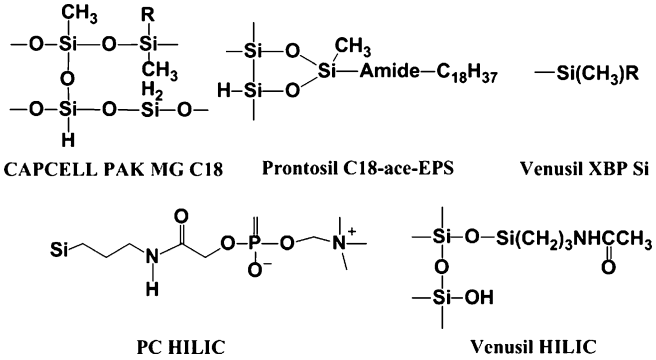


Figure 1. Functional entities on the HPLC columns.

According to Figure 2a and b, TAT and other polar compounds only had slight retention ($k < 0.2$) on RPLC columns (CAPCELL PAK MG C18 and Prontosil C18-ace EPS). Due to their polarity, TAT and other analytes have to be dissolved and analyzed in a polar mobile phase. Although Prontosil C18-ace EPS is a RPLC column with enhanced polarity, TAT and other analytes were not retained on it. There were no significant interactions between the polar analytes and the hydrophobic ligands on C18 stationary phase.

Venusil XBP Si has the best retention for TAT, TRAT, MBA, and DAPT according to Figure 2c. Free hydroxyl groups of XBP Si interact strongly with polar compounds through hydrogen bonding, and the retention factor reduced when water content increased. The result demonstrated a typical HILIC retention mechanism at higher ACN content (> 70 %), and a transition from HILIC to RPLC mode at around 70 % ACN content was observed. XBP Si, which employs SiO_2 as stationary phase, can retain polar analytes in polar mobile phase and the stationary phase will deteriorate quickly due to the collapse of SiO_2 in aqueous solvent. Thus poor stability and reproducibility of XBP Si column in aqueous mobile phase make it difficult for HILIC separation.

Cyano, amino, diol, zwitterionic, polyhydroxyethyl aspartamide, and cyclodextrin based packing are most commonly used as HILIC stationary phases. Most of these stationary phases are prepared by chemical modification of silica gel and are commercially available. We tested two HILIC columns: PC HILIC and Venusil HILIC, which were immobilized with phosphorylcholine and neutral amide groups, respectively (Figure 1). On the basis of Figure 2d and e, both of them provided remarkable retention to TAT and other polar compounds. Although phosphorylcholine on PC HILIC has a positively charged choline group, a negatively charged phospholipid group and can retain polar compounds very well, it failed to separate MBA and TAT. Thus, Venusil HILIC, due to its promising separation and reproducibility, was chosen to separate a mixture of the four analytes (Figure 3). To achieve a sensitive and quick separation of the analytes, the compositions of mobile phases and the flow rate were optimized, and the separation condition was set up as: ACN/H_2O (95/5, v/v) at 1.0 mL min^{-1}, detection at 215 nm, column temperature 25 °C, injection 10 μL. The an-

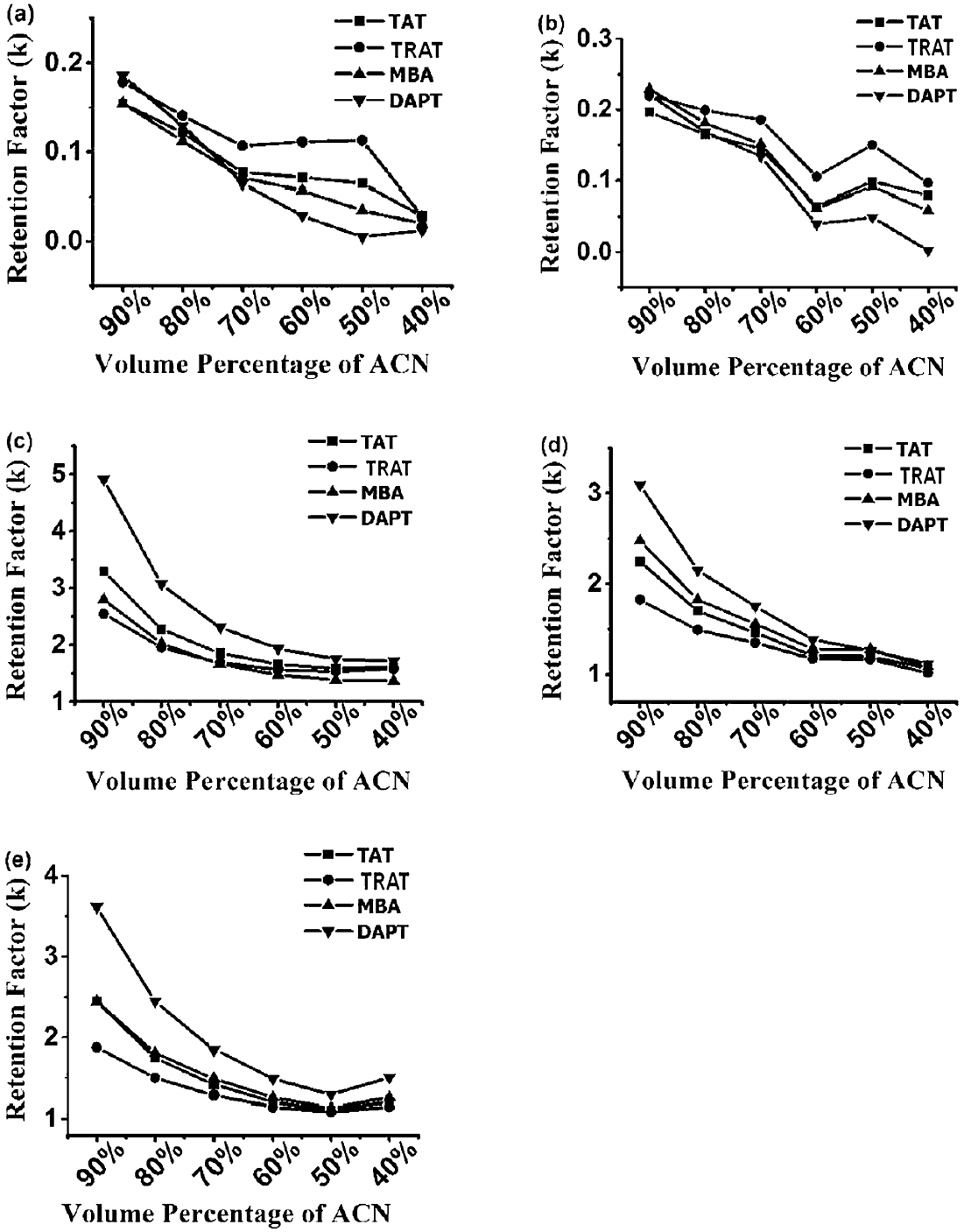


Figure 2. ACN content in mobile phase vs. retention factors of analytes on: (a) CAPCELL PAK C18; (b) Prontosil C18-ace-EPS; (c) Venusil XBP Si; (d) Venusil HILIC; (e) SHISEIDO PC HILIC.

alytes were baseline separated, and the retention for them are: 5.43 min (TRAT), 6.78 min (TAT), 7.70 min (MBA), 8.96 min (DAPT). Meanwhile, in order to follow the content changes of the related compounds in the reaction, we investigated the linearity of the four compounds, and the results are shown in Table 1, it demonstrated that all four compounds had broad linearity range and low LOD.

2.2 Analysis of Reaction Mixtures

The newly developed HILIC method was evaluated in the analysis of TAT synthesis reaction mixtures. Figure 4 a shows the HPLC analysis of the reaction mixture of the condensation of ACN and $(CH_2O)_3$ according to Scheme 1 c. Baseline separation was achieved for the three compounds: TAT,

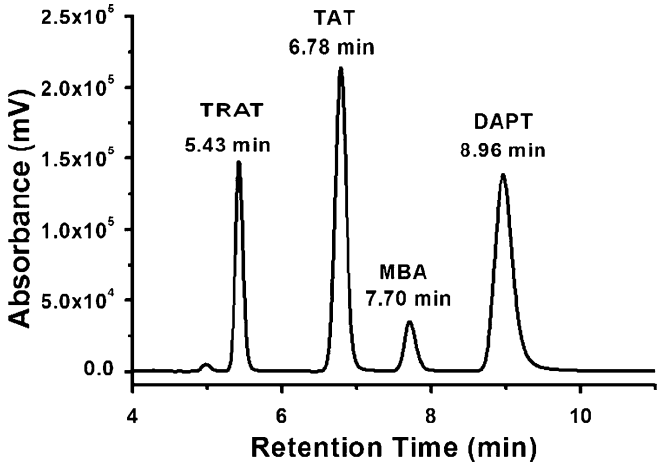
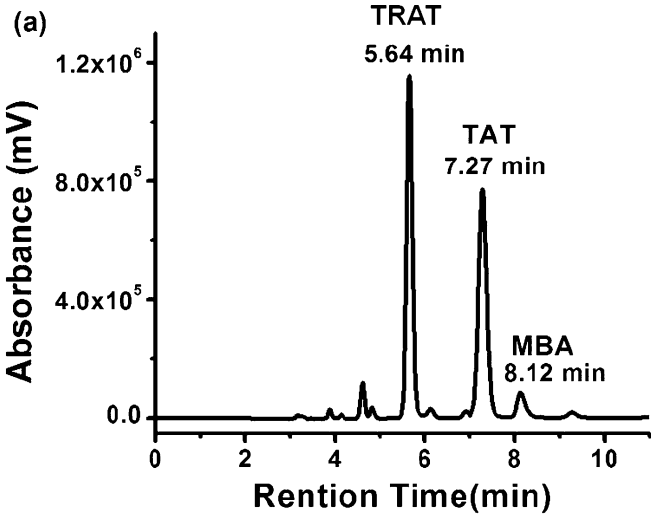


Figure 3. Seperation of TAT, TRAT, DAPT, and MBA on Venusil HILIC column.



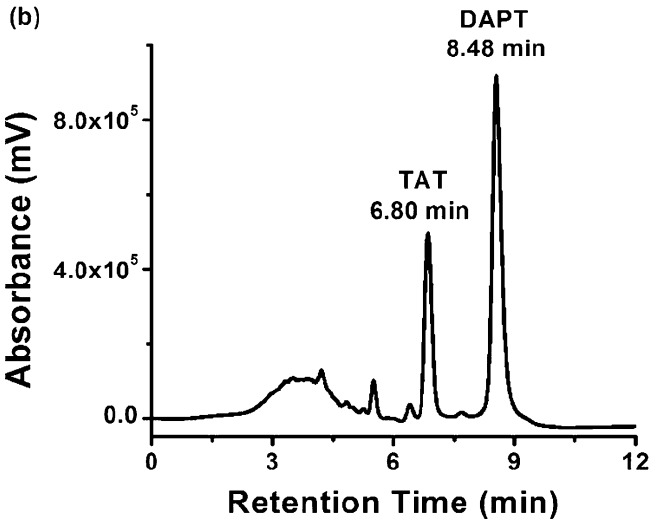


Figure 4. HPLC analysis of reaction mixtures: (a) reaction mixture of ACN and 1,3,5-trioxan; (b) reaction mixture of DAPT and acetic anhydride.

TRAT, MBA, and this result was further confirmed by HPLC-MS. The resolution factor (R_s) was 2.57 for TRAT and TAT, and 1.21 for TAT and MBA. In the meantime, baseline separation was also achieved for the acetylation mixture of DAPT according to Scheme 1a (Figure 4b). Owing to the presence of a large amount of acetic anhydride, the pH of reaction mixture was very low, which lead to a big and wide peak at about 3.5 min. However, it didn't affect the separation of TAT and DAPT. The R_s for TAT and DAPT was 1.42.

3 Experimental

3.1 Reagents and Chemicals

Acetic anhydride, ACN, H_2SO_4 (98%) were all of analytical grade and purchased from Beijing Chemical Plant. 1,3,5-Trioxan (analytical grade) was obtained from Acros, and the other materials were of analytical grade (AR) and used directly as purchased. TAT, TRAT, MBA, and DAPT were synthesized as reported in previous works [4b,d,9], and their purity was $>98\%$.

3.2 Instrumentation

HPLC analyses were performed with a Shimadzu LC-20 system equipped with an auto sampler and diode array detector. LC solution software was utilized for instrument control, data acquisition and analysis. HPLC analysis was carried out on the following columns: PC HILIC (SHISEIDO, Japan, 4.6×250 mm, 5 μm), CAPCELL PAK C18 (SHISEIDO, Japan, 4.6×150 mm, 3 μm), Venusil HILIC (Agela, China, 4.6×250 mm, 5 μm), Venusil XBP Si (Agela, China, 4.6×25 mm, 5 μm), and Prontosil C18-ace-EPS (B&W, Germany, 4.6×

Table 1. Seperation and detection limit of the analyts on Venusil HILIC column.

Analytes	Retention time [min]	Relative peak area[a)] [mv min^{-1}]	Linearity range [mg mL^{-1}]	Limit of detection [mg mL^{-1}]
TAT	6.78	888584	0.9–6.8	0.001
TRAT	5.43	1205228	0.7–10.3	0.003
MBA	7.70	2837684	0.08–8.2	0.008
DAPT	8.96	14358410	0.02–3.8	0.002

a) Detected separately and concentrations were all 1 mg mL^{-1}.

250 mm, 5 μm). Aliquots (10 μL) of sample solutions were injected, the mobile phase was ACN/water with a flow rate of 1.0 mL min^{-1}, the detection wavelength was 215 nm, and the column temperature was 25 °C.

3.3 Synthesis of TAT

3.3.1 Synthesis of TAT from DAPT

DAPT (0.010 mol) was mixed with acetic anhydride (0.030 mol), stirred and refluxed at 110 °C for 30 min. Afterwards, the reaction was quenched in ice bath. 100 μL of the obtained reaction solution was diluted by ACN/H_2O (95/5, v/v) 10-fold, and used for HPLC analysis.

3.3.2 Synthesis of TAT from 1,3,5-Trioxan

Droplets of H_2SO_4 were added to 5.2 mL ACN (0.1 mol) at 50 °C, and then $(CH_2O)_3$ (0.017 mol) was added. After the solution became turbid, the reaction was quenched in ice bath, sampled 100 μL and dissolved in ACN/H_2O (95/5, v/v) to 1 mL for HPLC analysis.

4 Conclusions

This study tested five columns to separate TAT and other polar compounds. It proved that RPLC can't retain these polar compounds and HILIC had a better separation. Completed within 10 min, the simple and efficient method was found useful for the analysis of TAT and the related polar compounds in its synthesis. Using HILIC chromatography, by which ACN/water (95/5, v/v) was used a mobile phase, reaction mixtures of TAT synthesis can be analyzed. This developed method will provide important information for the elucidation of reaction mechanism and optimization of synthetic process for TAT and HMX.

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