Synthesis and Quality Control of 3,3′-Diamino Diphenyl Sulfone by High Performance Liquid Chromatography

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INTRODUCTION

3,3′-Diamino diphenyl sulfone is mainly used as a curing agent of epoxy resins and the cured resins exhibit good mechanical and insulating properties and antimicrobial resistance. It is also the intermediate of heat-resistant resins, polysulfones and other polymers1–3. For instance, the addition of 3,3′-diamino diphenyl sulfone in polycondensation of 4,4′-diamino diphenyl sulfone and terephthaloyl chloride (TPC) endues the poly-(amide-sulfone), 4,4′-diamino diphenyl sulfone/terephthaloyl chloride/3,3′-diamino diphenyl sulfone (4,4′-DADPS/TPC/3,3′-DADPS), with higher solubility than 4,4′-diamino diphenyl sulfone/terephthaloyl chloride condensation polymer due to lower molecular symmetry of 3,3′-diamino diphenyl sulfone than 4,4′-diamino diphenyl sulfone4. Besides, 3,3′-diamino diphenyl sulfone is applied widely in the preparation of pesticides, medicines and dyes. The dyes using 3,3′-diamino diphenyl sulfone as intermediate present gorgeous color and excellent performance. Because the toxicity of 3,3′-diamino diphenyl sulfone is very low, it can substitute carcinogenic intermediates such as 3,3′-dimethoxybenzidine and consequently, it has broad application prospect5. Recently, 3,3′-diamino diphenyl sulfone dissolved in ethanol was mixed directly with monophosphoric acid to prepare a new organic-inorganic hybrid crystal material, [C6H5N2O2S2](HPO3)H2PO4, which has a noncentrosymmetric structure and can be a good candidate for nonlinear optic applications6.

The easiest method of introducing an amino group in 3-position appeared to be by nitration of the proper sulfone, a meta-directing group, followed by reduction7. In industry, 3,3′-diamino diphenyl sulfone is synthesized via reduction of 3,3′-dinitro diphenyl sulfone generated from the nitration reaction of diphenyl sulfone (DPS) as shown in Fig. 1. The reduction reaction can be performed by using iron powder8,9, sodium sulfide10, ammonium sulfide11, Adams’ catalyst12, hydrazine hydrate13 and zinc-hydrochloric acid14 as reducing agents, or through hydrogenation15 and electrolyzation1. Among them, the reduction by hydrazine hydrate only produces nitrogen and water as side-products, rather than side-products harmful to the environment and the reaction performed under atmospheric pressure not only has high conversion rate but also needs simple post-processing. Therefore, hydrazine hydrate has a great advantage in the reduction of nitro16.

From the synthetic route, it can be concluded that while 3,3′-dinitro diphenyl sulfone is generated from diphenyl sulfone, its isomers such as 2,2′-, 2,3′-, 2,4′-, 3,4′- and 4,4′-
dinitro diphenyl sulfone are inevitably produced since nitro group has different selectivity in different positions. These isomers would be converted into 2,2', 2,3', 2,4', 3,4'- and 4,4'-diamino diphenyl sulfone, respectively, via the subsequent reduction reaction. In addition, 3-amino-3'-nitro diphenyl sulfone (3,3'-ANDPS), as well as 2,2', 2,3', 2,4', 3,4'- and 4,4'-ANDPS may also exist in the product because of the partial reduction of 3,3'-dinitro diphenyl sulfone, as well as 2,2', 2,3', 2,4', 3,4'- and 4,4'-dinitro diphenyl sulfone, respectively. From the viewpoint of chromatographic fingerprint of fine chemicals, the relative substances mentioned above constitute the basic "impurity group" of 3,3'-diamino diphenyl sulfone for industrial use. The reason why it is called "basic" is because the structure of some impurities is not exactly clear. However, this ambiguity does not embarrass the establishment of chromatographic fingerprint. All of the above relative substances would influence the content and the quality of 3,3'-diamino diphenyl sulfone product, so they must be strictly controlled.

However, the studies of 3,3'-diamino diphenyl sulfone mainly focus on its preparation. At present, only non-aqueous titration method was reported for the assay of 3,3'-diamino diphenyl sulfone, which aimed at the determination of main content. There has not been any report about the analysis of related impurities in industrial 3,3'-diamino diphenyl sulfone up to date. In this paper, the separation of relative substances in 3,3'-diamino diphenyl sulfone for industrial use was realized by means of HPLC-UV detection. LC-MS/MS was employed to further identify the related impurities. In addition, chromatographic fingerprint of industrial 3,3'-diamino diphenyl sulfone was established on the basis of the analysis of a series of industrial 3,3'-diamino diphenyl sulfone through the same production method.

**EXPERIMENTAL**

Instrumentation for HPLC analysis was an Agilent 1200 series consisting of a vacuum degasser, a quaternary pump, an auto-sampler, a thermostatted column compartment, a diode array detector (DAD) and a chemstation (Agilent, Santa Clara, USA).

The LC-MS system consisted of an Agilent 1290 infinity LC system (Agilent, Waldbronn, Germany) coupled to a 6460 triple quadrupole mass spectrometer (Agilent, Santa Clara, USA). Data acquisition was carried out by Agilent MassHunter software.

Methanol and acetonitrile were both HPLC grade (Honeywell, Ulsan, Korea). Purified water (Wahaha Group Co., Ltd. Hangzhou, China) was used throughout the experiment. Reference substances (RSs) of 3,3'-diamino diphenyl sulfone and 4,4'-diamino diphenyl sulfone were kindly provided by Yangzhong Synthetic Chemical Plant (Zhenjiang, China). RS of 3-amino-3'-nitro diphenyl sulfone was supplied by Nanjing University of Technology. Industrial products of 3,3'-diamino diphenyl sulfone were also from Yangzhong Synthetic Chemical Plant.

**HPLC condition:** HPLC separation was achieved on an Ultimate XB-C18 column (150 × 4.6 mm I.D., 5 μm; Welch Materials, Inc., Shanghai, China). The column temperature was maintained at 30 °C. The mobile phase consisted of methanol and water (40/60, v/v) at a flow rate of 1 mL/min. The injection volume was 10 μL. The effluent was monitored by DAD detector set at 250 nm.

**LC-MS condition:** LC-MS separation was achieved on a ZORBAX Eclipse XDB-C18 column (2.1 × 150 mm I.D., 3.5 μm, Agilent Technology, USA) at a mobile phase flow rate of 0.2 mL/min. Injection volume was 2 μL. Other conditions were the same as those in HPLC. Electrospray ionization (ESI)-MS survey scan was conducted at mass range from 70 to 700 in positive ion mode. Parameters: gas temperature, 350 °C; gas flow, 8 L/min; nebulizer pressure, 45 psi; sheath gas temperature, 250 °C; sheath gas flow, 10 L/min; capillary voltage, 4000 V; The induced collision dissociation energy of MS/MS was 15 V.

**Standard solutions:** Stock solutions were prepared by weighting about 25 mg 4,4'-diamino diphenyl sulfone and 25 mg 3-amino-3'-nitro diphenyl sulfone RSs to two 25 mL volumetric flasks, respectively, adding 10 mL methanol to dissolve and make up to the mark with water after 1 min sonication. Mixed standard solutions at concentration of 1 × 10^{-3} to 0.1 g L^{-1} each component were prepared by serial dilution of the above stock solutions with mixture of methanol-water (40/60, v/v).

**Sample solutions:** For HPLC analysis, about 25 mg industrial 3,3'-diamino diphenyl sulfone was weighed to a 25 mL flask, dissolved by 10 mL methanol and made up to the mark with water after 1 min sonication. For LC-MS analysis, 3,3'-diamino diphenyl sulfone sample solution was diluted 10 times.

**RESULTS AND DISCUSSION**

**Selection of mobile phase**

**Organic modifier:** An optional 3,3'-diamino diphenyl sulfone sample solution spiked with 4,4'-diamino diphenyl sulfone and 3-amino-3'-nitro diphenyl sulfone standard solutions was analyzed using isocratic elution with acetonitrile-water and methanol-water as mobile phases, respectively. Typical separation performance is compared in Fig. 2. Almost all the components in the sample solution have good separation when acetonitrile-water (35/65, v/v) was used as mobile phase, but unknown peaks 4 in 3,3'-diamino diphenyl sulfone sample and I_2 from 3-amino-3'-nitro diphenyl sulfone RS were overlapped. While using methanol-water (40/60, v/v) as mobile phase, a baseline separation of peaks 4 and I_2 was realized in shorter running time. In addition, considering the toxicity and price of acetonitrile, methanol was finally selected as the organic modifier.

**Methanol proportion:** An optional 3,3'-diamino diphenyl sulfone sample solution spiked with 4,4'-diamino diphenyl sulfone and 3-amino-3'-nitro diphenyl sulfone RSs was analyzed...
It can be indicated that the structure of unknown impurity 2 is identical to that of 3,3'- and 4,4’-diamino diphenyl sulfone. Therefore, we can reasonably deduce that unknown impurity 2 is likely 3,4’-diamino diphenyl sulfone.
Neither distinct UV nor MS spectra of unknown impurities 4 and 5 in 3,3’-diamino diphenyl sulfone samples and 1 and 2 from 3-amino-3’-nitro diphenyl sulfone RS were not obtained probably because their contents were very low in respect of the normalized peak area percentage (A %) by HPLC-UV detection, respectively. Therefore, these impurities were not further identified.
A reliable RP-HPLC method with UV detection was developed for the separation and determination of 3,3’-diamino diphenyl sulfone for industrial use and its relative substances. On this basis, the chromatographic fingerprint of industrial 3,3’-diamino diphenyl sulfone was established, which can supply a facile way for quality control of 3,3’-diamino diphenyl sulfone, as well as its related products including 3-amino-3’-nitro diphenyl sulfone, 3,4’-diamino diphenyl sulfone, and the like.

Table 1 shows the recoveries of 3,3’-diamino diphenyl sulfone samples were prepared in quintuplicates separately to carry on intra-day precision measurements. The HPLC chromatogram of a typical industrial 3,3’-diamino diphenyl sulfone is shown in Fig. 7. The inter-day determination was accomplished by preparing and analyzing 3,3’-diamino diphenyl sulfone sample solutions (n=5) in five consecutive days. The analytical results with intra- and inter-day relative standard deviations (RSDs) of peak area and retention time of 4,4’-diamino diphenyl sulfone product is similar with the fingerprint, we can rapidly estimate that it is primarily eligible. Otherwise, it is unqualified. Consequently, the proposed fingerprint is of significant importance for supplying an easy way for quality assessment of 3,3’-diamino diphenyl sulfone and related industrial products.

Conclusion

A reliable RP-HPLC method with UV detection was developed for the separation and determination of 3,3’-diamino diphenyl sulfone for industrial use and its relative substances. On this basis, the chromatographic fingerprint of industrial 3,3’-diamino diphenyl sulfone was established, which can supply a facile way for quality control of 3,3’-diamino diphenyl sulfone, as well as its related products including 3-amino-3’-nitro diphenyl sulfone, 3,4’-diamino diphenyl sulfone, 4,4’-diamino diphenyl sulfone and the like.

Recoveries were obtained by spiking a known amount of 4,4’-diamino diphenyl sulfone and 3-amino-3’-nitro diphenyl sulfone RSs to a 3,3’-diamino diphenyl sulfone sample solution. Three levels of standards were added and three replicates at each level were performed for the test. The results are shown in Table 4. The recovery ranges of 4,4’-diamino diphenyl sulfone and 3-amino-3’-nitro diphenyl sulfone were 94.71-98.89 and 96.46-99.16 %, respectively, showing a good accuracy.
TABLE-5  
DETERMINATION OF PARTIAL RELATIVE  
SUBSTANCES IN EIGHT BATCHES OF  
3,3’-DIAMINO DIPHENYL SULFONE PRODUCTS  

<table>
<thead>
<tr>
<th>Batch</th>
<th>4,4’-DADPS</th>
<th>3,4’-DADPS*</th>
<th>3,3’-ANDPS**</th>
<th>Unknown impurity 4*</th>
<th>(%)</th>
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<tbody>
<tr>
<td>1</td>
<td>0.006</td>
<td>1.015</td>
<td>0.020</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.007</td>
<td>1.026</td>
<td>0.028</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.017</td>
<td>0.891</td>
<td>0.031</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.011</td>
<td>0.908</td>
<td>0.015</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.007</td>
<td>1.101</td>
<td>0.020</td>
<td>0.023</td>
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<tr>
<td>6</td>
<td>0.075</td>
<td>0.950</td>
<td>0.019</td>
<td>0.019</td>
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<tr>
<td>7</td>
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<td>0.971</td>
<td>0.016</td>
<td>0.024</td>
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</tr>
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<td>8</td>
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<td>1.138</td>
<td>0.019</td>
<td>0.030</td>
<td></td>
</tr>
</tbody>
</table>

*Self-control method; **Below the LOQ

ACKNOWLEDGEMENTS

This work was supported by National Basic Research Program of China (973 program, 2009CB421601, 2011CB-911003), National Natural Science Foundation of China (21275069, 90913012, 21121091) and Starting Fund for Young Teachers and Analysis & Test Fund of Center of Materials Analysis, Nanjing University.

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