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Interface for Online Coupling of Surface Plasmon Resonance to Direct Analysis in Real Time Mass Spectrometry

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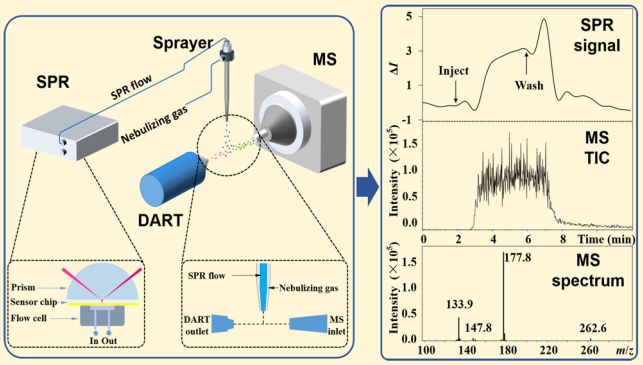
Supporting Information

ABSTRACT: The online coupling of surface plasmon resonance (SPR) with mass spectrometry (MS) has been highly desired for the complementary information provided by each of the two techniques. In this work, a novel interface for direct and online coupling of SPR to direct analysis in real time (DART) MS was developed. A spray tip connected with the outlet of the SPR flow solution was conducted as the sampling part of the DART-MS, with which the online coupling interface of SPR-MS was realized. Four model samples, acetaminophen, metronidazole, quinine, and hippuric acid, dissolved in three kinds of common buffers were used in the SPR-DART-MS experiments for performance evaluation of the interface and the optimization of DART conditions. The results showed consistent signal changes and high tolerance of nonvolatile salts of this SPR-MS system, demonstrating the feasibility of the interface for online coupling of SPR with MS and the potential application in the characterization of interaction under physiological conditions.



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Publication Date (Web): June 23, 2015 | doi: 10.1021/acs.analchem.5b01272

Surface plasmon resonance (SPR) is a powerful technique widely utilized in multiple areas related with analytical and biological concerns, especially the studies based on interaction processes such as cellular analysis[1] and clinical research.[2] Despite its versatility, there still exist some intrinsic deficiencies due to the principle of SPR, among which the insufficiency in qualitative analysis remains a significant one. Generally, the information acquired by conventional SPR instruments is inadequate for the identification of the samples, constraining the application of SPR in the research dealing with unknown species such as ligand fishing[3] or active ingredient identification.[4] Consequently, the combination of SPR with other analytical approaches that can provide molecular information has been highly desired. Since mass spectrometry (MS) is an extraordinary technique in qualitative analysis, it will be strongly complementary to SPR once their coupling can be realized. The combination of SPR with MS would be beneficial for the possibility of studying interaction processes in the molecular level.

Since the first attempt to combine SPR with MS,[5] great efforts have been paid to this area.[6−9] Evidently, the interface between SPR and MS is the most challenging issue.[8] For a SPR-MS study, the aim of using MS is to identify the participants of the interaction, which means all the molecules captured onto the sensor surface, remained in the flow solution, or eluted from the sensor surface may be detected by using MS. So far, the existing interfaces for SPR-MS were mainly developed from two MS ionization methods: matrix assisted laser desorption ionization (MALDI) and electrospray ionization (ESI). In typical applications, MALDI-based interface was used to study the substances on,[10−14] or eluted[15] from, the sensor surface. This could be called off-line SPR-MS. Interface based on ESI could be used for off-line SPR-MS as well.[16] But more importantly, it has the potential to be operated as online SPR-MS, which means acquiring MS data simultaneously with SPR data. As it is fast, high-throughput, precise in quantification, and easy for automation, online SPR-MS could greatly contribute to the study of ligand fishing, drug screening, and so on. However,

Received: April 3, 2015
Accepted: June 11, 2015
Published: June 11, 2015

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DOI: 10.1021/acs.analchem.5b01272
Anal. Chem. 2015, 87, 6505−6509

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interaction study using SPR usually requires the mimic of physiological condition using nonvolatile salts,[8] which brings incompatibility for the SPR-ESI-MS. Most SPR-MS experiments employing ESI-based interface usually needed additional chromatographic instrumentation,[17,18] and few direct online coupling of SPR with MS existed hitherto.

In recent years, various novel ionization methods operated under ambient circumstances have been developed, among which direct analysis in real time (DART) emerges to be one of the most promising techniques. Since its introduction by Cody et al.,[19] DART has been applied for diverse purposes, including food-quality analysis[20] and drug determination.[21] DART ionizes analytes mainly by the proton transfer via reactive species produced by its heated metastable plasma.[19,22] It has been proven to be simple, rapid, direct, and less influenced by the matrix effect, making its combination with other instruments or techniques easy and practical, such as solid-phase extraction (SPE),[23] solid-phase microextraction (SPME),[24] high-performance liquid chromatography (HPLC),[25−27] and capillary electrophoresis (CE).[28] Particularly, research on the combination of DART with HPLC and CE exhibited the high tolerance of nonvolatile salts, suggesting the potential of using DART to set up an interface to direct couple SPR with MS, minimizing the negative effects of the salts commonly required in SPR experiments.

In this work, a newly developed interface to couple SPR with MS using spray tip and DART was reported. The SPR flow solution was led into a sprayer, whose tip was put in middle of the DART outlet and the MS inlet, thus the solution could be sprayed and ionized. Proof-of-concept experiments using 4 chemicals dissolved in 3 types of salt-containing solvents were conducted, showing the practicability of this interface by observing the consistent change of the signals of MS and SPR. The performance of this interface and its salt tolerance suggested its high potential in the screening of the unknown interaction under physiological conditions using SPR-MS.

EXPERIMENTAL SECTION

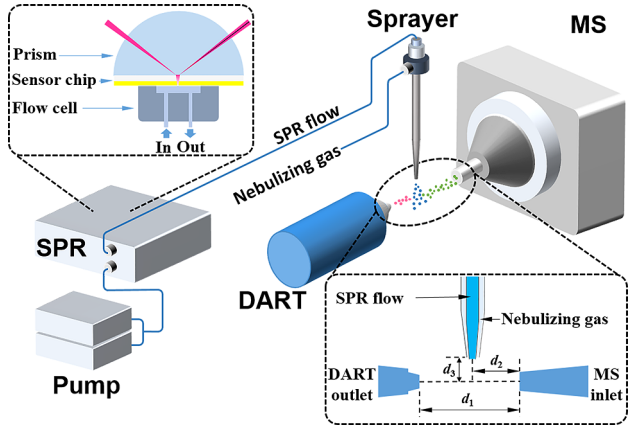
Chemicals and Solutions. 3-Mercaptopropionic acid (3-MPA), tris(2-carboxyethyl)phosphine hydrochloride (TCEP), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (EDC), *N*-hydroxysuccinimide (NHS), 4-acetamidophenol (acetaminophen), 2-methyl-5-nitro-1-imidazolethanol (metronidazole), and quinine were purchased from J&K Scientific Ltd. (Beijing, China). Human serum albumin (HSA) was purchased from Shanghai Yuanye Biological Technology Co., Ltd. (Shanghai, China). Ethanolamine was purchased from Xilong Chemical Co. Ltd. (Shantou, Guangdong, China). Ammonia solution was purchased from Beijing Tong Guang Fine Chemicals Company (Beijing, China). Hydrogen peroxide was purchased from Beijing Chemical Works (Beijing, China). *N*-Benzoylglycine (hippuric acid) was the product of Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Purified water was purchased from Hangzhou Wahaha Group (Hangzhou, Zhejiang, China). Phosphate buffered saline (PBS, containing 137 mmol/L NaCl, 2.7 mmol/L KCl, 10 mmol/L Na_2HPO_4, and 2 mmol/L KH_2PO_4) and tris buffered saline (TBS, containing 10 mmol/L tris(hydroxymethyl)aminomethane and 150 mmol/L NaCl) were purchased from Bionova Biotech Co., Ltd. (Beijing, China). Earle's balanced salt solution (EBSS, containing 116 mmol/L NaCl, 5.4 mmol/L KCl, 1.8 mmol/L $CaCl_2$, 0.81 mmol/L $MgSO_4$, 6.40 mmol/L Na_2HPO_4, 26.2 mmol/L $NaHCO_3$, 1.0 g/L glucose, and 0.01 g/L phenolsulfonphthalein) was purchased from Sigma-Aldrich Co., LLC. (Shanghai, China).

Apparatus and Interface. The SPR experiments were conducted using a light-intensity modulation SPR analyzer provided by DyneChem Instruments Corporation (Changchun, Jilin, China). It had a Kretschmann configuration using attenuated total reflection (ATR) in a prism to achieve the resonant condition. The intensity of the reflected light would change if the resonant condition should be achieved. The sensor chip with Au film deposited onto a glass substrate was purchased from Beijing Honoprof Sci&Tech Ltd. (Beijing, China). The SPR analyzer had a peristaltic pump itself, besides which additional HPLC pumps (Agilent Technologies, Palo Alto, CA) were connected to provide more stable solution delivery.

The MS experiments were conducted using an Agilent XCT ion trap mass spectrometer (Agilent). A DART-SVP ion source (IonSense, Saugus, MA) was coupled to the mass spectrometer after removing the original electrospray ion source and connecting a vacuum pump (Vacuubrand, Wertheim, Germany) to the MS inlet chamber. The vacuum pump could restrict excess ionization gas flowing into the mass spectrometer and balance the vacuum inside the mass spectrometer.

A commercial Agilent liquid sprayer (Palo Alto, CA) installed in the original electrospray ion source was employed for spraying the SPR flow solution. It was attached onto a 3D platform via a homemade holder, allowing the horizontal and vertical position adjustment. The tip was grounded, and no high voltage was applied, thus no electrospray would be created. The spray tip was set orthogonally with the DART outlet and the MS inlet. The end of it was put between the DART outlet and the MS inlet, thus the solution flowing out from SPR could be led into the sprayer and get sprayed, then ionized by the DART ion source and analyzed by the mass spectrometer. The schematic diagram illustrating the interface and the system was shown in Scheme 1.

Scheme 1. Schematic Diagram of the SPR-DART-MS System



SPR Sensor Chip Modification. The sensor chip was modified with HSA using the common EDC/NHS coupling method. The sensor chip was first cleaned by immersing it in a solution blended by ammonia solution, hydrogen peroxide, and water with the volume ratio of 1:1:5 and being kept at 90 °C for 10 min. After installing the cleaned chip into the SPR analyzer, the following modification process was carried out by

DOI: 10.1021/acs.analchem.5b01272
Anal. Chem. 2015, 87, 6505−6509

successively injecting and flowing: (a) 3-MPA with TCEP (4 mmol/L and 6 mmol/L), for 60 min; (b) EDC and NHS (0.05 g EDC and 0.01 g NHS dissolved in 4 mL H_2O), for 20 min; (c) HSA (0.01 g/L), for 12 h; and (d) ethanolamine (1 mol/L, pH 8.4), for 10 min. The SPR curves showing the whole modification process was shown in Figure S-1 (see the Supporting Information), and the change of the SPR angle was shown in Figure S-2 of the Supporting Information. The change of the SPR angle before and after the HSA modification proved that the protein had been successfully immobilized onto the sensor chip.

SPR-DART-MS Experiments. After the modification of the SPR sensor chip and the setup of the whole system, the SPR-DART-MS experiments were conducted. First of all, we would like to test the feasibility of direct SPR-DART-MS and the tolerance of salts. Acetaminophen, metronidazole, quinine, and hippuric acid were selected to be the model analytes, with PBS, TBS, and EBSS chosen as the representative solvents to simulate the physiological conditions that might be used in usual SPR experiments. There were all together 12 kinds of sample solutions: 25 mmol/L of acetaminophen dissolved in PBS, TBS, and EBSS, respectively; 25 mmol/L of metronidazole dissolved in PBS, TBS, and EBSS, respectively; 1.3 mmol/L of quinine dissolved in PBS, TBS, and EBSS, respectively; and 22 mmol/L of hippuric acid dissolved in PBS, TBS, and EBSS, respectively.

A single run was started by commencing SPR and MS data acquisition simultaneously. For the first 2 min, pure solvent was delivered. At the beginning of the third minute, the sample solution started to flow and lasted for 4 min. During these 4 min, the analyte might bind to the HSA immobilized on the sensor surface, leading to a change in the SPR signal. From the sixth minute, again the pure solvent was delivered, and the analyte would be washed away. After the SPR signal fell back to its baseline and the MS signal became stable, the data acquisition was stopped. The raw SPR data was denoised by fast Fourier transformation smoothing before further analysis.

The solution flow rate of all of the runs was 0.20 mL/min. The nebulizing gas was nitrogen at a pressure of 15 psi. The distances were set as following: d_1, 2.0 cm; d_2, 10 mm, and d_3, 6 mm (see Scheme 1). The SPR analyzer was set at constant angle mode recording the reflected light intensity at the SPR angle. For the DART ion source, the temperature was set at 450 °C, helium was used as a working gas. The MS parameters were capillary voltage, off; dry gas temperature, 325 °C; and dry gas flow rate, 5 L/min. The range of m/z between 100 and 400 was scanned with a maximum ion accumulation time of 200 ms. MS was operated at positive mode when analyzing solutions containing acetaminophen, metronidazole, or quinine and the negative mode for solutions of hippuric acid. All other parameters were set as default values.

RESULTS AND DISCUSSION

Optimization of the DART Conditions. As preliminary experiments, the following parameters that might affect the DART ionization and the MS analysis were optimized: DART source temperature, the vertical distance between the spray tip and the DART-outlet-MS-inlet plane (d_3), the total horizontal distance between the DART outlet and the MS inlet (d_1), the flow rate of the solution, and the nebulizing gas pressure for the spray. As these parameters were independent, a series of experiments based on the orthogonal experimental design were conducted, using 25 mmol/L acetaminophen dissolved in PBS as the sample. The design of the orthogonal tests was elucidated in Part S-2: Table S-1 and Table S-2 of the Supporting Information. The results of the effects of these parameters were shown in Figure 1.

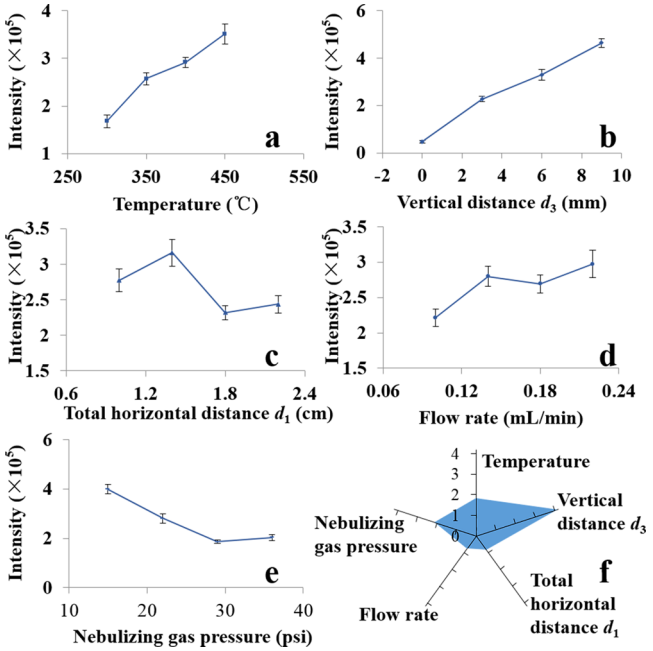


Figure 1. Results of the orthogonal experiments illustrating the effects of the parameters on DART ionization: (a) DART source temperature; (b) vertical distance d_3; (c) total horizontal distance d_1; (d) solution flow rate; (e) nebulizing gas pressure; and (f) the significance of these parameters. Each test was repeated 3 times.

It could be concluded from Figure 1 that the significance of the parameters were as follows: d_3 > nebulizing gas pressure > temperature > flow rate > d_1. For d_3, the temperature and the flow rate, higher values would lead to better signals, and for the nebulizing gas pressure, a lower value would be better. The values of d_1 showed no clear tendency. These effects could be explained by the principle of the interface. As the interface was spray-based, a better spray condition was of great concern. The droplets in the spray would get smaller and better distributed as they flew away from the spray tip, so a larger d_3 would be beneficial. Also, as the analytes were dissolved in the solutions and the sprayed droplets, the ionization would consist of the evaporation and desolvation process, thus a higher source temperature would be more productive. For the nebulizing gas pressure, if it was too high, the droplets would be blown away too fast from the DART ionizing stream, so a lower pressure would be better. The flow rate meant the amount of sample, and a higher value led to a stronger signal. The value of d_1 showed least importance, thus it was selected considering other parameters.

Besides these, the horizontal distance between the spray tip and the MS inlet (d_2) could also affect the results. However, as there was a restrictive requirement that d_2 must be less than d_1, the value of d_2 could not be included in the orthogonal experiments, and it was optimized separately. Generally, a smaller d_2 could allow more ions to go into the MS inlet, but it might also lead to the sample residue at the MS inlet. Also, a larger d_3 would result in more residue. With consideration to the signal intensity and the sample residue contamination, the

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DOI: 10.1021/acs.analchem.5b01272
Anal. Chem. 2015, 87, 6505−6509

following parameters were selected: DART source temperature, 450 °C; d_1, 2.0 cm; d_2, 10 mm; d_3, 6 mm; flow rate, 0.20 mL/min; nebulizing gas pressure, 15 psi. Additionally, either helium or nitrogen might be chosen as the DART working gas. Based on the previous experience, helium could give a better signal, thus it was used as working gas for all of the sample solutions.

Performance of the SPR-DART-MS Experiments. The recorded SPR curves along with the MS signals for the SPR-DART-MS experiments were shown in Figure 2.

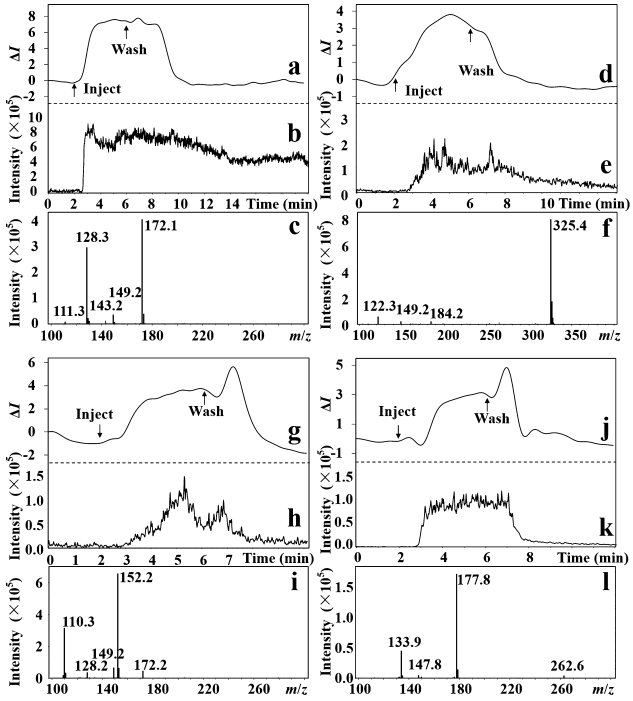

Figure 2. Representative results of the SPR-DART-MS experiments. Sample solutions: (a–c) metronidazole dissolved in PBS; (d–f) quinine dissolved in TBS; (g–i) acetaminophen dissolved in EBSS; and (j–l) hippuric acid dissolved in PBS. SPR curves: a, d, g, and j; extracted ion chromatograms: b (m/z = 172, $[M + H]^+$); e (m/z = 325, $[M + H]^+$); h (m/z = 152, $[M + H]^+$); k (m/z = 178, $[M\text{-}H]^-$); MS spectra of each analyte: c, f, i, and l.

As mentioned in the Experimental Section, there were 12 sample solutions. Figure 2 showed 4 sets of typical results, while all of the 12 results were shown in Figure S-3 and Figure S-4 of the Supporting Information.

From Figure 2, it was undoubtedly proven that the as-designed spray and DART-based interface could be used successfully and practically for online coupling of SPR with MS, as the MS signal changed consistently with the SPR signal. For the first 2 min during which the pure solvent flowed through the SPR analyzer, SPR signal stayed at its baseline, and so did the MS signal. As the solution containing analytes started to flow at the third minute, the SPR signal started to increase as the analyte bound with the HSA immobilized on the sensor chip. The MS signal also increased, as the excess analyte in the solution got sprayed and ionized. From the sixth minute, pure solvent flowed again, and the SPR signal changed to its original values because of the dissociation of the bound analytes, and the MS signal also decreased.

There is an observable lag of approximately 1 min between the increase of the MS signal and the injection of the sample solution. This was mainly because of the volume of the SPR flow cell and the connecting tubes. All of these volumes between the pump and the MS would act like the dead volume similar in a chromatography process, delaying the change of the MS signal. For some samples, there was another lag between the decrease of the MS signal and that of the SPR signal. Besides the dead volume, there were another two reasons explaining the delay of this decrease. First, there remained analytes bound on the sensor chip, the elution of these analytes would last for some time, thus the MS signal would remain high during all this elution process. Second, as the aqueous solutions containing nonvolatile salts were used, the evaporation of the sprayed droplets would often be incomplete, resulting in the residue of the analytes in the vicinity of the spray tip and the MS inlet, keeping the MS signal from decreasing. Notwithstanding this residue, it demonstrated the necessity and advantage of the DART-based interface, that it could prevent the residue from contaminating the conventional ESI source.

Salt Tolerance of the DART Interface. In order to study the salt tolerance of the spray and DART-based SPR-MS interface, a series of ionization experiments of the 4 analytes dissolved in water, PBS, TBS, and EBSS were conducted. The obtained intensities of the 4 analytes were plotted in Figure 3.

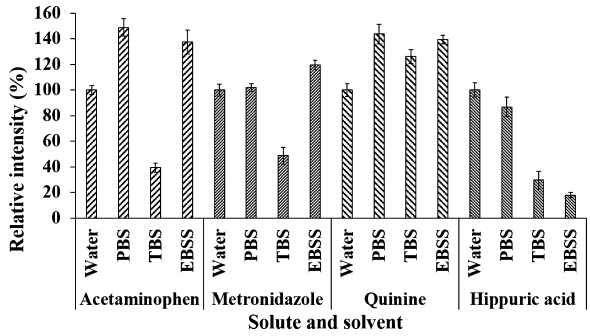

Figure 3. Relative intensities of the quasi-molecular ions of each analyte dissolved in different buffers using the designed interface. For each analyte, the intensity obtained from its extracted ion chromatogram was normalized using the intensity achieved from water matrix (n = 3). Extracted ions: acetaminophen (m/z = 152, $[M + H]^+$); metronidazole (m/z = 172, $[M + H]^+$); and quinine (m/z = 325, $[M + H]^+$) and (m/z = 178, $[M - H]^-$).

Figure 3 revealed that for most analytes and solvents, the interface showed a high tolerance of the nonvolatile salts. For the 3 analytes in positive mode, both of PBS and EBSS showed even higher signal intensity than water, indicating that the low-molecular-weight salts might help the proton transfer to form positive species. TBS showed lower signal intensity, which could be explained by the competitive ionization between the analyte and tris contained in TBS, which was supported by the strong tris peak (m/z = 122, $[M + H]^+$) observed in most of the MS spectra using TBS. For the analyte in negative mode, all of the salt containing solvents showed a depression in signal intensity, suggesting the salts' negative effects in negative mode. The mechanism for how the nonvolatile salts affected the DART ionization process was not clear, thus it would be further studied. Nevertheless, these results proved the as-designed interface had an adequate tolerance of the nonvolatile salts and should suffice the applications for direct online coupling of SPR with MS using salt-containing solutions.

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DOI: 10.1021/acs.analchem.5b01272
Anal. Chem. 2015, 87, 6505–6509

CONCLUSIONS

A novel interface relying on DART ionization and spray tip for direct and online coupling of SPR with MS was designed and developed. Experimental results using different model compounds and buffers exhibited the feasibility of the online combination of SPR and MS. This system showed a high tolerance of the nonvolatile salts during the test, suggesting its potential utilizations in SPR-MS experiments, especially when physiological conditions should be needed. This interface provided a new approach for online coupling of SPR-MS and would contribute to the fast detection of the interaction between substrate and the ligand and simultaneous identification of the ligand.

ASSOCIATED CONTENT

Supporting Information

The modification process of the SPR sensor chip, the details of the orthogonal experiments to optimize the DART parameters, and all of the SPR-DART-MS results. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.analchem.5b01272.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by the National Instrumentation Program of China (Grant 2012YQ090194-9) from the Chinese Ministry of Science and Technology, and the National Natural Science Foundation of China (Grant 21275012).

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