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Comprehensive two-dimensional liquid chromatography: Ion chromatography × reversed-phase liquid chromatography for separation of low-molar-mass organic acids

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ABSTRACT

In the work presented here a novel approach to comprehensive two-dimensional liquid chromatography is evaluated. Ion chromatography is chosen for the first-dimension separation and reversed-phase liquid chromatography is chosen for the second-dimension separation mode. The coupling of these modes is made possible by neutralising the first-dimension effluent, containing KOH, prior to transfer to the second-dimension reversed-phase column. A test mixture of 24 low-molar-mass organic acids is used for optimisation of the system. Three food and beverage samples were analysed in order to evaluate the developed methodology, the resulting two-dimensional separation is near-orthogonal, the set-up is simple and all instrumental components are available commercially. The method proved to be robust and suitable for the analysis of wine, orange juice and yogurt.

1. Introduction

Comprehensive two-dimensional liquid chromatography (LC × LC) has found its way into many application areas where very complex mixtures need to be separated. Examples of such areas include food analysis [1–5], environmental analysis [1], separation of biological samples, such as peptides [6,7] and proteins [8], pharmaceutical analysis [9], traditional Chinese medicines [10,11], synthetic polymers [12–14], and many more [1].

In LC × LC every part of the sample is subjected to two different separations. Ideally the separation mechanisms in each of these separation dimensions should be completely independent ('orthogonal'). Maximising differences in the separation mechanisms generally leads to more of the available two-dimensional separation space being occupied by peaks. Practical considerations can stand in the way of coupling completely independent separation mechanisms and quite often a truly orthogonal system is not employed [15]. Several approaches to LC × LC have been described in the literature, including reversed-phase liquid chromatography (RPLC) coupled to size-exclusion chromatography (SEC) [12,16], RPLC to RPLC [2,4,7,17,18], ion chromatography (IC) to SEC [14], ion-exchange chromatography with a strong cation-exchange column (SCX) to RPLC [8], normal-phase liquid chromatography (NPLC) to RPLC [19,20], or IC to IC [21].

None of the combinations are likely to offer true orthogonality in the mathematical sense, but in some cases orthogonality can be closely approached. For instance, orthogonality is closely approximated for peptide analysis using SCX × RPLC or with $RPLC_{pH=2.6} \times RPLC_{pH=10}$. In the latter case different pH values (*e.g.* 2.6 and 10) are chosen for the different dimensions and the differences in separation are strongly analyte dependent [15]. The combination of hydrophilic interaction chromatography (HILIC) and RPLC may provide a high degree of orthogonality. However, compatibility of the effluent from the first-dimension separation column with the second-dimension separation system may be problematic [15]. A number of papers describing theoretical and practical considerations for comprehensive two-dimensional liquid chromatography have been published [1,22–25].

Low-molar-mass organic acids (LMMOAs) are found in food and beverages where they contribute to the flavour, colour and aroma [26,27]. Thus LMMOAs can be used as indicators of product quality. Methods such as RPLC [26,28–30], IC [26], capillary electrophoresis [26,27] and gas chromatography [26] have been utilised for the analysis of LMMOAs. However, for complex matrices one-dimensional separations are not always able to fully resolve all the compounds. In the present study ion chromatography was coupled to reversed-phase liquid chromatography to exploit the differences in separation mechanism for the two-dimensional analysis of LMMOAs in wine, orange juice and yogurt.

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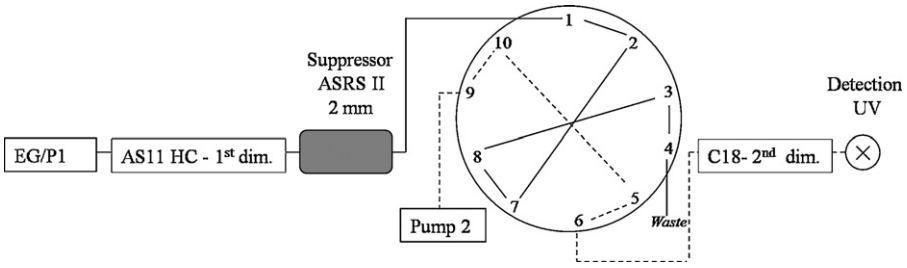

Fig. 1. Schematic of the instrument set-up used for IC × RPLC.

IC and RPLC are governed by very different separation mechanisms. IC is chosen as the first-dimension separation mode. The separation is achieved by employing a gradient of increasing hydroxide concentration. Upon completion of the first-dimension separation, the pH of the first-dimension eluent reaches 12.7. This causes a compatibility issue, since the RPLC second-dimension column is not suited to operation beyond pH 8. To overcome this problem and to allow transfer of fractions of the first-dimension effluent to the second-dimension RPLC column without destroying the C18 stationary phase, the effluent is neutralised using a membrane suppressor. This device provides electrolytically regenerated suppression of the hydroxide eluent by converting the eluent to essentially pure water. This has an important secondary advantage under the low-pH conditions chosen for the second dimension – namely the analytes concentrate in a narrow band at the head of the RPLC column. In this way, any band broadening that is incurred by the suppressor – or by the relatively large injection volume (200 μL) in the second dimension – can be effectively negated before the second-dimension separation commences. In comparison with LC × LC systems, in which this focussing effect on the top of the second-dimension column does not exist [22], we have the significant added advantage of a relatively large internal diameter (and flow rate) for the first-dimension column. The second-dimension column does not need to be much wider than the first-dimension column, which allows the sensitivity of the LC × LC system to be greatly increased.

2. Experimental

2.1. Instrumentation

A schematic of the instrument setup is provided in Fig. 1. A Dionex ICS-3000 ion chromatograph (Sunnyvale, CA, USA) was used throughout this work. Instrument control and data acquisition were performed using Chromeleon® software (Dionex). The first-dimension separation was performed on a Dionex IonPac AS11-HC column (250 mm × 2 mm I.D.) with an IonPac AG11-HC (50 mm × 2 mm I.D.) guard column. The hydroxide eluent was generated online utilising a Dionex Eluent Generator (EG) module fitted with a EluGen II KOH cartridge. A continuously regenerated anion-trap column (Dionex CR-ATC) was inserted after the KOH cartridge. The second-dimension column was a Dionex Acclaim C18 column (150 mm × 4.6 mm I.D., 5 μm packing material). Prior to transfer of the first-dimension effluent to the second dimension, the effluent was neutralised using a Dionex ASRS Ultra II 2-mm membrane suppressor. The suppressor was set at 8 mA throughout and the pH was measured off-line to confirm complete suppression of the hydroxide from the first-dimension separation, before it was connected to the second dimension. The two dimensions were interfaced by a high-pressure 10-port valve (Dionex HP valve) the 10-port valve was equipped with two 400-μL sample loops for storage and transfer of the first-dimension effluent to the second-dimension separation column. An external pump (Dionex I.C 25) was used to provide high-purity water (external mode) for the membrane suppressor. A Dionex AS autosampler equipped with a 25-μL sample loop was used for sample injection. A UV detector (AD Absorbance Detector, Dionex) was used throughout.

2.2. Reagents

The following 24 standard solutions were prepared (analytical reagent grade wherever possible): Quinate (D(-)quinic acid), lactate (DL-lactic acid sodium salt), butyrate (isobutytic acid), pyruvate (sodium pyruvate), galacturonate (D-galacturonic acid sodium salt), gluconate (sodium D-gluconate), maleate (maleic acid), α-ketoglutarate (α-ketoglutaric acid disodium salt), all from Fluka, St. Louis, MO, USA. Glucolate (glucolic acid), cis-aconitate (cis-aconitic acid), malate (DL-malic acid), and fumarate (fumaric acid) from Sigma, St. Louis, MO, USA. Glutarate (glutaric acid), tartarate (L-tartaric acid), iso-citrate (DL-isocitric acid tri-sodium salt, and trans-aconitate (trans-aconitic acid) from Aldrich, St. Louis, MO, USA. Formate (sodium formate) form Sigma–Aldrich, AUSTRALIA; Acetate (Sodium acetate) and adipate (adipic acid), Ajax Chemicals, Unilab, Auckland, New Zealand. Propionate (propoionic acid) fom Chem Supply, Adelaide, Australia. Succinate (sodium succinate), malonate (sodium malonate), oxalate (potasium oxalate), citrate (tri-sodium salt citrate) all from BDH, West Chester, PA, USA. All analytes were dissolved in deionized water and prepared as stock solutions at concentrations of 0.9 to 730 mg/L. The food and beverage samples, orange juice (freshly squeezed), yoghurt (Tamar Valley, Classic Natural, 98% fat free) and white wine (Sauvignon Blanc, Rosemount 2008) were all purchased from a local store.

2.3. Methods

All separations were performed at 30 °C. The detector was set at 210 nm throughout. The first-dimension gradient was generated on-line by programming the current applied to the eluent generator. The optimised first-dimension hydroxide gradient was found to be as follows: 0–22.5 min, gradient from 1 to 15 mM KOH; 22.5–25 min, isocratic at 15 mM; 25–50 min, gradient from 15 to 48 mM; 50–55 min, 48–50 mM; 56–95 min, isocratic re-equilibration at 1 mM. The first-dimension flow rate was 0.1 mL/min throughout. The second-dimension mobile phase (20 mM phosphate buffer at pH 2.25), was prepared by dissolving 20 mmol sodium dihydrogen phosphate monohydrate (Fluka, Puriss p.a, Steinheim, Germany) and about 22 mmol phosphoric acid (BDH, 88%, AnalaR) to reach a measured pH of 2.25 ± 0.02 in 1 L deionized water. Prior to use the mobile phase was filtered (Nylon membrane filters, 0.2 μm; Grace, Rowville, Australia). The phosphate buffer was mixed with methanol (LiChrosolv for Chromatography, Merck, Darmstadt, Germany) at a ratio of 90:10 phosphate buffer: methanol and was applied isocratically at 1.5 mL/min throughout. The modulation time (between two fractions injected in the second dimension) was 2 min. All water used

was treated with a Millipore (Bedford, MA, USA) Milli-Q system. Several sample mixtures were prepared from the stock solutions; each sample mixture contained four to six of the analytes. A mixture containing all the analytes was also prepared. The sample mixtures were prepared at three different concentrations and were used to evaluate the repeatability of the IC × RPLC system. The repeatability values (RSD%, $n = 3$) were evaluated for the retention times, peak area, and limit of detection (L.O.D.) was calculated at a signal-to-noise ratio of three. The orange juice, yoghurt, and white-wine samples were prepared by diluting 2.5 mL of the wine or orange juice with water into a total of 10 mL, the yoghurt sample was prepared by diluting 1.4 g to 10 mL. Prior to analysis the samples were centrifuged for 10 min, the supernatant was then filtered through 0.45-μL syringe filters (Nylon; from Grace) prior to analysis. Transform software (Fortner Software, VA) was used for visualisation of the two-dimensional data after transformation to two-dimensional format using 2D Translator Software (RMIT University, Melbourne, Australia).

3. Results and discussion

3.1. Optimisation of first and second dimensions

In two-dimensional separations the goal is to combine two methods that approach orthogonality as closely as possible and that show a high selectivity for the analysed compounds. Ideally the separation achieved in the first-dimension separation is maintained when transferring fractions of the first-dimension effluent to the second-dimension column. In this setup IC is the first-dimension separation and the observed separation of the analytes is based on charge, as well as on ion size and hydrophobicity. An IonPac 11-HC column was chosen for the first dimension. Several hydroxide gradients were evaluated; at the very best 15 of the 24 LMMOAs could be partially or fully separated from one another. By adding an additional dimension to this separation system one can achieve better separations and analyse more-complex mixtures. The separation mode chosen for the second dimension in this study was RPLC. In RPLC (at low pH) the separation will be based on the polarity (hydrophobicity) of the analytes. Two RPLC columns were evaluated, namely a Dionex Acclaim C18 column and a Phenomenex Onyx monolith. The two columns were compared using identical mobile-phase compositions. The total analysis time for the monolith was shorter than for the packed C18 column, but resolution between the LMMOAs was better for the packed C18 column. The packed C18 column was therefore chosen for further studies. The effects of changing the buffer concentration, the amount of organic modifier, and the second-dimension flow rate (1 and 1.5 mL/min) were also evaluated, with 1.5 mL/min providing the best compromise between speed and efficiency. In Fig. 2 the retention times obtained for the LMMOA in IC are plotted against the retention times obtained for RPLC. Fig. 2 shows that the LMMOAs are scattered across the two-dimensional space and that the correlation between the retention times in the two dimensions is very low (correlation coefficient 0.0057), in other words, orthogonality is approached.

3.2. Two-dimensional separation

As seen in Fig. 2, some of the LMMOAs need a rather long time to be eluted from the second-dimension RPLC column (^2t_R of slowest eluting LMMOA is about 11.8 min). Ideally, in comprehensive two-dimensional chromatography the collection (modulation) time of the first-dimension effluent should exceed the analysis the second dimension. In this case it would mean that we need a modulation time of about 12 min. This is far from ideal, since the volume of the fraction collected during this time at a first-dimension flow rate of 0.1 mL/min would be about 1.2 mL. There are several ways around this problem, one may, for example, reduce the first-dimension flow rate (and slow down the gradient correspondingly) to allow sufficient time for separation in the second dimension or run the two-dimensional separation with a stop-flow approach. Both these approaches will increase the separation time, which of course is not desirable. Instead, we chose a modulation time of 2 min. This gives us enough time to separate most of the LMMOAs in the second dimension. The late-eluting LMMOAs will "wrap around" [31] and are eluted in a later second-dimension chromatogram. This is an acceptable compromise, provided that the effective retention times of the wrapped-around peaks are not coincident with the effective retention times of other components. Fig. 3 shows the separation of the 24 LMMOAs with a modulation time of 2 min. This separation supports the prediction illustrated in Fig. 2 that there is little or no overlap of the different LMMOAs. The wrap-around effect of the late-eluting LMMOAs does not seem to be

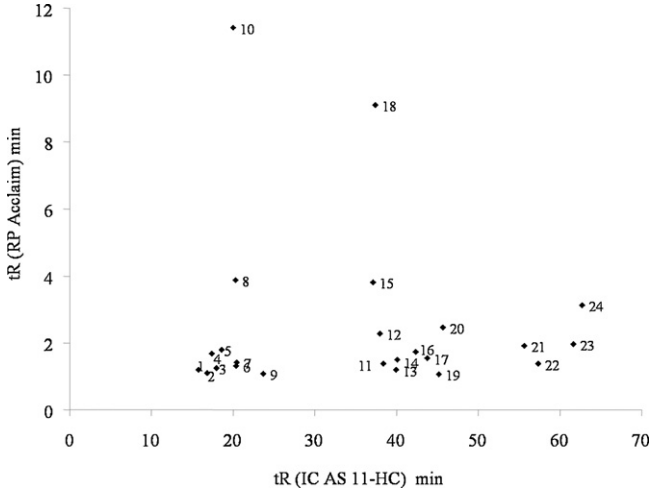

Fig. 2. Retention times for the LMMOAs achieved in IC (AS11-HC) plotted against retention times achieved in RPLC (C18 Acclaim). Peak assignment as seen in Table 1.

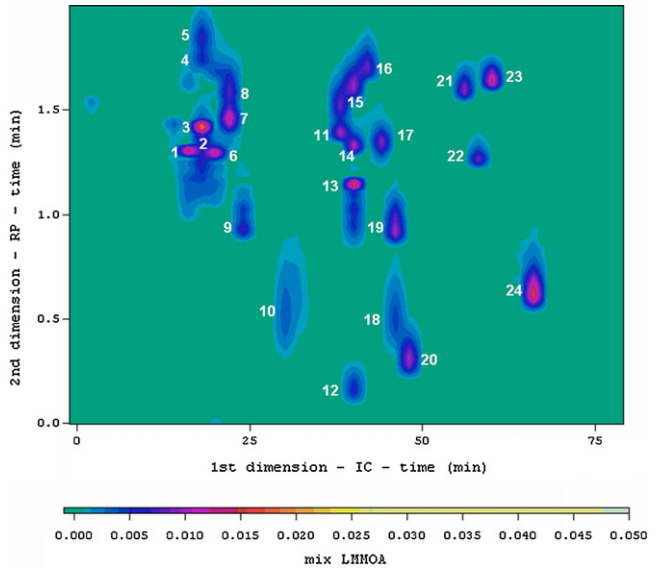

Fig. 3. Two-dimensional separation of LMMOAs, IC as separation mode in the first dimension and RPLC in the second dimension. The peak assignment can be seen in Table 1.

Table 1
Figures of merit for the two-dimensional IC × RPLC separation shown in Fig. 3. Peak area for each target analyte was determined by summation of peak areas of the individual peak slices in the raw (untransformed) chromatogram. Peak areas were determined using the Chromeleon® software. Regression equations for the calibration curves and analysis of linearity. L.O.D. calculations based on mid-range concentrations, $n = 3$.

Peak no.	Analyte	t_R		Peak area, RSD%	L.O.D., mg/L	Concentration range, mg/L	Regression equation	R^2
		Mean	%RSD					
1	Quinate	17.29	0.06	1.5	7.25	109.35–218.70	$y = 0.0021x + 0.2457$	0.7297
2	Gluconate	19.09	0.03	9.8	46.62	112.5–225.15	$y = 0.0112x - 0.6148$	0.9580
3	Glucolate	19.42	0.04	7.4	64.36	145.25–435.75	$y = 0.0034x + 0.5668$	0.9385
4	Lactate	19.71	0.03	0.7	1.59	52.83–105.70	$y = 0.0105x - 0.0184$	0.9894
5	Acetate	19.84	0.02	1.0	4.30	91.20–182.40	$y = 0.007x - 0.0035$	0.9984
6	Formate	21.30	0.02	5.7	8.11	23.83–71.49	$y = 0.0306x - 0.5238$	0.9826
7	Pyruvate	23.46	0.02	1.9	0.58	5.07–15.20	$y = 0.1773x - 0.1902$	0.9997
8	Propoinate	23.64	0.02	2.5	27.11	182.50–547.50	$y = 0.0074x - 0.0139$	0.9991
9	Galacturonate	24.93	0.02	3.7	22.13	100.00–547.50	$y = 0.0051x + 0.0367$	0.9792
10	Butyrate	30.62	0.02	3.4	20.77	135.18–270.36	$y = 0.0237x - 2.0528$	0.9773
11	Malate	39.40	0.02	3.9	7.31	31.30–93.90	$y = 0.0143x + 0.1644$	0.9984
12	Succinate	40.18	0.01	6.7	25.57	63.92–191.76	$y = 0.0136x - 0.2556$	0.9995
13	Tartrate	41.13	0.01	3.3	8.21	41.89–125.66	$y = 0.0269x - 0.3929$	0.9949
14	Malonate	41.33	0.005	0.8	1.74	38.52–115.55	$y = 0.012x + 0.0043$	0.9999
15	Glutarate	41.66	0.02	3.7	19.70	87.63–262.89	$y = 0.0096x - 0.0292$	0.9992
16	Maleate	43.72	0.01	1.9	0.03	0.21–0.64	$y = 1.4315x - 0.0097$	0.9984
17	α-Ketoglutarate	45.35	0.004	7.4	2.61	5.59–16.76	$y = 0.1281x + 0.0749$	0.9994
18	Adipate	46.79	0.15	7.7	15.79	33.98–101.95	$y = 0.0069x + 0.0804$	0.9700
19	Oxalate	46.93	0.01	0.8	0.20	4.17–12.51	$y = 0.2201x - 0.0619$	1.0000
20	Fumarate	48.30	0.01	4.6	0.09	0.33–0.98	$y = 2.2129x - 0.1379$	1.0000
21	Citrate	57.61	0.01	0.9	2.39	43.50–130.50	$y = 0.0196x - 0.2513$	0.9998
22	Iso-citrate	59.26	0.01	2.4	6.14	42.30–126.90	$y = 0.0123x + 0.0821$	0.9958
23	Cis-aconitate	61.68	0.01	5.9	0.34	0.95–2.84	$y = 0.4157x - 0.0358$	0.9952
24	Trans-aconitate	66.67	0.01	3.1	0.16	0.82–2.46	$y = 1.0569x + 0.1222$	0.9995

an issue and the late-eluting LMMOAs are easily recognised by their broader width at baseline in the second-dimension separation. If much-more-complex samples would need to be analysed, which contain many more different LMMOAs, this situation may change. In that case, a better solution may be to opt for gradient-elution separations in the second dimension. This may lead to a better spreading of peaks in a shorter time. In the present case the added complexity of gradient elution was not needed to achieve satisfactory separations.

The two-dimensional system was further evaluated by injecting the test mixtures at three different concentration levels in triplicate. Limit of detection (L.O.D.), regression equation and relative standard deviation (%RSD) were calculated. The results are presented in Table 1. The %RSD found for ^2t_R was very low indicating that the repeatability for t_R is high. The %RSD value for the LMMOAs peak areas varied from 0.7 to 9.8. The higher %RSD values can be explained by the fact that the response for a single LMMOA sometimes are cut into more than one peak and that small fractions at the edges of the peak might be below the L.O.D.

3.3. Application of IC × RPLC method

The optimised two-dimensional method was applied to real food and beverage samples in order to evaluate the set-up. White wine, yoghurt and orange juice were analysed. Prior to analysis the food samples were diluted in water, centrifuged and filtered. No other type of sample preparation was performed. The resulting two-dimensional chromatograms can be seen in Fig. 4, (A) white wine, (B) orange juice and (C) yoghurt. A summary of the LMMOA concentrations found in the analysed food samples can be seen in Table 2. The concentrations were calculated by using the regression equations listed in Table 1. The repeatability was assessed based on triplicate injections. Once again the observed %RSD value for the t_R was very low, the %RSD for the peak area of the LMMOAs was also satisfactory, ranging between 0.8 and 6.8. The developed IC × RPLC method proved suitable for the analysis of LMMOAs in food and beverage samples. No significant interferences were found to be present. Some of the observed peaks in the food samples do not correspond with those of the LMMOAs in the standard mixture; hence they cannot be identified at this stage.

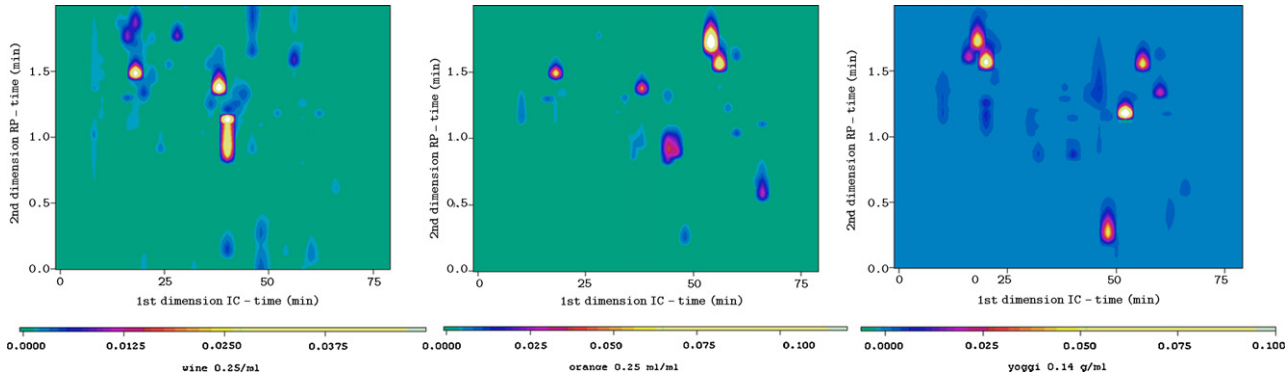

Fig. 4. IC × RPLC analysis of (A) white wine, (B) orange juice and (C) yoghurt.

Table 2
Summary of results for analysed food samples. Concentrations of LMMOAs (calculated using the regression equation from Table 1) found in the food samples are listed along with %RSD for t_R and peak area; samples were analysed in triplicate.

	White wine				Orange juice				Yoghurt			
LMMOAs	Avg. t_R	t_R, RSD%	Area, RDS%	Conc., mg/L	Avg. t_R	t_R, RSD%	Area, RSD%	Conc., mg/L	Avg. t_R	t_R, RSD%	Area, RDS%	Conc., mg/kg
Quinate	–	–	–	–	17.30	0.019	2.74	211.46	–	–	–	–
Gluconate	–	–	–	–	19.15	0.020	5.91	395.17	–	–	–	–
Lactate	–	–	–	–	–	–	–	–	19.73	0.010	0.95	10769.94
Acetate	19.87	0.010	3.05	459.17	–	–	–	–	–	–	–	–
Formate	–	–	–	–	21.34	0.009	2.71	161.00	–	–	–	–
Pyruvate	23.49	0.008	6.78	12.76	23.47	0.008	5.22	4.30	23.45	0.008	1.57	20.22
Galacturonate	24.92	0.013	1.69	192.12	–	–	–	–	–	–	–	–
Malate	39.38	0.010	3.61	1978.24	39.38	0.010	2.74	1191.44	–	–	–	–
Succinate	40.15	0.008	1.08	340.15	–	–	–	–	–	–	–	–
Tartrate	41.14	0.005	1.17	1775.97	–	–	–	–	41.15	0.000	3.49	143.01
α-Ketoglutarate	45.34	0.013	3.10	31.09	45.33	0.011	3.71	25.02	45.33	0.004	1.67	15.91
Oxalate	46.91	0.007	3.02	19.18	46.91	0.012	2.93	561.40	46.91	0.004	0.81	6.97
Fumarate	48.28	0.017	3.9	1.52	48.26	0.008	4.70	2.97	48.27	0.004	1.55	26.32
Citrate	57.59	0.009	1.6	246.20	57.56	0.009	0.81	8974.63	57.56	0.003	1.43	2138.23
Iso-citrate	59.26	0.003	8.4	28.69	59.23	0.012	5.25	201.94	–	–	–	–
Cis-aconitate	–	–	–	–	61.63	0.016	4.45	9.96	61.62	0.003	2.76	6.69
Trans-aconitate	66.61	0.006	1.9	0.39	66.60	0.013	1.28	17.81	66.59	0.000	3.21	2.91

4. Conclusions

The comprehensive two-dimensional combination of ion chromatography and reversed-phase liquid chromatography (IC × RPLC), described in this paper constitutes, a novel pathway of coupling IC to RPLC without damaging the reversed-phase packing material. This is achieved by suppressing the concentration of hydroxide after the first-dimension separation. The analyte peaks were effectively trapped at the top of the second-dimension column after the modulation. The coupled IC and RPLC separations were approaching orthogonality under the selected experimental conditions. The set-up is simple and all the instrument parts and columns are readily available. The method proved to be robust and suitable for analysis of food and beverage samples. The %RSD for t_R and the peak area were satisfactory for standard mixtures, as well as for the food samples.

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