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Part-per-Trillion Determination of Pharmaceuticals, Pesticides, and Related Organic Contaminants in River Water by Solid-Phase Extraction Followed by Comprehensive Two-Dimensional Gas Chromatography Time-of-Flight Mass Spectrometry

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An analytical procedure based on comprehensive two-dimensional gas chromatography (GC × GC) coupled with time-of-flight mass spectrometry (TOF-MS) for the simultaneous determination of 97 organic contaminants at trace concentration in river water is presented. The target analytes included 13 pharmaceuticals, 18 plasticizers, 8 personal care products, 9 acid herbicides, 8 triazines, 10 organophosphorous compounds, 5 phenylureas, 12 organochlorine biocides, 9 polycyclic aromatic hydrocarbons (PAHs), and 5 benzothiazoles and benzotriazoles. The best resolution of the target analytes in the contour plots was obtained when a nonpolar stationary phase was used in the first dimension and polar one in the second. However, in the opposite configuration, polar−nonpolar, the retention time in the second dimension exhibited a strong correlation with the log Kow ($p < 0.01$), and it was proposed as an additional identification criteria. The developed methodology is based on a polymeric solid-phase extraction followed by in GC-port methylation and GC × GC/TOF-MS determination. Moreover, limits of detection (LODs) and quantification (LOQs) ranged from 0.5 to 100 ng/L and from 2 to 185 ng/L, respectively. Repeatability was always lower than 20%. Finally, the developed method has been successfully applied to the determination of incurred target analytes in four river waters subjected to a different anthropogenic pressure.

A general trend in environmental monitoring is the periodical updates of the target analyte lists by the regulatory agencies. Both the European Union (EU) and United States Environmental Protection Agency (US EPA) have issued dangerous and hazardous contaminant lists, the so-called priority substances, whose concentration and occurrence in waters has been strictly regulated (Directive 2000/60/EC; Decision No. 2455/2001/EC and Clean Water Act). However, the so-called emerging pollutants, which include both pharmaceuticals and personal care products (PPCPs) are not yet included in the priority substances category. Nevertheless, the incorporation of several PPCPs in the priority pollutant lists due to their high mass discharge into the aquatic environment is under scrutiny.[1,2] In fact some PPCPs have been recently included in candidate contaminant lists either from US EPA (CCL3) and the EU commissions. Therefore, because of the probable enforcement of new regulations on emerging pollutants in surface waters, it seems timely to look for a suitable analytical methodology that includes a large number of these micropollutants.

A variety of multiresidue analytical methodologies are already available including either priority or emerging pollutants in aqueous matrixes;[3−9] few of them allow the simultaneous determination of these pollutants.[10] Most of these methodologies included a preconcentration enrichment step based on a polymeric solid-phase extraction (SPE) that enables the simultaneous extraction of polar and apolar compounds followed by a liquid chromatography coupled to mass spectrometry (LC/MS) or by gas chromatography/mass spectrometry (GC/MS). From these meth-

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odologies, SPE−LC/MS/MS is the most widely extended.[10−12] However, due to the dissolved organic matter coextracted in environmental matrixes such as river waters, the phenomenon of ionic suppression cannot be excluded in most of the electrospray ionization techniques used in LC/MS.[13,14]

Comprehensive two-dimensional gas chromatography (GC × GC) has emerged as a powerful separation technique that is especially well-suited for complex sample characterization.[15−17] The three main benefits of GC × GC are (i) an increased chromatographic resolution, (ii) improved analyte detectability due to the cryofocusing in the thermal modulator, and (iii) chemical class ordering in the contour plots.[15] The potential of the GC × GC/MS coupling has already been shown in the determination of several environmental contaminants:[17−20] nonylphenol isomers in river water[21] and oxygenate (gasoline additives) and aromatic compounds in spiked waters.[22] However, the capability of GC × GC coupled to mass spectrometry (MS) for multiresidue analysis in environmental matrixes has not been addressed yet. In fact, GC × GC offers the highest peak capacity among the chromatographic techniques allowing increased resolution from analytes and matrix such as the unresolved complex mixtures of hydrocarbons.[23] To the best of our knowledge, this is the first time that GC × GC has been employed for the determination of multiresidue analysis of priority, pharmaceuticals, and other emerging pollutants in aqueous matrixes. In its early beginnings, GC × GC has been used as a qualitative tool, and other techniques have been preferred for quantification due to the complexity of GC × GC data management.[24] However, software improvements in recent years have allowed GC × GC for quantification. Because GC × GC increases resolution and peak capacity, it should be coupled to a fast detector such as a micro electron capture detector (μ-ECD), flame ionization detector (FID), or time-of-flight mass spectrometer (TOF-MS) enabling enough identification points per peak. In comparison to other mass spectrometry detectors, TOF-MS allows highly sensitive full range nonskewed mass spectral information along with fast acquisition rates.

This paper demonstrates, for the first time, the advantages and limitations of using GC × GC/TOF-MS for the simultaneous screening of 97 contaminants in aqueous river water, and the strong correlation between the second dimension retention time and the log Kow of compounds is proposed as additional identification criteria. Moreover, application of the developed analytical methodology to the determination of the selected contaminants incurred in four rivers from northeastern (NE) Spain is also presented.

EXPERIMENTAL SECTION

Chemicals and Reagents. All analytical-grade chemicals (purity >95%) included in this study were purchased from Sigma-Aldrich (Steinheim, Germany), Dr Ehrenstorfer (Augsburg, Germany), or Accustandard (New Haven, CT). All the solvents used were SupraSolv-grade from Merck (Darmstadt, Germany). Strata-X 100 mg polymeric SPE cartridges were obtained from Phenomenex (Torrance, CA). Trimethylsulfonium hydroxide (TMSH) was purchased from Fluka (Buchs, Switzerland).

Experimental Sampling Design. Discrete samples from four Catalonian rivers (NE Spain), namely, Ebro, Llobregat, Besòs, and Ter, were collected at 5−10 km from the river mouth. Samples were collected in 1 L amber glass bottles and kept refrigerated during transportation to the laboratory, where they were stored at 4 °C until processing (holding time <24 h). Briefly, samples of 200 mL was filtered through 0.7 μm GF/F Whatman filters and then acidified to pH 2 with hydrochloric acid.

Preconcentration Step. Samples were percolated through a Strata-X cartridge (100 mg, 6 mL) conditioned with 10 mL of ethyl acetate, 10 mL of MeOH, and 10 mL of ultrapure water (pH = 2). The flow rate was adjusted to approximately 10 mL/min. Cartridges were left to dry for 30 min. Finally, the target analytes were then eluted five times with 2 mL of ethyl acetate. Then, the recovered extract was gently evaporated to ca. 100 μL under a nitrogen stream, and 25 μL (ca. 0.2 μg) of the instrumental standard (IS) triphenylamine solution was added.

Instrumentation. The GC × GC/TOF-MS system consisted of an HP 6890N (Agilent Technologies, Palo Alto, CA) gas chromatograph equipped with a split/splitless injector, a secondary oven to fit the secondary column, and a ZX1 (Zoex, Houston, TX) two-stage thermal modulator operating at 3−6 s per modulation. Liquid nitrogen was used to cool down the nitrogen gas for cold pulses and automatically filled from a Dewar using a liquid leveller, which accessed to a 60 L liquid nitrogen storage tank. The modulation time (5 s), detector frequency (100 Hz), secondary oven temperature shift related to the primary oven (+10 °C), and second-dimension column length (2 m) were chosen based on a previous study.[29] The MS system was a Pegasus 4D TOF system (LECO, St. Joseph, MI) working at 70 eV of ionization potential with the transfer line and ion source set at 250 and 200 °C, respectively. Scanning was performed from 50 to 500 m/z at 100 Hz with a detector voltage of 1600 V. As a first dimension, either a 30 m × 0.25 mm i.d., 0.25 μm film thickness TRB5-MS coated with 5% diphenyl 95% dimethylpolysiloxane from Teknokroma (Sant Cugat del Vallès, Spain), TRB-50HT coated with 50% diphenyl 50% dimethylpolysiloxane from Teknokroma, or a 30 m × 0.25 mm i.d., 0.25 μm film thickness TRB1701-MS coated with 14% cyanopropylphenyl 86% dimethylpolysiloxane from Teknokroma was used. As second dimension, either a 2 m × 0.10 mm i.d., 0.10 μm film thickness TRB-50HT or TRB-5MS was used. Table 1 summarizes the experimental conditions for the different column sets. The secondary oven was kept 10 °C above the first-dimension temperature throughout the chromatographic run.

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Table 1. Summary of the Used Experimental Conditions for the Different Column Sets

	first dimension	second dimension	program temperature
set 1	TRB-5MS 30 m × 0.25 mm i.d., 0.25 μm film	TRB-50HT 2 m × 0.1 mm i.d., 0.1 μm film	65 °C (1 min), 10 °C/min 130 °C, 5 °C/min 215 °C, 7 °C/min 320 °C (10 min)
set 2	TRB-50MS 30 m × 0.25 mm i.d., 0.25 μm film	TRB-5MS 2 m × 0.1 mm i.d., 0.1 μm film	65 °C (1 min), 5 °C/min 300 °C (5 min)
set 3	TRB-1701MS 30 m × 0.25 mm i.d., 0.25 μm film	TRB-5MS 2 m × 0.1 mm i.d., 0.1 μm film	65 °C (1 min), 5 °C/min 275 °C (5 min)

Helium was used as the carrier gas at a constant flow of 1.2 mL/min. Data was acquired and processed by using ChromaTOF 3.32 software.

Identification and Quantification. The samples were automatically processed in order to find, identify, integrate, and quantify the chromatographic peaks in the sample. The parameters related to each of these steps were modified depending on the column set used. Triphenylamine was used as the IS for centring both MS response correction and chromatographic retention time (in both dimensions). Recoveries were calculated by analyzing a river sample in triplicate. The first group of samples was spiked (0.2−1 μg/L) at the beginning of the sample treatment procedure, and the second group of samples was spiked after SPE elution. By comparing the results, we were able to evaluate the recovery yields.[25] Procedural blanks were obtained by analyzing 200 mL of acidified ultrapure water in the same way as the real samples. Procedural blanks were carried out by the direct elution of activated SPE cartridges. Precision of the analytical method, determined as relative standard deviation (RSD), was obtained from the analysis of three spiked river samples. Limit of detection (LOD) was calculated as the content of the blank plus three times its standard deviation. Limit of quantification (LOQ) was calculated as the level of the blank plus 10 times its standard deviation. Quantification of target pharmaceuticals, pesticides, and related organic contaminants was performed using external standard methodology based on peak areas. Correlation coefficients were always greater than 0.98.

ChromaTOF 3.32 software automatically identifies chromatographic peaks coming from a single compound and calculates the total area. Data processing was linked to a calibration, in which case the identified target analytes would be automatically quantified.

RESULTS AND DISCUSSION

Preconcentration Step. Strata-X SPE sorbent, a surface-modified styrene−divinylbenzene, has been selected as a preconcentration stationary phase because of the high efficiency of polymeric sorbents in the extraction of polar and nonpolar analytes.[3,26,27] In this study, two sample pH values (i.e., 2 and 7) were evaluated on spiked river samples (0.2−1 μg/L). As expected, better recoveries were obtained at pH 2 for acidic compounds (pK_a 3−5), since the protonated neutral forms possesses a stronger interaction and sorption with the SPE polymeric phase. Because nonacidic compounds yielded similar recoveries at acid or neutral pH, pH 2 was finally selected. Recoveries obtained with the proposed method are shown in Table 2 and ranged from 60% to 113%. Two out of 97 compounds showed poor recoveries (<40%), which is mainly attributable to the fact that the extraction conditions (extraction technique, stationary phase, and/or elution solvents) were not the most appropriate for these compounds. In spite of low recoveries for these analytes, the high sensitivity obtained by TOF-MS allows us to monitor their occurrence (Table 2). The repeatability (n = 3) was lower than 10% for the 95% of the analyzed compounds and lower than 20% in all cases.

Separation Optimization. Table 1 shows the three column configurations evaluated in this study. Set 1 was a nonpolar−polar combination, whereas sets 2 and 3 were polar−nonpolar ones. The obtained contour plots are shown in Figure 1 where compounds with different physicochemical properties are highlighted. In the first column set and as example, phthalates with higher polarity than alkanes eluted at higher retention time in the second dimension than *n*-alkanes (Figure 1, panel 1). Nevertheless this relationship was reversed in the column sets 2 and 3. Globally in the column set 1, analytes eluted at higher retention times in the second dimension (t_{R2}). Moreover, for column set 3, due to the lower maximum allowable operation temperature (MAOT) for the cyanopropyl-substituted polysiloxane (280 °C) and to the enhanced interaction between high-polarity compounds and this column stationary phase, not all compounds eluted from the chromatographic system in the run time (e.g., 17-α-ethynylestradiol, furosemide, chrysene). On the other hand, when using the TRB-50MS as the first dimension, due to its higher MAOT (350 °C) all the analytes eluted. Tailing of carboxylic acids and other strongly polar analytes was overcome through a derivatization step as will be discussed below.

Figure 2 shows the global intercomparison of three column configurations plotting the t_{R2} against the log Kow for selected analytes. Log Kow has already been reported as a good predictor of retention time in the second dimension for lipids using a nonpolar−polar GC × GC configuration.[28] Whereas column set 1 has not a statistical significance correlation against log Kow, column sets 2 and 3 present a significant positive correlation. It was attributable to their different behavior as related to the relative interaction of the target analytes with the second-dimension stationary phase (e.g., for column set 1 high-polarity compounds are more retained than low-polarity ones). Since high correlation factors should be preferred in order to use this relationship as an identification confirmation tool, the column sets 2 and 3 should be chosen. Despite the poor correlation of set 1, it could be useful when trying to avoid coelutions between compounds with similar polarities and the sample matrix. Hence, a better separation was achieved on the contour plot between matrix constituents and target analytes with column set 1 than with column sets 2 and 3. Consequently

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Table 2. Summary of Method Quality Parameter Data for the Selected Pollutants[a]

name	diagnostic ions[b]	dimension time (s) TRB-5MS 1st	dimension time (s) TRB-50HT 2nd	linearity	recovery (%, n = v3)	repeatbility (%RSD n = 3)	LOD (ng/L)	LOQ (ng/L)
naphthalene	129/**128**/102/74	684	3.15	0.9993	83 ± 12	15	110	158
salicylic acid, *methyl ester*	152/123/**120**/92	706	3.01	0.9953	107 ± 7	7	22	57
benzothiazole	**135**/108/82/69	733	3.66	0.9957	66 ± 6	10	4	6
hydrocinnamic acid, *methyl ester*	164/133/**104**/91	777	3.21	0.9971	82 ± 6	8	4	8
diuron isocyanate	173/**171**/136/100	821	3.15	0.9917	73 ± 5	8	4	9
3,5 dichlorobenzoic acid, *methyl ester*	204/**173**/145/109	926	3.22	0.9993	90 ± 5	7	5	6
dimethyl phthalate	194/**163**/133/77	1008	4.04	0.9990	81 ± 6	7	13	18
acenaphthalene	**152**/141/126/76	1014	4.07	0.9991	85 ± 5	6	14	28
methacrifos	240/208/180/**125**	1058	3.67	0.9989	85 ± 6	8	13	20
acenaphthene	154/**153**/126/76	1058	3.96	0.9939	83 ± 6	7	6	7
benzotriazole[c]	147/**118**/91/77	1063	4.43	0.9979	66 ± 6	10	6	13
clofibric acid, *methyl ester*	228/169/**128**/99	1063	3.36	0.9986	82 ± 2	5	3	4
cashmeran	206/**191**/163/135	1069	3.29	0.9872	80 ± 4	5	51	90
BHT[d]	220/**205**/177/145	1074	3.03	0.9989	69 ± 6	9	100	185
benzenosulfonamide methyl	**170**/155/107/91	1085	4.60	0.9996	81 ± 2	3	18	22
dicamba *methyl ester*	234/205/**203**/188	1091	3.75	0.9945	113 ± 6	8	7	9
pentachlorobenzene	252/**250**/215/108	1102	3.47	0.9864	66 ± 6	9	7	8
ibuprofen, *methyl ester*	220/177/**161**/117	1107	3.23	0.9972	85 ± 2	5	5	13
MCPA methyl ester	**214**/155/141/125	1162	3.52	0.9977	92 ± 4	3	3	6
fluorene	**166**/165/139/82	1184	3.87	0.9889	76 ± 2	3	10	15
diethyl phthalate[d]	222/177/**149**/105	1184	3.71	0.9998	91 ± 5	5	90	120
1*H*-benzotriazole, 4-methyl-	**133**/104/77/51	1201	4.19	0.9835	102 ± 11	12	38	73
p-tert-octylphenol	206/**135**/107/92	1206	3.28	0.9898	88 ± 4	5	12	15
benzothiazole, 2-(methylthio)-	**181**/148/108/69	1212	4.19	0.9992	81 ± 2	3	6	10
dichlorprop, *methyl ester*	248/189/**162**/109	1212	3.47	0.9915	90 ± 4	2	7	9
tributyl phosphate	267/211/155/**99**	1239	3.02	0.9991	94 ± 6	6	3	9
2,4-D *methyl ester*	234/**199**/175/111	1256	3.59	0.9924	94 ± 4	6	7	11
methyl dihydrojasmonate	156/153/109/**83**	1261	3.18	0.9964	92 ± 5	5	23	49
celestolide	244/**229**/173/128	1344	3.01	0.9993	86 ± 5	8	8	18
hexachlorobenzene	**284**/249/214/142	1349	3.44	0.9882	74 ± 7	9	4	6
prometon	225/210/183/**168**	1371	3.52	0.9893	100 ± 5	5	10	18
simazine	**201**/186/173/158	1377	3.97	0.9983	88 ± 5	8	9	12
atrazine	215/**200**/173/132	1388	3.74	0.9963	89 ± 5	5	3	5
propazine	229/**214**/187/172	1399	3.51	0.9899	102 ± 6	6	16	26
tri(2-chloroethyl) phosphate	249/205/143/**63**	1399	3.88	0.9961	105 ± 5	5	5	10
silvex, *methyl ester*	284/223/**196**/167	1399	3.28	0.9985	100 ± 5	4	6	12
terbutylazine	229/**214**/173/132	1416	3.60	0.9956	98 ± 5	8	5	18
chloramben *methyl ester*	219/**188**/160/124	1426	3.99	0.9953	78 ± 8	9	10	13
dyfonate	246/174/137/**109**	1432	3.67	0.9975	93 ± 3	3	2	5
2,4,5-T *methyl ester*	268/**233**/209/145	1437	3.46	0.9991	95 ± 6	7	15	19
diazinone	304/179/152/**137**	1443	3.20	0.9987	94 ± 4	5	2	3
anthracene	179/**178**/152/89	1454	3.91	0.9844	85 ± 3	3	3	6
phenanthrene	179/**178**/152/89	1459	3.89	0.9899	90 ± 2	2	3	6
benzothiazolone[c]	165/**136**/109/69	1470	3.74	0.9881	85 ± 2	3	15	20
galaxolide	258/**243**/228/213	1514	3.10	0.9972	88 ± 4	4	6	9
diisobutyl phthalate[d]	278/223/167/**149**	1514	3.18	0.9904	100 ± 5	5	47	80
caffeine	**194**/165/109/67	1525	4.29	0.9989	65 ± 3	5	25	34
tonalide	258/**243**/201/187	1525	3.02	0.9951	96 ± 4	4	5	9
2,4 Db *methyl ester*	262/231/162/**101**	1536	3.26	0.9899	80 ± 10	10	9	15
chloropyrifos-methyl	321/288/**286**/125	1558	3.55	0.9886	89 ± 6	7	12	20
methyl parathion	**263**/200/125/109	1564	3.70	0.9861	94 ± 5	5	41	84
alachlor	269/237/188/**160**	1569	3.36	0.9998	96 ± 2	3	4	6
tolclofos methyl	300/**265**/250/125	1569	3.71	0.9950	92 ± 3	3	3	5
heptachlor	372/337/272/**100**	1575	3.29	0.9885	68 ± 3	5	3	6
ametryn	**227**/212/185/170	1580	3.57	0.9944	92 ± 8	9	10	14
prometrin	**241**/226/199/184	1580	3.45	0.9966	92 ± 8	9	8	13
ambrettolide	252/109/**96**/82	1602	3.05	0.9899	41 ± 3	7	2	6
terbutryn	241/**226**/185/170	1613	3.45	0.9995	93 ± 10	11	2	22
pirimiphos methyl	305/**290**/276/233	1613	3.34	0.9967	90 ± 8	9	6	7
dibutyl phthalate[d]	278/223/205/**149**	1619	3.15	0.9995	102 ± 5	5	27	44
phenitrothion	**277**/260/125/109	1619	3.61	0.9939	97 ± 4	4	7	10
aldrin	364/293/**263**/66	1652	3.28	0.9951	57 ± 4	6	5	15
chloropyriphos	349/314/**199**/97	1657	3.31	0.9985	90 ± 3	4	7	13
carbamazepine[c]	**193**/165/139//63	1668	4.07	0.9999	101 ± 1	1	25	45
bromophos-methyl	**331**/213/125/79	1696	3.48	0.9843	91 ± 4	4	4	6
naproxen *methyl ester*	244/**185**/170/141	1701	3.47	0.9969	93 ± 1	2	1	3
oxybenzone	**227**/151/105/77	1707	3.65	0.9897	94 ± 4	3	40	71
cis-chlorfenvinphos	358/323/295/**267**	1712	3.30	0.9850	101 ± 5	5		
flunixin *methyl ester*	310/**295**/263/251	1712	3.10	0.9945	104 ± 2	3	7	11
bisphenol A[c]	256/**241**/226/133	1734	3.41	0.9980	95 ± 8	8	7	12
trans-chlorfenvinphos	358/323/295/**267**	1740	3.41	0.9984	98 ± 3	3		
heptachlor-endoepoxide	353/253/217/**183**	1740	3.50	0.9985	90 ± 7	8	4	6

Table 2. Continued

name	diagnostic ions[b]	dimension time (s) TRB-5MS 1st	dimension time (s) TRB-50HT 2nd	linearity	recovery (%, n = v3)	repeatbility (%RSD n = 3)	LOD (ng/L)	LOQ (ng/L)
fluoranthene	203/**202**/101/88	1751	3.89	0.9997	83 ± 4	4	5	8
phthalic acid, bis(2-ethoxyethyl) ester	266/193/**149**/72	1767	3.34	0.9872	100 ± 3	3	18	35
bromophos-ethyl	**359**/331/242/97	1778	3.23	0.9991	75 ± 5	6	1	3
triclosan[c]	304/**302**/252/63	1795	3.41	0.9998	93 ± 4	4	3	5
dipentyl phthalate	306/237/219/**149**	1800	3.02	0.9901	84 ± 1	2	3	5
pyrene	203/**202**/101/88	1800	4.07	0.9894	87 ± 4	4	8	11
ketoprofen *methyl ester*	268/**209**/191/105	1806	3.59	0.9862	86 ± 9	7	2	5
DDE	318/281/**246**/176	1839	3.33	0.9982	68 ± 1	1	2	5
dieldrin	380/345/263/**79**	1850	3.53	0.9953	90 ± 3	3	2	3
diclofenac, *methyl ester*	309/242/214/**214**	1877	3.71	0.9898	89 ± 10	8	1	4
endrin	380/345/263/**81**	1888	3.74	0.9882	94 ± 3	4	3	6
phthalic acid, dihexyl ester	334/251/233/**149**	1954	3.01	0.9906	71 ± 2	3	4	8
benzyl butyl phthalate[d]	312/206/**149**/91	1965	3.63	0.9919	96 ± 2	2	70	89
phthalic acid, 2-ethylhexyl hexyl ester	251/233/167/**149**	2026	3.01	0.9973	37 ± 9	9	1	2
bis(2-butoxyethyl) phthalate	249/193/**149**/101	2048	3.30	0.9928	96 ± 8	8	5	9
p,p′-methoxychlor	344/274/**227**/152	2070	3.92	0.9892	81 ± 6	7	6	9
benz[*a*]anthracene	**228**/200/150/114	2070	4.25	0.9985	81 ± 7	9	15	19
chrysene	**228**/202/113/101	2081	4.34	0.9995	86 ± 8	10	12	18
dicyclohexyl phthalate	249/167/**149**/104	2092	3.80	0.9941	96 ± 2	2	0.5	1
estrone *methyl ether*	**284**/227/199/160	2147	4.15	0.9926	106 ± 6	6	6	13
estradiol 3-*methyl ether*	**286**/227/186/160	2180	4.08	0.9987	82 ± 6	8	50	89
17-α-ethynylestradiol, *methyl ether*	310/284/**227**/174	2207	4.15	0.9929	95 ± 3	3	36	55
di-*n*-octyl phthalate	279/167/**149**/104	2218	3.22	0.9984	20 ± 4	20	2	5
phthalic acid, dinonyl ester	236/167/**149**/57	2251	3.35	0.9935	41 ± 4	10	4	7
furosemide *trimethyl derivative*	372/231/140/**81**	2345	5.38	0.9938	106 ± 5	6	5	10

[a] Methyl ester corresponds to TMSH derivatization of carboxylic groups (in cursive). [b] In bold is the quantification mass. [c] Polar compounds without carboxylic groups but derivatized by TMSH. [d] High LOD and LOQ attributable to cartridge contamination.

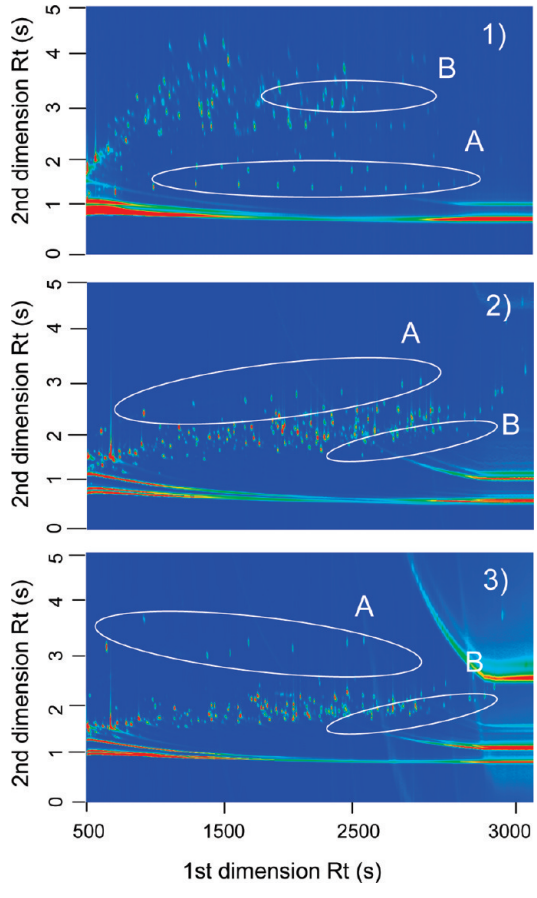

Figure 1. Standard mixture contour plots using different column sets (1 μg/mL): (1) TRB-5 × TRB-50, (2) TRB-1701 × TRB-5, and (3) TRB-50 × TRB5. A shows alkanes, and B is phthalates.

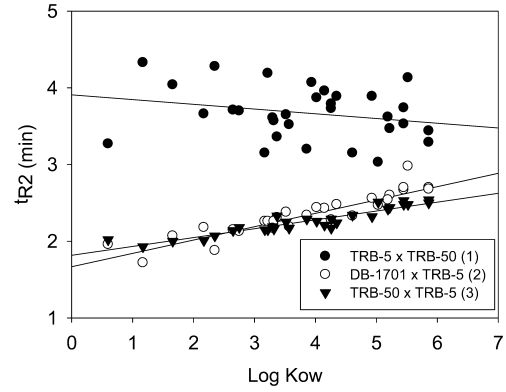

Figure 2. Correlation plot of t_{R2} for three configuration sets against the log Kow (n = 32): (1) Pearson coefficient = −0.244 (p = 0.186); (2) Pearson coefficient = 0.858 (p < 0.01); (3) Pearson coefficient = 0.933 (p < 0.01).

quality method assurance and validation with real samples was carried out with column set 1.

Different derivatization agents have already been employed for multiresidue analysis by GC/MS to improve the peak shapes, decreasing the elution temperature and improving the resolution between target analytes and matrix constituents.[3] Derivatization agents like bis(trimethylsilyl)-trifluoroacetamide (BSFTA) or *N*-methyl-*N*-trimethylsilyl-trifluoroacetamide (MSTFA) lead to trimethylsilyl ether formation, whereas diazomethane does methyl esters. In the present paper, TMSH has been chosen as derivatization agent as it enables the methylation into the GC injector port[29] without a pretreatment step that is time-consuming and often requires a temperature and evaporation step that could remove some semivolatile com-

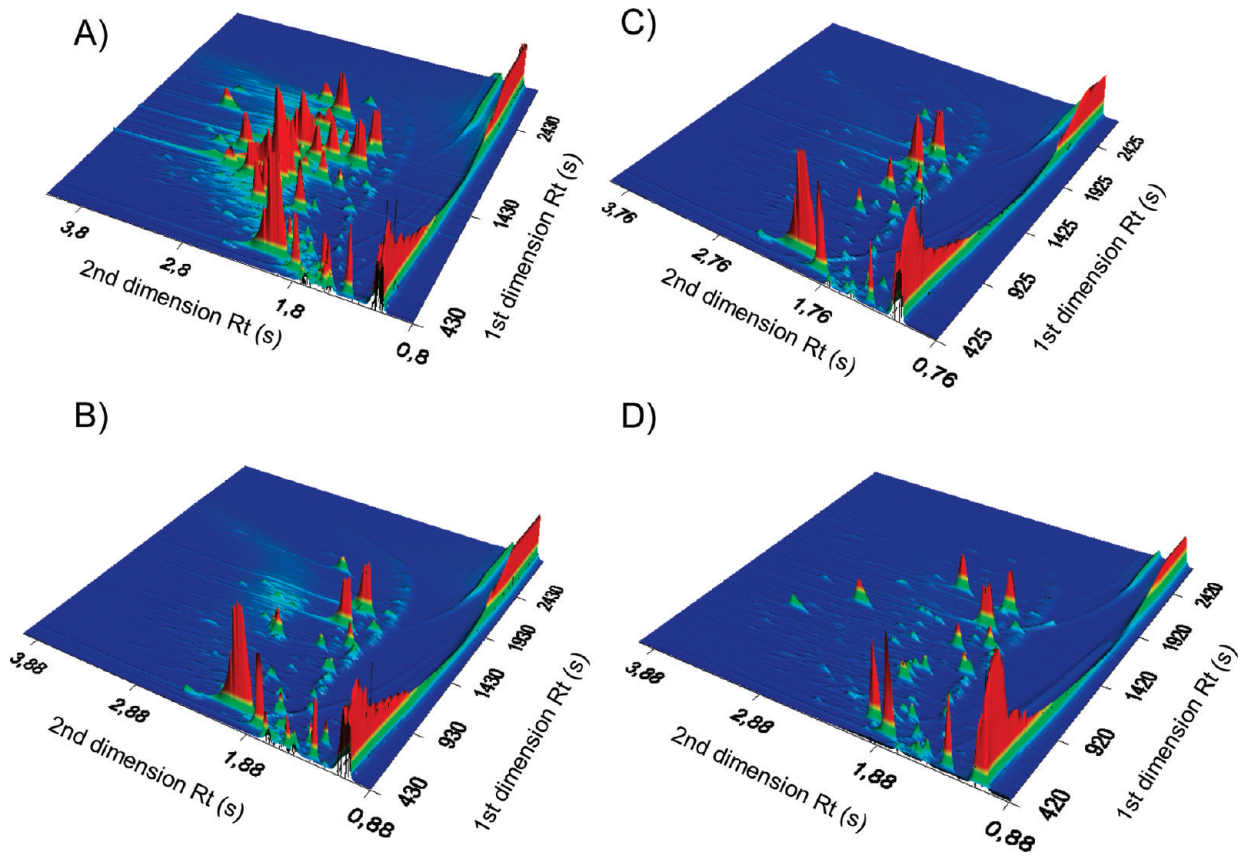

Figure 3. 3D contour plots of four rivers sampled in this study in which the total ion chromatogram is shown: Ebro (A), Llobregat (B), Ter (C), and Besòs (D).

pounds such as fragrances from sample extracts. All carboxylic compounds (e.g., ibuprofen and clofibric acid) were methylated as well as some polar compounds (e.g., bisphenol A, benzotriazole, and triclosan). Hence, this analytical preparation methodology enables the straightforward determination of 97 compounds in one single chromatographic run.

Quality Method Assurance. The overall method precision was satisfactory, with RSD values ranging from 1% to 20%. The linear response from calibration curves covered 3 orders of magnitude, and the calibration curves ranged from 2/10 up to 1000/4000 μg/L. Linearity of the calibration plots exceeded in all the cases an r^2 of 0.98. These results are in accordance with other methodologies described in the literature for similar compounds.[4,10] Compounds that exhibited a lower repeatability were those with low recovery (i.e., di-*n*-octyl phthalate with poor recovery, which showed an RSD of 20%).

Regarding to the sensitivity, LODs and LOQs ranged from 0.5 to 51 ng/L and from 2 to 90 ng/L, respectively. Those results were comparable with the ones reported when using HPLC/MS/MS[30] or HPLC/QTRAP-MS,[10] employing a similar water sample volume. As expected, some ubiquitous compounds such as plasticizers (phthalates and BHT) or naphthalene are present in the procedural blanks at remarkably high concentration leading to an increase in the procedural LODs (27−110 ng/L) and LOQs (44−185 ng/L).

According to the EU regulations (EU Commission Decision 2002/657/EC)[31] the ratio of the first-dimension chromatographic retention time of the analyte to that of the IS between sample to calibration standard was always checked to be lower than 0.5%. Four ions with a relative significant intensity from background (>10%) were employed per each analyte. Hence, analyte identification and confirmation fulfill the stringent criteria by the EU regulations, obtaining enough identification points per compound to ensure the adequate identification of target compounds.

Quantification. In this study, the automatic quantification of the 97 compounds was applied to four different Spanish river waters. The contour plots shown in Figure 3 reveals many 1D-GC coelutions (compounds eluting at the same t_{R1}) that were able to be resolved by the use of GC × GC enhanced chromatographic resolution. These coelutions cause quantification errors (overestimations) when working in 1D-GC, as the peak area is the sum of the target analyte area and the area of the coeluting matrix compounds. In many cases, these coelutions cannot be completely avoided in the 1D-GC/MS even when characteristic ionic trace fragmentograms are used. Overestimation was calculated by peak area of characteristic selected m/z in 1D-GC and comparing that with the ones in GC × GC. As an example, overestimations for compounds highlighted in

(30) Kuster, M.; López de Alda, M. J.; Hernando, M. D.; Petrovic, M.; Martín-Alonso, J.; Barceló, D. *J. Hydrol.* **2008**, *358*, 112–123.

(31) Commission Decision 2002/657/EC of 12 August 2002 implementing Council Directive 96/23/EC concerning performance of analytical methods and the interpretation of results. *Off. J. Eur. Commun.* **2002**, *L221*, 8.

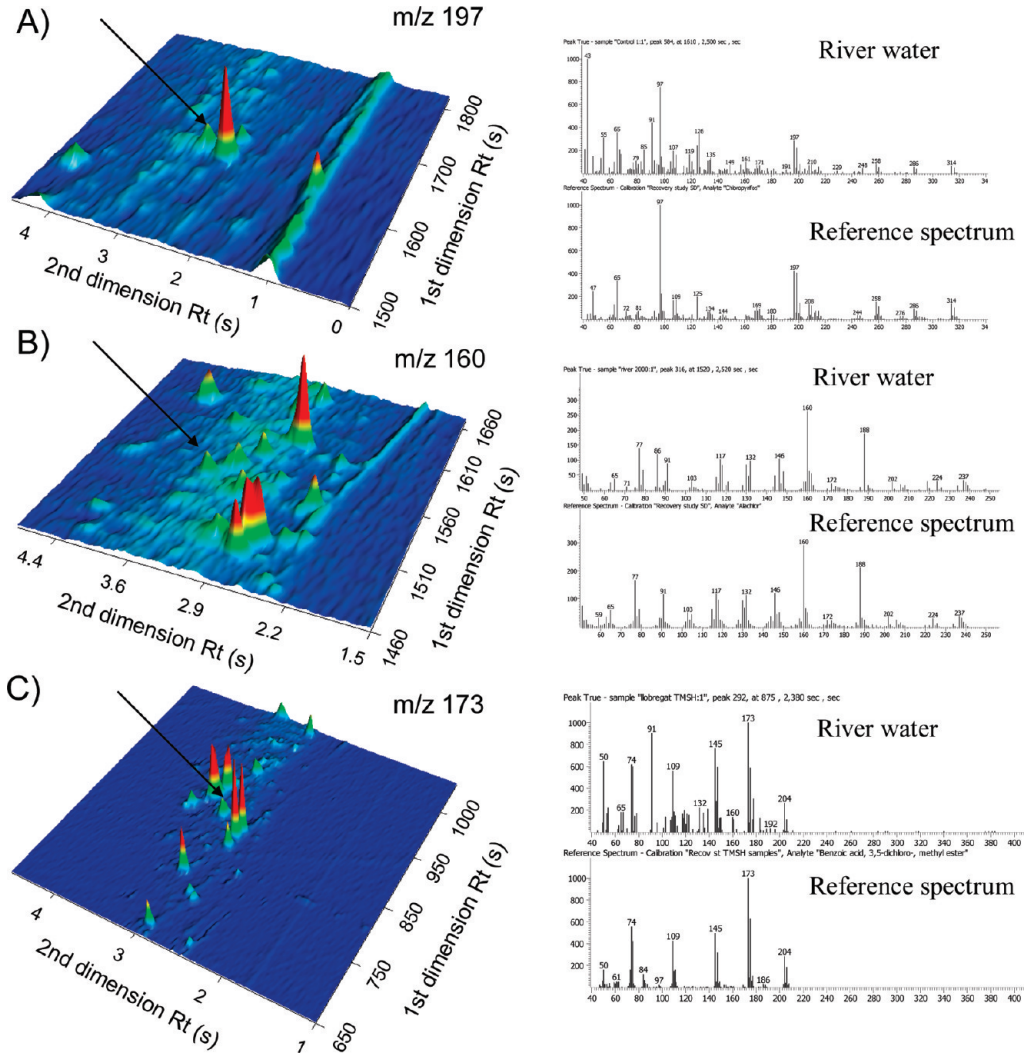

Figure 4. Example of contaminants identified in real river water samples. Contour plots are shown at left and comparison between sample spectrum and reference at right. Note that the contour plots show the mass ion signal intensity of selected compounds: (A) clorpyrifos at 7 ppt in river Besòs (170% overestimation), (B) alachlor at 15 ppt in river Besòs (87% overestimation), and (C) 3,5-dichlorobenzoic acid at 12 ppt in river Llobregat (94% overestimation).

Figure 4 ranged from 80% to 200%, in accordance with previously reported data for benzothiazoles and benzotriazoles.[32] Nevertheless, deconvolution software are commercially available that enable the resolution of two or more coeluted peaks in 1D-GC, but these require at least a small difference on retention time and/or different spectral data. For these compounds, GC × GC or other chromatographic techniques are mandatory. Once again, the suitability of the bidimensional separation approach for the determination of these compounds by GC at low concentration levels is manifested.

Real Sample Application. Figure 3 shows the total ion current (TIC) of four river samples analyzed. Although looking to these chromatograms, the river Ebro sample could be suggested as the most polluted, the compounds shown in the TIC are not at all those analyzed in this study. When ChromaTOF software was applied for sample characterization, the presence of a high amount of fatty acid was observed. It should be pointed out that all these nontarget compounds could interfere in target analytes detection and quantification. Figure 4 shows how the increase of chromatographic resolution by using a GC × GC/TOF-MS permitted the acquisition of MS spectra of analytes in real samples similar to the ones in a standard reference, even at concentrations of a few parts per trillion. Hence, the suitability of GC × GC/TOF-MS for the analysis of 97 compounds belonging to different chemical classes has been proven in this paper.

Table 3 shows the application of the analytical methodology to four real river samples. Whereas plasticizers (e.g., phthalates and bisphenol A), pharmaceuticals (e.g., naproxen, ibuprofen), and personal care products (e.g., tonalide and methyl dihydrojasmonate) were the most abundant in concentration and detection frequency, pesticides (e.g., simazine and alachlor) and polycyclic aromatic hydrocarbons (PAHs) were the lowest. That is in accordance with related data from different European river waters where wastewater inputs (plasticizers, pharmaceuticals, and

(32) Jover, E.; Matamoros, V.; Bayona, J. M. *J. Chromatogr., A* **2009**, *1216*, 4013–4019.

Table 3. Detection Frequency and Concentrations of Selected Organic Contaminants in Four Catalonian Rivers (Ebro, Ter, Llobregat, and Besòs)

name	frequency of detection[a]	range (ng/L)[b]	name	frequency of detection[a]	range (ng/L)[b]
naphthalene	4/4	(167−403) 281	chloropyrifos-methyl	0/4	
salicylic acid	4/4	(95−388) 237	methyl parathion	0/4	
benzothiazole	4/4	(27−92) 65	alachlor	1/4	7
hydrocinnamic acid	4/4	(10−23) 16	tolclofos methyl	0/4	
diuron isocyanate	1/4	21	heptachlor	0/4	
3,5 dichlorobenzoic acid	3/4	(8−15) 12	ametryn	0/4	
dimethyl phthalate	3/4	(45−248) 80	prometrin	0/4	
acenaphthalene	1/4	15	ambrettolide	2/4	(62−64)
methacrifos	1/4	22	terbutryn	2/4	(45−54)
acenaphthene	1/4	9	pirimiphos methyl	0/4	
benzotriazole	4/4	(48−103) 73	dibutyl phthalate	4/4	(93−521) 275
clofibric Acid	4/4	(7−22) 15	phenitrothion	0/4	
cashmeran	1/2	(122−217) 170	aldrin	0/4	
BHT	1/4	284	chloropyriphos	2/4	(15−21) 18
benzenosulfonamide methyl	1/4	204	carbamazepine	4/4	(64−77) 70
Dicamba	1/4	13	bromophos-methyl	0/4	
Pentachlorobenzene	0/4		naproxen	4/4	(21−329) 197
ibuprofen	4/4	(14−47) 41	oxybenzone	2/4	(80−729) 405
MCPA	4/4	(14−387) 113	*cis*-chlorfenvinphos	0/4	
fluorene	1/2	(21−42) 32	flunixin	2/4	(17−491) 254
diethyl phthalate	4/4	(363−2523) 1396	bisphenol A	4/4	(43−1746) 512
1*H*-benzotriazole, 4-methyl-	1/2		*trans*-chlorfenvinphos	0/4	
p-tert-octylphenol	4/4	(17−131) 42	heptachlor-endoepoxide	0/4	
benzothiazole, 2-(methylthio)-	4/4	(15−305) 89	fluoranthene	1/4	11
dichlorprop	1/4	23	phthalic acid, bis(2-ethoxyethyl) ester	0/4	
tributyl phosphate	4/4	(10−97) 31	bromophos-ethyl	1/4	4
2,4-D	3/4	(16−66) 42	triclosan	4/4	(10−161)
methyl dihydrojasmonate	4/4	(68−583) 264	dipentyl phthalate	0/4	
celestolide	1/4	89	pyrene	2/4	(17−18)18
hexachlorobenzene	0/4		ketoprofen	4/4	(20−57)40
prometon	0/4		DDE	0/4	
simazine	1/4	13	dieldrin	2/4	(5−9) 7
atrazine	1/4	17	diclofenac	4/4	(22−84) 46
propazine	0/4		endrin	0/4	
tri(2-chloroethyl) phosphate	4/4	(54−219) 105	phthalic acid, dihexyl ester	1/4	7
silvex	0/4		benzyl butyl phthalate	0/4	
terbutylazine	4/4	(31−328) 111	phthalic acid, 2-ethylhexyl hexyl ester	0/4	
chloramben	1/4	17	bis(2-butoxyethyl) phthalate	0/4	
dyfonate	1/4	6	*p,p′*-methoxychlor	1/4	22
2,4,5-T	0/4		benz[*a*]anthracene	0/4	
diazinone	4/4	(4−8) 5	chrysene	0/4	
anthracene	0/4		dicyclohexyl phthalate	2/4	(2−4) 3
phenanthrene	4/4	(7−12) 9	estrone	3/4	(36−54) 46
benzothiazolone	3/4	(32−77) 49	estradiol	0/4	
galaxolide	4/4	(21−476) 167	17-α-ethynylestradiol	0/4	
diisobutyl phthalate	4/4	(265−1107) 536	di-*n*-octyl phthalate	0/4	
caffeine	4/4	(145−824) 382	phthalic acid, dinonyl ester	1/4	12
tonalide	0/4	(22−103) 54	furosemide	1/4	175
2,4 Db	0/4				

[a] Number of samples with concentrations greater than LOD/total number of samples. [b] Average values are given with minimum and maximum values in parentheses.

personal care products) into rivers are more significant than agricultural runoff (pesticides).[33]

CONCLUSIONS

This paper has showed that the combination of SPE and GC × GC/TOF-MS determination allowed the simultaneous determination of 97 compounds, including both priority and emerging pollutants, in river waters. The potential of GC × GC/TOF-MS, by using different column sets, enables an unambiguous and accurate identification of target compounds in the river samples. The method yielded detection limits in the low nanogram per liter range for most of the analytes, providing a reliable and robust tool that can be used for routine analysis of multiresidue compounds (priority or emerging pollutants) in river samples.

(33) Loos, R.; Gawlik, B. M.; Locoro, G.; Rimaviciute, E.; Contini, S.; Bidoglio, G. *Environ. Pollut.* **2009**, *157*, 561–568.

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