Sensors and Materials, Vol. 11, No. 4 (1999) 209–218
MYU Tokyo

S & M 0366

Enantioselective Monitoring of Chiral Inhalation Anesthetics by Simple Gas Sensors

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(Received March 20, 1998; accepted May 28, 1999)

Key words: sensors, thickness shear mode resonators (TSMRs), chiral discrimination, enantiomers, cyclodextrins, inhalation anesthetics, volatile organic compounds (VOCs)

The enantiomers of chiral anesthetics (enflurane, isoflurane, desflurane) can be recognized, and, additionally, extremely low concentrations of all common inhalation anesthetics in ambient air can be monitored using simple on-line-operable gas sensors with cyclodextrin coatings.

1. Introduction

Enantioselectivity plays an important role in biological systems and in pharmacology. In the case of the chiral inhalation anesthetics, an enantiomeric bias has been proposed.[1] However, chiral inhalation anesthetics are still produced and clinically administered as racemic mixtures, although the consequences of the (unintended) introduction of a chiral center into these haloethers and its impact on enantioselective biological reactions are still debated.[1,2]

One of the most popular methods of chiral recognition includes intramolecular entrapment into cavities such as cyclodextrins used as coatings for sensors,[3,4] or in gas chromatography (GC).[5,6] Here we report on the chiral recognition of the anesthetics using a

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sensor array, which takes advantage of such entrapment mechanisms. Achieving chiral discrimination with gas sensors is fundamentally more difficult than with GC, because the former employ only one "theoretical plate" (one absorption/desorption step), whereas in GC, discrimination typically results from the cumulative effect of thousands of successive absorption/desorption equilibria.[5-8] GC, however, is an off-line procedure, whereas gas sensors offer the unique advantage of fast and continuous monitoring.

2. Materials and Methods

The chiral model receptor used in this study was a very versatile modified γ-cyclodextrin derivative (octakis(3-*O*-butanoyl-2,6-di-*O*-n-pentyl)-γ-cyclodextrin, CD, Fig. 1),[9] which had been dissolved in a polysiloxane matrix. This matrix is a polysiloxane backbone bearing phenyl-, vinyl-, and methyl groups, and is commercially available from Macherey and Nagel, Düren, Germany (SE-54). Solutions of these polymers were sprayed onto quartz plates (airbrush).[10] The layer thickness ranged between 250 and 300 nm. In

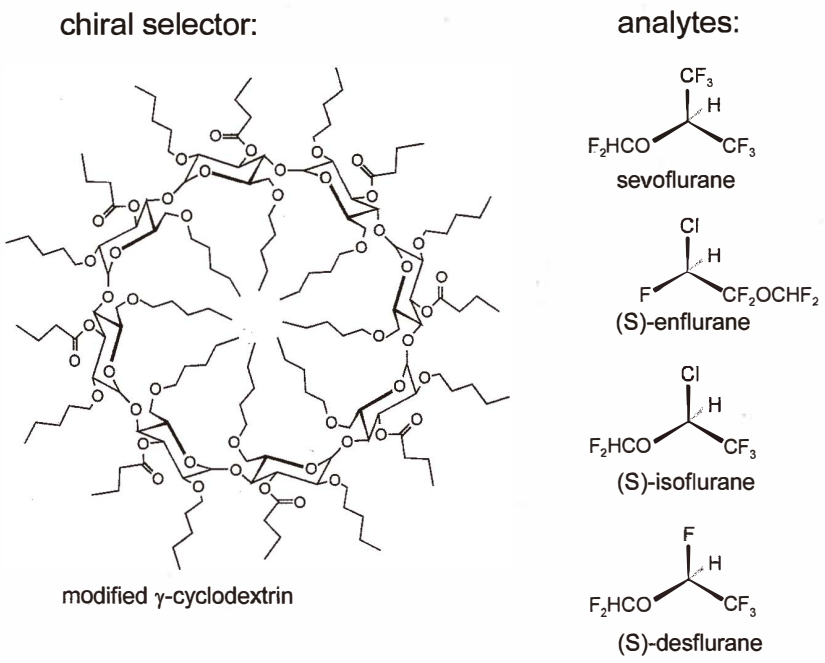

Fig. 1. Coatings and analytes investigated in this study: enantioselective octakis(3-*O*-butanoyl-2,6-di-*O*-n-pentyl)-γ-cyclodextrin, nonchiral sevoflurane, chiral enflurane, isoflurane and desflurane. Only the respective (S)-enantiomers are shown.

addition to the chiral sensors, reference devices coated with the non-enantioselective polymer poly(etherurethane) (PEUT, Thermedics Inc., Woburn, MA, USA) were included in the sensor arrays for the recognition of artefacts due to fluctuating gas phase concentrations or contaminations of the (S)- and (R)-analytes.

Signal transduction (chemical to electrical) was achieved using thickness shear-mode resonators (TSMRs). TSMRs are mass-sensitive transducers commonly used for monitoring volatile organic compounds (VOCs) using polymer layers as sensitive coatings (Fig. 2). The TSMR array consisted of discrete piezoelectric quartz crystals (AT-cut) with gold electrodes operating at a fundamental frequency of 30 MHz (quartz plate thickness: 55.6 μm) purchased from Kristallverarbeitung Neckarbischofsheim, Germany. Each crystal was powered by an oscillator circuit (bipolar, parallel resonance) constructed in our laboratory. Only one single coaxial cable is required for voltage supply and signal transmission. As shown by Sauerbrey,[11] the vibrating frequency of a TSMR changes to a first approximation in proportion to the mass deposited onto or removed from the surface. When the polymer-coated TSMRs are exposed to analyte gas, sorption of molecules by the polymer generates a change in the oscillating mass which in turn causes a shift in the operating frequency (Fig. 2).[12,13] The sorption strength depends on the interaction mechanisms and forces (H-bridge bonds and dispersion forces) between matrix and analyte molecules.

A self-developed scanner (up to 16 channels) operating at frequencies between 100 kHz and 100 MHz was controlled by a PCL 726 interface card (Labtech, Wilmington, MA) in an IBM-compatible PC-AT and allowed for the sequential monitoring of each TSMR output using a Hewlett-Packard 5334 B frequency counter. The computer acquired the frequency values via an IEEE 488 interface bus. The first monitored frequency value of each device was set equal to zero, hence the frequency differences were monitored in

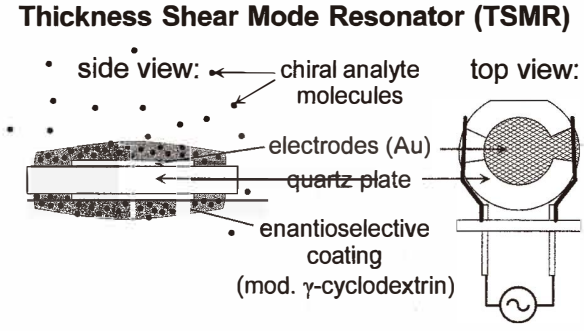

Fig. 2. Signal transduction by thickness shear-mode resonators (TSMRs). TSMRs are mass-sensitive transducers. Upon exposure to volatile organic compounds, sorption of analyte molecules by the polymer generates a change in the oscillating mass which in turn causes a shift in the operating frequency.

reference to this first value.

The frequency outputs of the TSMRs were recorded every 30 s at 0.1 Hz resolution. The gate time of the counter (HP 5334 B) was set to 1 s for all the devices. The absolute sensor responses were given by the frequency difference between gas exposure and purging.

The complete sensor array containing three sensors coated with 10% (w/w) cyclodextrin in SE-54, four sensors coated with 50% (w/w) cyclodextrin in SE-54, four sensors coated with pure cyclodextrin as well as five nonchiral reference sensors (three SE-54, two PEUT) was mounted in the flow-through cell. Hence all sensors were simultaneously exposed to the analyte gas at a constant temperature of 303 K. The array approach was chosen here to demonstrate the reproducibility of the sensor results (from sensor to sensor) and to ensure statistically significant conclusions (especially α–values) from a broad database. It is no more appropriate to rely on single sensors showing incidental signal behavior (see Tables 1a and 1b).

The chiral analytes (Fig. 1) included both enantiomers of enflurane (2-chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane), isoflurane (2-chloro-2-(difluoro–methoxy)-1,1,1-trifluoroethane), and desflurane (2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane). The enantiomers were separated by preparative GC on cyclodextrin-containing stationary phases. A racemic mixture of the gaseous anesthetics was fed to a preparative column containing 80% (w/w) ceramic support (Chromosorb®, P(AW-DMCS) 80–100 mesh, Macherey-Nagel, Düren, Germany) and 20% (w/w) of a mixture of 90% (w/w) SE-54 and 10% (w/w) modified γ-cyclodextrin (Fig. 1). The pure enantiomers were condensed at the bottom of the column and collected in cooling traps by using liquid nitrogen (details of the preparative enantioseparation procedure are given in ref. 14). The purity was checked by GC-analysis: (R)-(–)-isoflurane 88.5%, (S)-(+)-isoflurane > 97%, (R)-(–)-enflurane > 99%, (S)-(+)-enflurane > 99%,(R)-(–)-desflurane 69%, and (S)-(+)-desflurane 94%. For extensive studies on monitoring extremely low anesthetic concentrations in ambient air (operation theaters), we additionally investigated the nonchiral inhalation anesthetic sevoflurane (Fig. 1, fluoromethyl-2,2,2-trifluoro-1-(trifluoromethyl)-ethylether).

The test vapors were generated by thermally controlled vaporizers using synthetic air as carrier gas.[15] Since the available quantities of the analytes in enantiomeric purity (between 150 and 50 μL liquid) were very small, and the anesthetics are extremely volatile, we cooled the vaporizers to 223 K and injected the liquids through septa. The thermostat used for this purpose was an Ultra Kryomat® RUK 60 from Lauda Dr. Worbser GmbH, Lauda-Königshofen, Germany. The gas flow rate to the sensors was 200 ml/min at a total pressure of 10^5 Pa. The response time of the sensors is on the order of seconds (< 1 s). However, the time necessary to reach an equilibrium state in our setup is about 5 min (t_{90} = 120 s) and results from adjusting a constant gas concentration in the chamber (volume 20 mL) at the chosen flow rate. The analyte liquids and the syringes were kept in dry ice to limit the vaporization loss during the transfer into the vaporizers. Typical experiments consisted of repeated, alternating exposures (10 min) of the sensors to air and entrained vapor. The absolute sensor responses are the differences in the signals between analyte equilibration and the purging state (dry air).

The chiral separation factors derived from GC measurements, α_{GC}, were determined at

coating			PEUT		SE-54			10% γ-cyclodextrin (w/w) in SE-54			50% γ-cyclodextrin (w/w) in SE-54				γ-cyclodextrin (pure)			
sensor index			E5	E6	T1	T2	T3	O9	P1	P2	R9	S1	S2	S6	T5	T6	T7	T9
$\Delta f_{polymer}$ [kHz]			75	75	68.2	68	65.8	77.1	75.5	75.5	75.7	75.9	75.7	75.9	77.6	79	77.2	155
enflurane	c [ppm]	c [µg/L]	$\Delta f_{analyte}/\Delta f_{polymer} \cdot [10^{-3}]$															
(S)-(+)-enflurane 99%	400	2960	0.771	0.778	0.142	0.161	0.156	0.547	0.500	0.514	4.353	4.666	4.766	4.250	9.323	10.083	9.893	9.919
	300	2220	0.592	0.592	0.108	0.121	0.116	0.425	0.388	0.399	3.454	3.704	3.782	3.371	7.005	7.967	7.832	7.868
	200	1480	0.385	0.390	0.072	0.084	0.078	0.287	0.262	0.269	2.377	2.551	2.603	2.318	5.105	5.496	5.391	5.426
	150	1110	0.285	0.279	0.047	0.056	0.052	0.207	0.187	0.195	1.738	1.862	1.902	1.692	3.731	4.031	3.960	3.990
	100	740	0.191	0.194	0.034	0.037	0.035	0.143	0.131	0.134	1.226	1.319	1.346	1.197	2.669	2.834	2.802	2.831
	50	370	0.092	0.094	0.018	0.020	0.019	0.073	0.067	0.067	0.616	0.665	0.676	0.601	1.368	1.450	1.426	1.438
enflurane (racemic mixture)	400	2960	0.735	0.739	0.137	0.154	0.152	0.452	0.415	0.427	3.313	3.534	3.616	3.238	7.036	7.366	7.326	7.358
	300	2220	0.541	0.548	0.100	0.113	0.110	0.340	0.311	0.320	2.525	2.696	2.758	2.467	5.395	5.617	5.599	5.643
	200	1480	0.360	0.362	0.072	0.079	0.078	0.230	0.210	0.215	1.724	1.843	1.885	1.686	3.681	3.861	3.833	3.867
	150	1110	0.269	0.270	0.051	0.057	0.055	0.172	0.157	0.161	1.301	1.392	1.423	1.271	2.796	2.928	2.907	2.934
	100	740	0.165	0.176	0.037	0.041	0.040	0.118	0.107	0.110	0.876	0.939	0.959	0.857	1.899	1.999	1.972	1.984
	50	370	0.086	0.084	0.020	0.021	0.021	0.056	0.052	0.052	0.435	0.462	0.472	0.422	0.958	0.999	0.981	0.994
(R)-(-)-enflurane 99%	400	2960	0.757	0.762	0.141	0.157	0.155	0.397	0.375	0.381	2.418	2.565	2.630	2.373	5.122	5.582	5.438	5.427
	300	2220	0.568	0.572	0.100	0.115	0.112	0.297	0.279	0.283	1.838	1.951	2.002	1.805	3.912	4.227	4.151	4.155
	200	1480	0.381	0.377	0.070	0.079	0.078	0.201	0.189	0.193	1.242	1.318	1.353	1.219	2.658	2.891	2.815	2.815
	150	1110	0.288	0.281	0.050	0.058	0.055	0.150	0.140	0.144	0.931	0.987	1.013	0.912	2.001	2.175	2.117	2.118
	100	740	0.185	0.188	0.035	0.037	0.035	0.100	0.093	0.095	0.629	0.666	0.683	0.615	1.366	1.461	1.438	1.442
	50	370	0.089	0.091	0.018	0.020	0.019	0.049	0.046	0.047	0.310	0.340	0.338	0.305	0.700	0.739	0.728	0.728
$\alpha_{calculated}$, $\Delta f_S/\Delta f_R$ (100 ppm)			1.034	1.031	0.966	1.000	1.016	1.439	1.405	1.408	1.948	1.980	1.972	1.947	1.954	1.940	1.949	1.963
mean separation factor $\alpha_{calc.}$								1.417 ± 0.019			1.962 ± 0.017				1.951 ± 0.010			

Table 1a

Data for the chiral discrimination of desflurane and enflurane at 303 K. The array configuration (16 sensors), the sensor index, the type of coatings (PEUT, SE-54, 10% and 50% (w/w) CD in SE-54, pure CD) and the frequency shifts due to coating ($\Delta f_{Polymer}$) are listed in the upper lines. Relative sensor signals with respect to $\Delta f_{Polymer}$ for exposure to different concentrations (in µg/L and ppm (volume, ideal gas behavior)) of (R)- and (S)-enflurane are given. The ratio of the (S)- to the (R)-analyte signal ($\Delta f_S/\Delta f_R$) and calculated chiral discrimination factors (α_{calc}) are found at the bottom of the table.

coating			PEUT		SE-54			10% γ-cyclodextrin (w/w) in SE-54			50% γ-cyclodextrin (w/w) in SE-54				γ-cyclodextrin (pure)			
sensor index			E5	E6	T1	T2	T3	O9	P1	P2	R9	S1	S2	S6	T5	T6	T7	T9
$\Delta f_{polymer}$ [kHz]			75	75	68.2	68	65.8	77.1	75.5	75.5	75.7	75.9	75.7	75.9	77.6	79	77.2	155
desflurane	c [ppm]	c [µg/L]	$\Delta f_{analyte}/\Delta f_{Polymer} \cdot [10^{-3}]$															
(R)-(-)-desflurane	3000	20300	0.768	0.787	0.199	0.226	0.219	0.601	0.572	0.584	2.890	3.009	3.078	2.818	5.758	5.809	5.864	5.829
(R:S = 69:31)	2500	16900	0.640	0.648	0.169	0.191	0.185	0.499	0.473	0.483	2.421	2.516	2.573	2.354	4.684	4.867	4.917	4.885
	2000	13500	0.511	0.517	0.130	0.150	0.147	0.398	0.380	0.385	1.934	2.021	2.067	1.892	3.941	3.925	3.961	3.937
	1500	10100	0.383	0.385	0.101	0.115	0.109	0.301	0.287	0.293	1.485	1.535	1.568	1.435	2.990	2.985	3.010	2.992
	1000	6760	0.256	0.256	0.065	0.074	0.073	0.201	0.192	0.195	0.996	1.034	1.053	0.966	2.032	2.020	2.040	2.025
	500	3380	0.136	0.127	0.031	0.037	0.036	0.096	0.093	0.094	0.507	0.518	0.527	0.484	1.055	1.014	1.041	1.039
desflurane	3000	20300	0.759	0.763	0.211	0.235	0.229	0.588	0.559	0.570	2.639	2.739	2.798	2.577	5.193	5.285	5.284	5.221
(racemic mixture)	2500	16900	0.640	0.648	0.170	0.191	0.187	0.489	0.466	0.474	2.223	2.306	2.355	2.169	4.420	4.461	4.487	4.457
	2000	13500	0.519	0.515	0.129	0.149	0.146	0.390	0.372	0.377	1.798	1.858	1.900	1.747	3.561	3.585	3.624	3.604
	1500	10100	0.377	0.384	0.101	0.115	0.111	0.294	0.279	0.286	1.358	1.404	1.433	1.319	2.745	2.728	2.749	2.728
	1000	6760	0.249	0.257	0.063	0.074	0.071	0.193	0.185	0.187	0.897	0.937	0.954	0.880	1.843	1.828	1.850	1.843
	500	3380	0.112	0.123	0.032	0.038	0.038	0.095	0.091	0.093	0.457	0.468	0.473	0.439	0.954	0.922	0.940	0.929
(S)-(+)-desflurane	3000	20300	0.777	0.789	0.208	0.234	0.229	0.565	0.546	0.555	2.227	2.273	2.341	2.175	4.343	4.381	4.420	4.358
(R:S = 6:94)	2500	16900	0.661	0.653	0.167	0.191	0.184	0.470	0.453	0.461	1.863	1.895	1.952	1.813	3.634	3.652	3.696	3.649
	2000	13500	0.524	0.525	0.132	0.151	0.149	0.374	0.359	0.367	1.486	1.519	1.563	1.452	2.925	2.925	2.969	2.936
	1500	10100	0.387	0.387	0.103	0.118	0.116	0.281	0.272	0.275	1.106	1.142	1.174	1.091	2.229	2.225	2.241	2.208
	1000	6760	0.256	0.256	0.064	0.074	0.071	0.184	0.176	0.180	0.746	0.760	0.782	0.726	1.495	1.472	1.508	1.494
	500	3380	0.125	0.124	0.035	0.038	0.036	0.092	0.089	0.091	0.374	0.377	0.386	0.360	0.773	0.748	0.766	0.748
$\Delta f_R/\Delta f_S$ (1000 ppm)			1.000	1.000	1.016	1.000	1.021	1.092	1.090	1.081	1.335	1.360	1.346	1.330	1.359	1.372	1.353	1.355
$\alpha'_{calc.} = 1 + (100/63 \cdot (\Delta f_R/\Delta f_S - 1))$								1.145	1.143	1.128	1.531	1.572	1.550	1.524	1.571	1.591	1.560	1.564
mean separation factor $\alpha'_{calc.}$								1.139 ± 0.009			1.544 ± 0.021				1.572 ± 0.014			

Table 1b

Data for the chiral discrimination of desflurane and enflurane at 303 K. The array configuration (16 sensors), the sensor index, the type of coatings (PEUT, SE-54, 10% and 50% (w/w) CD in SE-54, pure CD) and the frequency shifts due to coating ($\Delta f_{Polymer}$) are listed in the upper lines. Relative sensor signals with respect to $\Delta f_{Polymer}$ for exposure to different concentrations (in µg/L and ppm (volume, ideal gas behavior)) of (R)- and (S)-enflurane are given. The ratio of the (S)- to the (R)-analyte signal ($\Delta f_S/\Delta f_R$) and calculated chiral discrimination factors (α_{calc}) are found at the bottom of the table.

303 K using a fused silica capillary column (length: 25 m, inner diameter: 0.25 mm) coated with 50% (w/w) modified γ-cyclodextrin dissolved in SE-54. The average film thickness was 0.25 μm. Helium was used as carrier gas at an inlet pressure of 1.1×10^5 Pa.

3. Results and Discussion

For all chiral analytes the responses of the chiral sensors to the individual enantiomers showed an unprecedented difference in contrast to the signals of the reference sensors (Tables 1a and 1b). An array of 16 sensors was used: three sensors coated with 10% (w/w) CD, four sensors with 50% (w/w) and pure CD as well as five reference sensors. Two reference sensors were coated with PEUT and three with the pure SE-54. The relative sensor responses (with respect to the frequency shift associated with the coating deposition) averaged over 3 – 5 subsequent identical runs are displayed for (R)-, (S)-enantiomers and the racemates for enflurane and desflurane. Sensor index, type of coating and frequency shift due to coating are given in the upper part. The experimentally determined α-values for a certain concentration are listed at the bottom of the tables. In going from 50% (w/w) CD in SE-54 to the pure CD, the α'_{sensor}-values for both anesthetics increase only slightly. This is in agreement with findings in GC measurements. There is a maximum α'-value for a certain mixing ratio of the recognition unit and the polymer matrix depending on the nature of the coating and of the analyte. In our case, this optimum value is reached for mixtures between 50% and 60% (w/w) CD in SE-54.

The fast sensor response, the complete desorption upon purging with air and the repeated enantioselective absorption are depicted for enflurane in Fig. 3 (top). The frequency change, Δf, of the sensor coated with 50% (w/w) cyclodextrin in SE-54 is more pronounced for the S-(–)-enantiomer compared to the R-(+)-enantiomer of enflurane. Hence, the interaction between the CD-recognition unit and the (S)-enantiomer is considerably stronger than that between the CD-cage and the (R)-enantiomer. The sensor signals upon exposure to the racemic mixture are of intermediate height. This finding is in agreement with the results of GC and ^{1}H-NMR spectroscopy: longer retention time of the S-(-)-enantiomer on a chiral stationary phase containing CD [16] (Fig. 3, bottom) and larger downfield shift in the presence of CD as a chiral shift reagent.[17] The enantiomers of the other chiral anesthetics, isoflurane and desflurane could be discriminated analogously to enflurane.

Table 2 shows the chiral discrimination factors α_{sensor} (α_{sensor} is defined as the ratio of the frequency shift upon exposure to the more strongly sorbed enantiomer to the frequency shift upon exposure to the less sorbed enantiomer) and those obtained by GC (α_{GC} is defined as the ratio of the net retention times of the respective enantiomers) for the chiral anesthetics using CD (50% (w/w) in SE-54) as the selective coating. The standard deviations were calculated for a subset of five sensors with comparable layer thicknesses. The discrimination factors obtained using the nonchiral reference sensors equal unity with a standard deviation of 1.3%, which proves the identical gas phase concentrations of both enantiomers of the chiral analyte. For structurally related isoflurane and desflurane, the (R)-enantiomers produce a larger frequency shift compared to the (S)-enantiomers. For

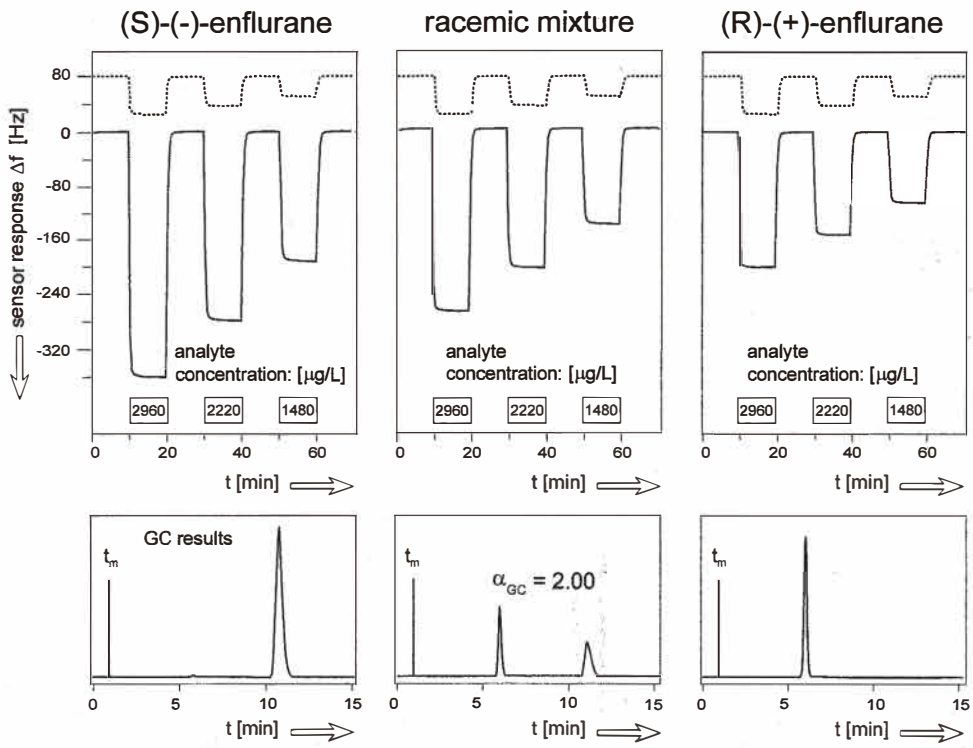

Fig. 3. Corresponding sensor signals and gas chromatograms of enflurane obtained with a selective layer of 50% (w/w) modified γ-cyclodextrin in SE-54 (solid line). In addition, the sensor responses of the nonchiral reference sensor (PEUT-coating) are shown (dashed line). The sensor responses upon alternate exposure to the enantiomers and synthetic air as a reference gas are given in Hz, the analyte concentrations in µg/L. The corresponding GC retention times (fused silica capillary column, 25 m, 0.25 mm inner diameter, 1.1 bar He) are displayed in min.

Table 2
α-values at 303 K obtained through sensor measurements (five sensors) and GC investigations (fused silica capillary column, 25 m, 0.25 mm diameter, 1.1 bar He). The sensitive layer consisted of 50% (w/w) modified γ-cyclodextrin dissolved in SE-54.

	Gas chromatography		Gas sensors	
Analyte	α_{GC} (303 K)	Retention factor	α_{sensor} (303 K)	Signal height
Enflurane	2.00	S > R	1.85± 0.017	S > R
Isoflurane	1.34	R > S	1.28± 0.005	R > S
Desflurane	1.72	R > S	1.54± 0.021	R > S

enflurane, the reverse holds true. This is in perfect agreement with the results of GC, where the retention factors of the (R)-enantiomers of isoflurane and desflurane are larger than those of the (S)-enantiomers, and an inversion can be observed in the case of enflurane. The GC elution order, representing the strength of the occurring interactions, is hence reflected in the signal intensities of the sensor responses. The numerical sensor α-values clearly correspond to those obtained by gas-chromatographic methods involving high plate numbers (Table 2). Thus, the detectability of enantiomers by cyclodextrin-coated gas sensors and the coincidence of these results with those of GC measurements were established for the first time. In a related study on chiral amides,[18,19] quantitative determination of the enantiomeric purity or the enantiomeric composition of chiral analytes could be successfully demonstrated. The methods and algorithms used there can be analogously applied to the cyclodextrins in the present study. In comparison to gas chromatography, the advantages of enantioselective sensors include, in addition to on-line capability, the defined sorption conditions, i.e., defined analyte concentration, steady-state signals, and a single theoretical plate, all of which are beneficial for elucidating mechanisms of chiral recognition. Their drawbacks include the need for calibration with pure enantiomers. In practical applications, it would be sufficient to have one sensor coated with CD (50% w/w or alternatively pure CD) and another coated with PEUT to perform reliable enantiomeric discrimination. The purpose of using an array was to demonstrate the general viability of this approach and the reproducibility of the sensing performance.

Furthermore, the detectability of inhalation anesthetics is improved by a factor of 20 to 50 using selective modified cyclodextrin instead of, *e.g.*, a pure polysiloxane or another standard polymer. The extrapolated threshold values at a rather conservatively estimated noise level of 1 Hz (compare ref. 10) are 45 μg/L (7 ppm) for desflurane, 20 μg/L (2.5 ppm) for isoflurane, 5 μg/L (0.6 ppm) for enflurane, and 13 μg/L (1.6 ppm) for sevoflurane in the case of using a sensor coated with pure CD. An important feature for immediate practical application thus includes the on-line detection of minimal concentrations of these anesthetics in operating theaters.

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