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# Optical $CO_2$-sensing layers for clinical application based on pH-sensitive indicators incorporated into nanoscopic metal-oxide supports

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**Abstract**

We describe $CO_2$-selective films designed for clinical application based on the co-incorporation of different phenol dyes, α-naphtholphthalein (NAF), naphthol blue black (NBB) and calmagite (CMG), with a phase-transfer agent, tetraoctylammonium hydroxide (TONOH), into metal-oxide nanoporous matrices. The metal-oxide coatings consist of aluminum (AlOOH), silicon ($SiO_2$) and zirconium ($ZrO_2$) oxides. The chemical reaction principle and preparation of these new sensing layers are described in detail. We have investigated the effect of the type and concentration of the pH-indicator and TONOH together with that of the composition and morphological characteristics of the nanostructured material. The influence of external parameters such as flow-rate, humidity and interfering gases (NO, CO, $NO_2$ and $SO_2$) were also looked into. The sensing films responded to $CO_2$ concentrations in the gas phase between 0.25% and 40% $CO_2$ (v/v) for NAF–TONOH, 4.1% and 30% $CO_2$ for NBB–TONOH and 0.6% and 40% $CO_2$ for CMG–TONOH, with detection limits of 0.25%, 4.1% and 0.6% $CO_2$ (v/v) for NAF–TONOH, NBB–TONOH and CMG–TONOH, respectively. The nanoporous membranes provided higher dispersion and accessibility of the dye, and thus a quick response time, lower probability of aggregation, the possibility of sterilization by gamma radiation, insulation from reactive chemicals and higher ambient stability.


*Keywords:* $CO_2$ gas sensor; α-Naphtholphthalein; Naphthol blue black; Calmagite; Medical application; Breath-by-breath analysis

## 1. Introduction

The quantitative detection of $CO_2$ is important in such fields as environmental protection [1], food packaging [2,3] and medical monitoring (breath-by-breath analysis) [4]. The use of optical sensors for quantitative $CO_2$ analysis offers potential advantages over other analytical methods such as, for example, electrical isolation, reduced noise interference, the possibility of miniaturization and remote sensing, and when coupled to optical fibers it provides a non-invasive monitoring system that is free from electromagnetic interferences. The materials can also be disposable.

Many papers have been published on the development of optical $CO_2$-sensing layers and several patents have been filed. These can be classified into three types: some sensing-films are membranes that register the change in color of pH-indicator dyes caused by the dissolution of gaseous $CO_2$ [4–8]; others are based on the change in fluorescence induced by $CO_2$ in luminescent dyes [2,3,9–12]; and a third type of film is based on the overlay of the $CO_2$-induced change in absorbance of a pH indicator with a luminescent internal reference dye [13–16]. Nevertheless, the response and recovery times of these methods are often too slow for breath-by-breath analysis and also the number of fluorescent compounds that change in intensity in the presence of $CO_2$ is

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extremely limited and their useful lifetime tends to be short and unpredictable.

A suitable $CO_2$ sensor for clinical applications must provide a linear response function within a range of about 2% and 20% $CO_2$ (v/v) in air; it must not be very sensitive to humidity, should be stable for at least one month and easy to produce. In addition, the change in its absorbance should ideally be above 600 nm in order to avoid interference with hemoglobin [17].

In 1997 Mills et al. [4] developed an optical sensor which proved to be suitable for breath-by-breath analysis. This sensor was based on a plastic film (ethyl cellulose) containing the pH-sensitive hydrophilic indicator dye phenol red combined with a phase-transfer agent, tretraoctylammonium hydroxide (TONOH), and a plasticizer. Since then our research group has optimized Mills's membrane with regard to its dynamic range response, recovery times and absorption wavelength, by varying the membrane polymer and dye. The screening of a series of pH-sensitive dyes described by Cannas et al. [17] revealed three very stable candidates for $CO_2$ measurement in medical applications: α-naphtholphthalein (NAF); naphthol blue black (NBB); and calmagite (CMG). The membranes were reversible and stable for more than a month at 4 °C. They were fairly easy to produce; the response time was generally below 30 s; they showed low sensitivity to humidity and the response functions were linear in the most relevant concentration range between 0% and 10% $CO_2$ (v/v).

Our research group has also developed and characterized novel metal-oxide nanostructured supports into which gas-selective compounds can easily be incorporated [18–21]. These sensing layers, which rely on the immobilization of dyes into metal-oxide nanostructured supports, behave extremely well, due mainly to the controlled pore-size of the nanostructured sensing layer. The nanoporous material and the procedure can theoretically be combined with all known chemical compounds that are selective for a specific gas. The nanoporous structure allows the co-retention of more than one compound without aggregation. It admits chemical processes between compounds to run reversibly thus providing increased photostability and stability to gamma radiation. In addition, the insulation of reactive chemicals makes it more stable within its ambience. The higher dispersion, the controlled capillarity and the excellent accessibility of selective agents and indicators provide quick response times and a lessened probability of aggregation of the dyes by their insulation within the nanopores [18–21].

We describe here the co-incorporation of the pH-sensitive dyes NAF, NBB and CMG with TONOH into nanoporous metal-oxide membranes to increase their linear response range, their stability both at 25 °C (room temperature) and 40 °C (body temperature), to avoid the agglomeration of the dye and to allow their sterilization by gamma-rays.

## 2. Experimental

### 2.1. Chemicals and reagents

The following compounds were used to prepare the $CO_2$-selective cocktail: α-naphtholphthalein (NAF), naphthol blue black (NBB) (puriss. Aldrich, Switzerland www.sigmaaldrich.com), calmagite (CMG) and tetraoctylamonium hydroxide (TONOH, 20% in MeOH) (Fluka Chemie AG, Buchs. www.sigmaaldrich.com).

The following compounds were used to prepare the aluminum oxide-hydroxide membranes: aluminum oxide/hydroxide (AlOOH) DISPERSAL 100/2 (Sasol GmbH, Hamburg, Germany www.sasoltechdata.com), concentrated (80%) acetic acid (Aldrich Chemie, Buchs, Switzerland), polyvinyl alcohol (PVA), 10% by weight and 85,000–146,000 molecular weight (Aldrich Chemie, Buchs, Switzerland) and 175-μm-thick transparent polyester (PET) support (Dupont de Nemours, www.dupont-imagineering.com), referred to hereafter as P72.

Dry synthetic air, quality 5.5, was supplied from a 50 L bottle at 200 bars (Sauerstoffwerk Lenzburg AG, www.slgas.ch), $CO_2$, quality 4.8, from 7 L bottles at 49.5 bars (Messer Griesheim GmbH, Notruf, http://www.messer.de), $NO_2$, (10 ppm in synthetic air from Carbagas, Switzerland, http://www.carbagas.ch), NO 10 ppm in nitrogen (Carbagas, Switzerland), CO, 1000 ppm in nitrogen (Pan-Gas, Switzerland, www.pangas.ch) and $SO_2$, 200 ppm in nitrogen (Carbagas, Switzerland).

### 2.2. Preparation of nanostructured nanoporous membranes

As an example we describe the preparation of the nanostructured matrix with aluminum oxide hydroxide, AlOOH [22]. Fifty gram of aluminum oxide/hydroxide (AlOOH) DISPERSAL 100/2 (Sasol GmbH, Hamburg, Germany) was stirred vigorously for 15 min in 948 g of doubly distilled water at 20 °C. The temperature was then raised to 90 °C and stirring continued for 15 min to enable extensive dispersion in the form of AlOOH nanocrystals. The solid was filtered, washed three times with doubly distilled water and dried at 110 °C, at which point 8 g of the solid was added to a mixture of 63 g of doubly distilled water and 0.96 g of concentrated (80%) acetic acid (Aldrich Chemie, Buchs, Switzerland). The resulting dispersion was exposed to ultrasound for 3 min at 40 °C. Subsequently 8 g of a solution of polyvinyl alcohol (PVA) 10% by weight with a molecular weight of 85,000 to 146,000 (Aldrich Chemie, Buchs, Switzerland) was added and the resulting coating solution was again exposed to ultrasound for 3 min. A 175-μm-thick, transparent polyester (PET) support (Dupont de Nemours), referred to as P72, was curtain-coated with 100 g/m$^2$ of this solution at 40 °C. The coated support was then dried for 60 min at 30 °C.

Using similar procedures [23] we obtained positively and negatively charged $SiO_2$, $ZrO_2$ and AlOOH nanoporous membranes with agglomerate particles of 10–60 nm diameter and controlled and reproducible porosity consisting of 1–50 nm nanopores and >50 nm macropores. These membranes were between 1 and 100 μm thick when dry and had a pore volume in the range of 0.1 to at least 1.4 mL g$^{-1}$.

### 2.3. Preparation and characterization of sensing films

The cocktails were prepared in sealable 4 mL flasks. 2.45 mg mL$^{-1}$ ($5.85 \times 10^{-3}$ M) of NAF, 3.80 mg mL$^{-1}$ ($6.16 \times 10^{-3}$ M) of NBB and 6.6 mg mL$^{-1}$ ($1.84 \times 10^{-2}$ M)