Plasticizers of High Lipophilicities for Clinically Relevant Ion-Selective Electrodes (ISE) and Multisensing Field Effect Transistors (ISFET)**

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Abstract: Two new types of plasticizers based on tetracarboxylated benzophenone and benzhydrol, respectively, are presented. They exhibit superior performance particularly in ion-selective solvent polymeric membrane electrodes. Their high lipophilicity, their high viscosity as well as their reduced migration tendency and favourable adhesive characteristics in poly(vinyl chloride) (PVC) formulations make them especially attractive in miniaturized ion-sensing devices (such as catheter-electrodes and ISFET's) for clinical applications.

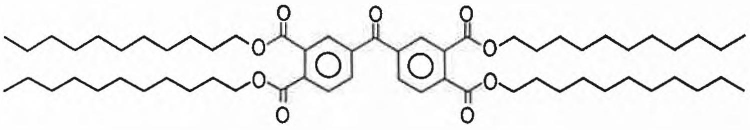
Ion-selective liquid-membrane electrodes have found widespread application in analytical chemistry[1] and especially in clinical chemistry[2–4]. The membranes of these sensors usually consist of an ion-selective component (ion exchanger or ion carrier[2]), of a polymer matrix (e.g. polyvinyl chloride[5]), of a plasticizer, and if necessary of additives (e.g. lipophilic salts[6]). The lifetime of such a sensor is limited by substantial and irreversible changes in the membrane composition. To assure a reproducible electromotive behaviour, all the membrane components have to be confined to the membrane phase over an analytically relevant time period[7]. Theoretical models and experimental observations indeed show that the lipophilicity of the membrane components is the determining parameter describing the lifetime[7]. Therefore an appropriate adjustment of the lipophilicity P, defined as the partition coefficient between 1-octanol and water, for each membrane component will lead to long-lived membrane systems.

To obtain a lifetime of one month for a membrane in permanent contact with a flowing solution of blood serum, a lipophilicity lg P of at least 12.8 is recommended for the plasticizers incorporated[7]. However, the lipophilicity of plasticizers commonly used in ion-selective membrane electrodes is considerably lower[8]. Even the plasticizers bis(1-butylpentyl)decane-1,10-diyl diglutarate (ETH 469)[8] and diisodecyl phthalate[8, 9] with lipophilicities lg P of 10.8 and 10.1, respectively, which have been designed and recommended for a use in clinically relevant ion sensors, do not meet this target. We therefore designed plasticizers of considerably higher lipophilicity. Here we report on the syntheses of two representatives (**1**, **2**), their physicochemical properties, and on the electromotive behaviour of ion-selective membranes based on them.

Experimental

Synthesis of tetra-n-undecyl 3, 3′, 4, 4′-benzophenonetetracarboxylate (**1**, ETH 2041): 1 g sulfuric acid dissolved in 5 mL of toluene was added to a solution of 5 g (15.5 mmol) 3, 3′, 4, 4′-benzophenonetetracarboxylic anhydride (Aldrich, Steinheim) and 10.96 g (63.6 mmol) 1-undecanol in 100 mL toluene under stirring at room temperature. The mixture was then refluxed for 4 h while water was collected in the refluxing column. The solvent was evaporated and the residue dissolved in $CHCl_3$ which was washed subsequently with water and twice with 10% $NaHCO_3$. The crude product **1** (13.8 g, 91%) was purified by flash chromatography (35 kPa) on silicagel 60 (230–400 mesh ASTM) with ethyl acetate/hexane (1:4) as eluent.

Synthesis of tetra-n-undecyl 3, 3′, 4, 4′-benzhydroltetracarboxylate (**2**, ETH 2112): 95 mg (2.5 mmol) sodium tetrahydroborate (Fluka, Buchs) dissolved in 10 mL of methanol was added dropwise to a stirred solution of 2 g (2.05 mmol) **1** in 50 mL of methanol under N_2 atmosphere at room temperature. After 2.5 h of stirring 10 mL of 3 M acetic acid was added and after another hour of stirring the solvent was evaporated, the residue dissolved in 100 mL 0.1 M sodium carbonate and extracted into $CHCl_3$. The crude product **2** from the evaporated $CHCl_3$ solution (1.97 g, 98%) was pu-



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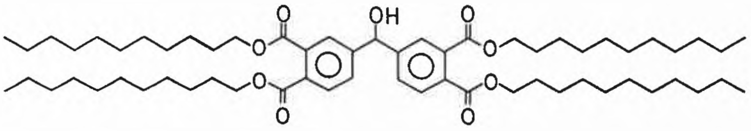

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Table 1. Physico-chemical parameters of PVC plasticizers at 22°C.

	oNPOE	DEHS	1	2
lipophilicity (lg P_{TLC})	5.9	10.1	22.3	23.8
dynamic viscosity (η [g cm^{-1} s^{-1}])	0.138	0.202	9.025	—[a]
density (ρ [g cm^{-3}])	1.020	0.900	0.982	—[a]
refractive index (n_D)	1.5116	1.4503	1.4978	—[a]
solubility (in BSA solution [M])	$2 \cdot 10^{-3}$	$1.6 \cdot 10^{-4}$	$< 10^{-6}$	
diffusion coefficient[b] (lg D [cm^2 s^{-1}])				
tracer component: **3**[c]		−8.1		−10.5
anthracene		−6.5	− 7.6	− 7.5
permeability for CO_2 (lg kD [cm^2 s^{-1}])[d]	−6.4	−6.4	− 6.9	
initial migration rate[e] (lg J^{init} [mol cm^{-2} s^{-1}])	−7.5	− 8.4	−12.4	

[a] *m.p.* 28°C. [b] Diffusion coefficient of the tracer component within PVC membranes (70 wt.-% plasticizer, 30 wt.-% PVC). [c] *N,N′*-bis[(11-ethoxycarbonyl)undecyl]-*N,N′*-dimethyl-2,3-naphthalenedioxydiacetamide[19]. [d] For PVC membranes (70 wt.-% plasticizer, 30 wt.-% PVC), k: partition coefficent, D: diffusion coefficient. [e] Initial migration rate of the membrane plasticizer (30 wt.-% PVC) into reference plasticized PVC (73.4 wt.-% PVC, 36.6 wt.-% DEHP).

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rified by flash chromatography under the same conditions as for **1**, *m.p.* 28 °C.

The constitutions of both synthesized plasticizers have been fully confirmed by elemental analysis, ^{1}H-NMR (300 MHz, $CDCl_3$), ^{13}C-NMR (25 MHz, $CDCl_3$), IR ($CDCl_3$), and mass spectrometry and the purities have been determined by HPLC (PL gel 100, THF, RI-detection).

Other membrane materials: High molecular weight poly(vinyl chloride) (PVC), potassium tetrakis(p-chlorophenyl)borate (KTpClPB), *o*-nitrophenyl octyl ether (oNPOE), bis(2-ethylhexyl) sebacate (DEHS), valinomycin, Na$^{\oplus}$-ionophore ETH 227, and Ca$^{2\oplus}$-ionophore ETH 1001 have been obtained from Fluka, CH-9470 Buchs.

Electrode and membrane system: The membranes have been prepared according to ref.[10]. The typical composition has been ≈ 1wt.-% ionophore, ≈ 69 wt.-% plasticizer, and ≈ 30 wt.-% PVC. In cases where KTpClPB was added, the applied amount has been 70 mol-% relative to the ionophore. The electrode housing in which the membrane has been mounted and the arrangement of the cell used for electromotive studies is described in detail in ref.[11].

EMF measurements: For the equipment used see ref.[11]. The measured EMF values were corrected for changes in the liquid-junction potential according to the Henderson equation and the single ion-activities were calculated using the Debye-Hückel theory[4]. The selectivity factors, lg K_{MN}^{Pot}, have been determined by the separate solution method (SSM)[12]. All measurements have been performed at 20 ± 1 °C.

The *electrical membrane resistance* was determined by use of the method of potential attenuation by known shunt[13, 14].

The *lipophilicities* of the plasticizers, lg *P*, were determined by thin layer chromatography[10].

Diffusion coefficients of tracer compounds in the membranes were determined spectrophotometrically by contacting a blank membrane with a tracer containing membrane[15].

Initial migration rates[14] of membrane plasticizers into contacting commercial plasticized PVC have been assessed by a corresponding sandwich arrangement and monitoring the transfer spectrophotometrically as well as by GPC analysis (PL gel 100, THF, RT detection)[15]. Common laboratory PVC tubing consisting of 36.6 wt.-% bis(2-ethylhexyl) phthalate (DEHP) and 73.4 wt.-% PVC has been used as the reference PVC material.

The *permeabilities* of the membranes for carbon dioxide are reported as *kD*-values[16] of the blank membranes. For their determination see ref.[15].

The *solubilities* of the plasticizers in a bovine serum albumin (BSA) solution (7 g BSA in 100 mL water) as a human serum model have been determined gravimetrically by weight loss of the blank membranes.

The *dynamic viscosities* of the pure plasticizers have been determined by an Ostwald-viscosimeter (Schott, Mainz) at 22 °C.

Table 1 summarizes some important physico-chemical parameters of the newly synthesized plasticizers **1** and **2**. The corresponding data for two commonly and traditionally in solvent polymeric membranes applied plasticizers (DEHS and oNPOE) are given in Table 1 for comparison.

The plasticizers **1** and **2** exhibit an extremely high lipophilicity due to the four long alkyl chains. The lipophilicity value (Table 1) outmatches by far the required value set by lifetime considerations (see above). Accordingly, the solubility in a bovine serum albumin solution (as a model solution for human serum) is significantly reduced as expected[17, 18].

The long alkyl chains not only increase the lipophilicity but also the dynamic viscosity of the liquid plasticizer due to the large relative molecular mass and alkyl chain interactions. It could be assumed that this in turn will reduce the mobility and thus restrict the diffusion behaviour of an ionophore dissolved within the plasticizer. Indeed, the diffusion coefficient for the ionphore **3** (*N,N'*-bis[(11-ethoxycarbonyl)undecyl]-*N,N'*-dimethyl-2,3-naphthalenedioxydiacetamide)[19] is drastically decreased in a membrane plasticized with **2** as compared to DEHS as plasticizer. This effect is even more pronounced than excepted on the basis of the diffusion coefficient/viscosity correlation[20] since an additional reduction of the translatory mobility occurs in plasticized PVC membranes due to entanglements with the polymer chains. For small molecules like anthracene the reduction in the diffusion coefficient is indeed not so significant (Table 1). Such a behaviour can as well be seen for the permeability of carbon dioxide through such membranes (Table 1).

These features are particularly attractive in respect to miniaturized multi-ion-sensing systems, where sensing areas will be arrayed in close proximity. Thus, cross-contamination by laterally diffusing ionophores within the membrane coating on top of the sensor array is almost inhibited. Yet the diffusion of small molecules, such as carbon dioxide, will still be fast enough to satisfy the requirements set by mass transfer-based sensor systems such as e.g. carbon dioxide[16, 21], oxygen[22] or hydrogencarbonate[23] sensors.

The performance of **1** and **2** as plasticizers in solvent polymeric membranes of ion-selective electrodes is shown in Table 2 for three cation-selective neutral carriers. The determined potentiometric selectivity factors K_{MN}^{Pot} are as expected for the neutral carriers under the consideration of the polarity of the plasticizer[18, 24]. A highly polar membrane solvent (e.g. oNPOE, dielectric constant $\varepsilon \approx 24.2$ [25]) exhibits an increased selectivity of a divalent ion over monovalent ions as compared to a nonpolar membrane solvent (e.g. DEHS, $\varepsilon \approx 4.19$[25]). This effect is strikingly seen in the selectivity factors of the Ca$^{2\oplus}$-selective membranes (Table 2). On this basis it is concluded that plasticizers **1** and **2** have a somewhat moderate polarity. The selectivity factors for the ion-selective membranes using the plasticizers **1** and **2** as given in Table 2 cope all with the required selectivity factors for a reliable clinical use[2]. The only exception is the too poor Na$^{\oplus}$/Ca$^{2\oplus}$ selectivity in the case of the Na$^{\oplus}$-selective membrane based on ETH 227 which is due to the moderate polarity of the new plasticizers. While the slope of the electrode function using **1** or **2** reaches in general nearly theoretical or equivalent values to the conventional plasticizers it is markedly reduced to values below 95% of the theoretical value in the case of valinomycin-based K$^{\oplus}$-selective membranes, for which there has not been found an explanation yet. The electrical membrane resistance encountered with **1** and **2** are significantly increased by two orders of magnitude as compared to DEHS. This could impose a drawback in the use of these new plasticizers for certain applications. But the incorporation of lipophilic ions (as e.g. in the case of the Ca$^{2\oplus}$-selective membranes, Table 2) or the reduction of the membrane thickness (as it will be found in planar membrane multi-ion-sensing systems) or the use of *in-situ* impedance conversion (as e.g. in the case of ISFET's) will cope with this apparent problem.

Table 2. Electromotive behaviour of Na$^{\oplus}$-, K$^{\oplus}$-, and Ca$^{2\oplus}$-selective solvent polymeric membranes based on neutral carrier using the new plasticizers **1** and **2**.

primary ion M (ionphore)	plasticizer	selectivity factor lg K_{MN}^{Pot} for interfering ion N						slope for primary ion M [mV]	detection limit lg a_M[M]	electrical membrane resistance[a] lg *R* [Ω]
		H$^{\oplus}$	Li$^{\oplus}$	Na$^{\oplus}$	K$^{\oplus}$	Mg$^{2\oplus}$	Ca$^{2\oplus}$			
Na$^{\oplus}$ (ETH 227)	**1**	–0.6	0.5	0	–1.6	–2.7	0.6	56.4	–4.0	9.2
	2	–0.9	0.8	0	–1.6	–2.0	0.5	56.6	–3.7	9.6
	DEHS	–0.2	0.6	0	–1.2	–3.1	–1.6	57.7	–4.4	7.7
K$^{\oplus}$ (valinomycin)	**1**	–4.2	–3.9	–4.1	0	–4.9	–4.8	54.5	–5.4	9.6
	2	–3.9	–3.9	–3.7	0	–4.0	–3.8	53.9	–5.5	10.1
	DEHS	–4.3	–4.2	–4.3	0	–5.9	–5.5	57.9	–5.5	7.7
Ca$^{2\oplus}$ (ETH 1001, KTpClPB)	**1**	–3.3	–3.4	–3.6	–4.5	–4.7	0	29.7	–5.7	7.9
	2	–4.6	–3.3	–3.6	–4.6	–4.2	0	28.5	–5.7	8.1
	DEHS	–2.5	–1.9	–2.3	–2.8	–4.1	0	28.2	–5.5	7.1
	oNPOE	–4.6	–4.3	–5.3	–6.0	–4.0	0	29.7	–5.6	5.4

[a] Approximate membrane geometry: $A = 12.6\ mm^2$, $d = 200\ \mu m$.

Membranes with **1** or **2** as plasticizer can be produced down to thicknesses of at least 3 µm by standard solvent-casting techniques[15]. These membranes are very tacky, have a high elasticity, and exhibit improved adhesion behaviour on glass, on poly(methyl methacrylate), and on silicon/SiO_2 or Si_3N_4 substrates as compared to traditionally plasticized membranes. Membranes cast on such supports resist repeated rubbing (finger rub test) while conventional membranes will easily peel off under rubbing.

Membranes cast or sealed onto PVC supports or PVC tubings as it is done for catheter-type electrodes suffer generally from mutual migration of the tubing and the membrane plasticizer and therefore deteriorating the electromotive performance of the ion-selective membranes with time[26]. The plasticizer migration data given in Table 1 reflect a qualitative measure of the migration tendency of the membrane plasticizer. Plasticizer **1** (and presumably also plasticizer **2**) has a reduced migration tendency by about five orders of magnitude as compared to oNPOE. Therefore they are extremely attractive membrane plasticizers for catheter-type electrodes as well.

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