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# Syntheses and evaluation of 7-deoxycholic amide-based tweezer-type copper(II) ion-selective ionophores

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ABSTRACT

Seven tweezer-type copper(II) ion-selective ionophores; that is, 3α,12α-bis[[[*N*-(*R*)thiocarboxamino]acetyl]oxy]-*N*,*N*-dioctyl-5β-cholan-24-amides and 3α,12α-bis[[[*N*-(*R*)thiocarboxaminomethyl]acetyl]oxy]-*N*,*N*-dioctyl-5β-cholan-24-amides (R = alkyl and phenyl), were newly designed and synthesized. Their potentiometric evaluation of the poly(vinyl chloride) (PVC) membranes showed excellent affinity and selectivity to copper(II) ions over those of other transition metal ions and alkali/alkaline earth metal ions. These membranes exhibited super-Nernstian responses toward copper(II) ions (34–36 mV/decade), with detection limits of $10^{-6}$–$10^{-7}$ M.

Selective metal ion recognition by neutral receptors has attracted increasing interest in recent years because of their importance and potential applications in biological, environmental, and supramolecular chemistry.[1] Ion-selective electrodes (ISEs), especially those with neutral carrier-based solvent polymeric membranes, have been routinely employed for direct or indirect potentiometric measurements of various ionic species.[1,2]

Copper is one of the main transition metals extensively used for industrial, agricultural, and pharmaceutical purposes due to its properties of high electrical conductivity, chemical stability, germicidal efficacy, and its capacity to form alloys with many metals.[3] However, the widespread use of copper poses a serious environmental threat due to its toxicity, which is generally attributed to its ionic forms such as the copper(II) ion ($Cu^{2+}$).[4] Excess levels of copper(II) ion in the human body cause dyslexia, liver and kidney damage, gastrointestinal problems, hypoglycemia, and Wilson's disease.[5] The design of highly selective and sensitive copper(II) ion receptors and the construction of ISEs have, thus, attracted much attention from environmental and clinical analysts. Accordingly, a variety of ionophoric molecules, including calix[*n*]arenes,[6] Schiff bases,[3,7] non-cyclic neutral carriers,[8] polythiacrown ethers,[9] and tripodal derivatives[10] have been employed for the selective detection of copper(II) ions. Such neutral receptors typically possess soft heteroatoms such as nitrogens and/or sulfurs, as electron donors to coordinate with metal cations,[6–11] including commercially available copper(II) ionophores like *o*-xylene-bis(*N*,*N*-diisobutyldithiocarbamate)[8b,12] and *N*,*N*,*N*′,*N*′-tetra-cyclohexyl-3-thiaglutaric diamide.[8e,12] Most of the abovementioned ionophores, however, suffer from poor detection limits, narrow working concentration ranges, a non-Nernstian response property, slow response times, and/or serious interference from various transition and alkali metal ions, especially $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $K^+$, and $Na^+$.[3,7b,8d] A rigid frame, such as a benzene or macrocyclic structure, has been widely used as a building block for extended, well-defined molecular architecture and as a scaffold of synthetic receptors.[1c,13] Furthermore, the introduction of block-wall subunits in the rigid scaffold allows for the control of 'size-fit' complex formation with target cations or anions, ultimately resulting in improved selectivity over those of interfering species.[13]

In our group, molecular tweezer-type neutral carriers based on a rigid steroidal ring frame, including cholic, deoxycholic, and chenodeoxycholic acid derivatives, have been successfully utilized to yield selective ionophores for carbonate,[14] chloride,[15] calcium,[16] magnesium,[15] and silver.[17] Particularly, 7-deoxycholic acid backbone (DCAB) has two hydroxyl linkers at the C3 and C12 carbons, which are parallel and approximately 6.1 Å apart, an appropriate distance for tweezing various ionic species.[15] Although we have successfully developed several DCAB-based ion-selective ionophores for various ionic species, DCAB-based copper(II) ion-selective ionophores, which are valuable for environmental and clinical reasons, have not yet been studied fully. The copper(II) ion-selective tweezing ability of a DCAB-based ionophore is highly expected (1) by introducing the proper ion-recognizing groups that contain sulfur and nitrogen atoms according to the hard–soft acid base (HSAB) concept[18] and also (2) by controlling the cavity size between the two binding sites. The cavity size can be differentiated easily by changing the length of the linking chain between the substituent and the hydroxyl linker at C3 and C12. Thus, based on our and others' previous results, we expand our work to design and synthesize a new class of DCAB-based ionophores in a search for molecular tweezers highly selective for copper(II) ions.

Thus, newly designed DCAB-based tweezer-type molecules for copper(II) ion-selective ionophores, which contain the ion-recogniz-

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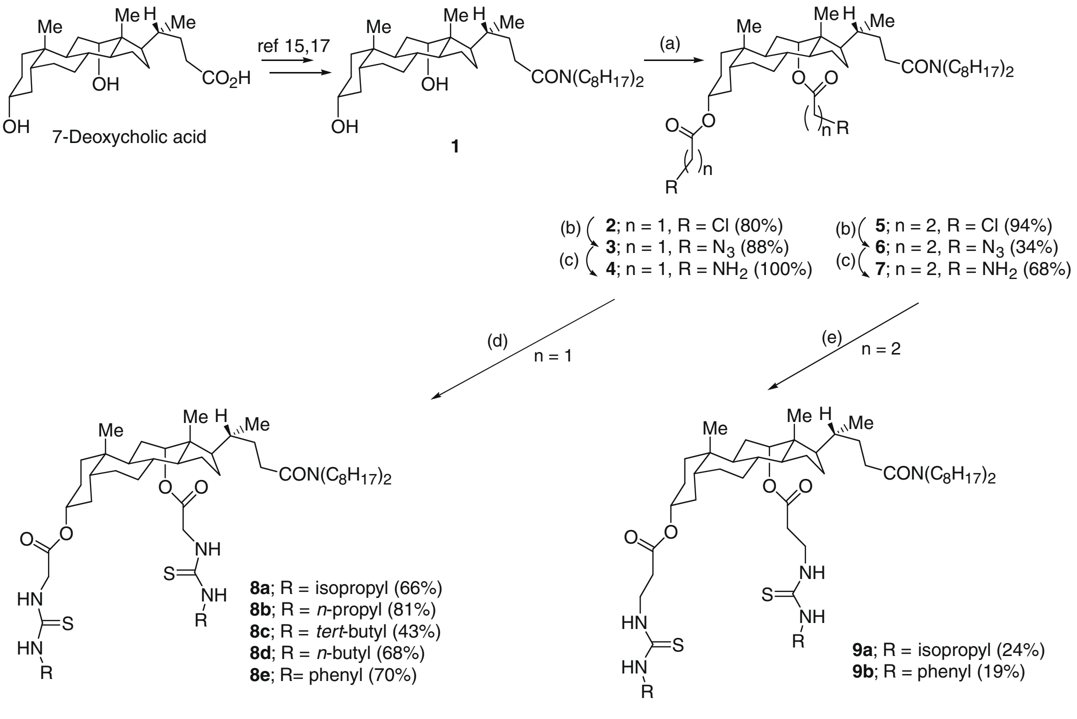
ing functional groups at C3 and C12 of the DCAB, were prepared starting from 7-deoxycholic acid (Scheme 1). $3\alpha,12\alpha$-Dihydroxy-*N*,*N*-dioctyl-$5\beta$-cholan-24-amide (**1**) was synthesized using a routine synthetic path that was described in our previous papers.[14–17] Prior to an introduction of ion-recognition groups, **1** was reacted with chloroacetyl chloride or chloromethylacetyl chloride to lengthen the linkage at C3 and C12 of the DCAB, which were basically desired for the proper space for tweezing of an incoming cation. Subsequently, this key intermediate was transformed into $3\alpha,12\alpha$-bis(chloroacetoxy)-*N*,*N*-dioctyl-$5\beta$-cholan-24-amide (**2**) or $3\alpha,12\alpha$-bis(chloromethylacetoxy)-*N*,*N*-dioctyl-$5\beta$-cholan-24-amide (**5**), which have chloro-leaving groups on the edge of the linker at C3 and C12. Compounds **2** and **5** were then transformed into amino group-containing derivatives **4** or **7**, respectively, by sodium azide addition (step (b) in Scheme 1) followed by triphenylphosphine treatment (step (c) in Scheme 1). To link the desired binding sites (the ion-recognition groups) to the amino edge of the linkage, coupling reactions between **4** or **7** and ion recognition group-containing R-NCS (R = isopropyl, *n*-propyl, *tert*-butyl, *n*-butyl, and phenyl) were done in THF at 60 °C for 2 h. As a result, seven different prospective ionophores (i.e., **8a**–**e**, **9a**, and **9b**) were prepared successfully in reasonable yields (refer to Scheme 1) and their structures were fully identified with $^1$H NMR, $^{13}$C NMR, FTIR, and FAB MASS.[19]

To evaluate the potentiometric characteristics of the newly synthesized copper(II) ionophores (i.e., **8a**–**e** and **9a**, **b**), the effect of plasticizers on the overall ISE performance was first investigated using the poly(vinyl chloride) (PVC) membranes doped with five different plasticizers including bis(2-ethylhexyl) adipate (DOA), bis(1-butylpentyl) adipate (BBPA), 2-nitrophenyloctyl ether (*o*-NPOE), dioctyl phthalate (DOP), and benzyl butyl phthalate (BBP).[20,21] Although the membranes does not contain a lipophilic additive for this study, the solvent polymeric membranes exhibited cationic responses because of the presence of anionic impurities from the polymer matrix (i.e., from the plasticizer and PVC).[1a,22] Therefore, the resulting effect of plasticizers may be attributed to both the nature (mainly the dielectric property) of the plasticizer used and its impurities. Since it is difficult to determine the identities and concentrations of impurities for each plasticizer, the overall plasticizer effect may not be limited to only the dielectric characteristics of plasticizers. However, considering dielectric dependence of the plasticizer on potentiometric responses may still be meaningful to elucidate the formation of ion pairs in the organic phases. The membranes doped with DOA, and BBPA possessing relatively low dielectric constants ($\varepsilon = 4.2$ and 4.1, respectively)[23] exhibited good potentiometric properties. On the other hand, the membranes containing DOP, BBP, and *o*-NPOE with relatively high dielectric properties ($\varepsilon = 7.0$, 6.4, and 23.9, respectively)[21] showed significantly reduced response toward copper(II) ion. For example, the compound **8a**-containing membranes incorporated with DOA and BBPA were characterized by super-Nernstian response toward copper(II) ion (i.e., 36.2 and 35.1 mV/decade, respectively) as shown in Figure 1a and b. In contrast, the DOP-plasticized membrane exhibited a fatally diminished sensitivity toward copper(II) ion (i.e., 11.1 mV/decade) (Fig. 1c). The potentiometric response of the membranes doped with BBP and *o*-NPOE was even negligible toward all transition metal ions tested (i.e., $Ag^+$, $Cu^{2+}$, $Co^{2+}$, $Cd^{2+}$, $Fe^{2+}$, $Ni^{2+}$, $Pb^{2+}$, and $Zn^{2+}$). A similar trend was observed with the membranes doped with other synthetic ionophores (i.e., compounds **8b**–**e**). Although both membranes plasticized with DOA and BBPA showed Nernstian slopes, DOA was ultimately chosen as the plasticizer for preparing copper(II) ion-selective membranes since the DOA-doped membranes exhibited faster response time than BBPA-doped ones ($t_{90\%}$ <70 s vs >90 s), and required less time for stabilizing the membranes.

In spite of the fortuitous presence of anionic sites from the impurities, the effect of using a lipophilic additive, potassium tetrakis(4-chlorophenyl)borate (KT*p*ClPB) on the potentiometric properties of the DOA-doped PVC membranes was also evaluated. Notably, anionic additives such as T*p*ClPB$^-$ have been widely used to prepare polymeric cation-selective membranes with improved selectivity over interfering ions.[17,24] However, the incorporation of KT*p*ClPB into the DOA-plasticized PVC membranes containing the tweezer-type ionophores yielded considerable deterioration in selectivity over other transition metal ions: for example, for



**Scheme 1.** (a) $CaH_2$, $Bu_4NBr$, $Cl(CH_2)_nCOCl$, toluene, 90 °C, 5 h; (b) $NaN_3$, DMF, 60 °C, 24 h; (c) $Ph_3P$, $H_2O$, THF, rt, 20 h; (d) R-NCS, THF, 60 °C, 1.5 h; (e) R-NCS, THF, 60 °C, 2 h.

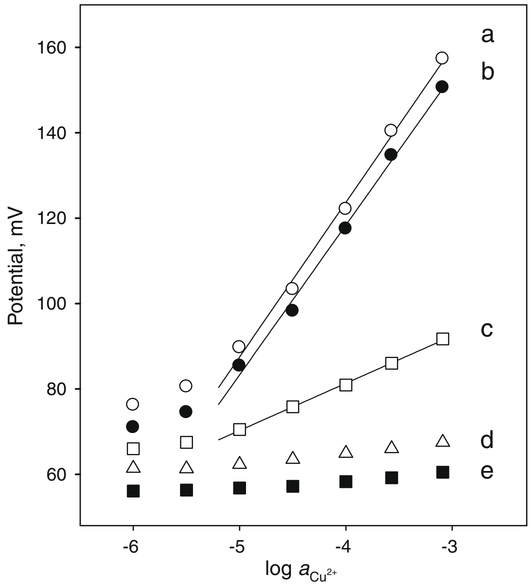


**Figure 1.** Effect of plasticizer on potentiometric response to copper(II) ion: (a) DOA, (b) BBPA, (c) DOP, (d) *o*-NPOE, and (e) BBP.

the compound **8a**-containing membrane doped with KT*p*ClPB (50 mol %), $\log K^{POT}_{Cu^{2+},M^{z+}} = -2.17$, $-2.58$, and $-2.94$ for $M^{z+} = Cd^{2+}$, $Pb^{2+}$, and $Zn^{2+}$. The added anionic sites may more easily form the ion pairs with the interfering transition metal ions, rather than with copper(II) ion in the organic membrane phase.

Figure 2 shows the dynamic response curves and calibration plots of the copper(II) ion-selective membrane electrodes based on each synthetic ionophore (i.e., compounds **8a–e**) to copper (II) ion. The plots include only response toward copper(II) ion for clarity in the range of $10^{-6}$–$10^{-3}$ M. The potentiometric response to other transition metal ions (i.e., $Co^{2+}$, $Cd^{2+}$, $Fe^{2+}$, $Ni^{2+}$, $Pb^{2+}$, and $Zn^{2+}$) was negligible up to its concentration of $10^{-3}$ M. Furthermore, it was observed that the response toward alkali/alkaline earth metal ions (i.e., $Li^+$, $K^+$, $Na^+$, $Ca^{2+}$, and $Mg^{2+}$) which may exist at the higher concentrations than those of transition metal ions in environmental and biological samples were insignificant even up to $10^{-1}$ M concentration.

The binding affinity of the tweezer-type receptors toward anions was also investigated. Indeed, a variety of anions (i.e., $Cl^-$, $Br^-$, $HPO_4^{2-}$, $NO_3^-$, $SO_4^{2-}$, $AcO^-$, $HCO_3^-$, $SCN^-$, and $ClO_4^-$; counter cation = $Na^+$) were employed to evaluate their influence on potentiometric characteristics. In a result, the electrodes showed negligible responses toward $Cl^-$, $Br^-$, $HPO_4^{2-}$, $NO_3^-$, $SO_4^{2-}$, $AcO^-$, and $HCO_3^-$ even up to $10^{-1}$ M. For the lipophilic anions such as $SCN^-$ and $ClO_4^-$, the electrodes exhibited some responses at the high concentration range from $10^{-3}$ to $10^{-1}$ M with slopes of 8–12 mV/decade (data not shown). The resulting anionic effect may be attributed to the well-known hydrophobic interaction between the polymeric PVC matrix and lipophilic anions.

Table 1 lists the potentiometric characteristics of **8a–e** and **9a**, **b** ionophores doped in the DOA-plasticized PVC membranes. Comparing overall ISE performance in terms of slope, detection limit, linear response range, response time, and selectivity over various transition metal ions and alkali/alkaline earth metal ions, it was observed that the copper(II) ion-selective membrane doped with compound **8e** exhibited the best potentiometric properties: slope = 36.4 mV/decade ranging from $10^{-6}$ to $10^{-4}$ M, detection limit = $1.48 \times 10^{-7}$ M, and response time ($t_{90\%}$) = 35 s concentration change from $10^{-5}$ to $3 \times 10^{-5}$ M and 24 s from $3 \times 10^{-5}$ to $10^{-4}$ M. More importantly, the compound **8e**-doped membrane showed outstanding copper(II) ion selectivity over various metal ions: $\log K^{POT}_{Cu^{2+},M^{z+}}$ −3.5, −3.5, −3.5, −4.6, −4.6, and −3.5 for $M^{z+} = Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $K^+$, $Na^+$, and $Ca^{2+}$. Notably, the selectivities obtained using tweezer-type DCAB-based receptors significantly surpass those of commercially available ionophores: e.g., for copper(II) ionophore I[12] from Fluka,

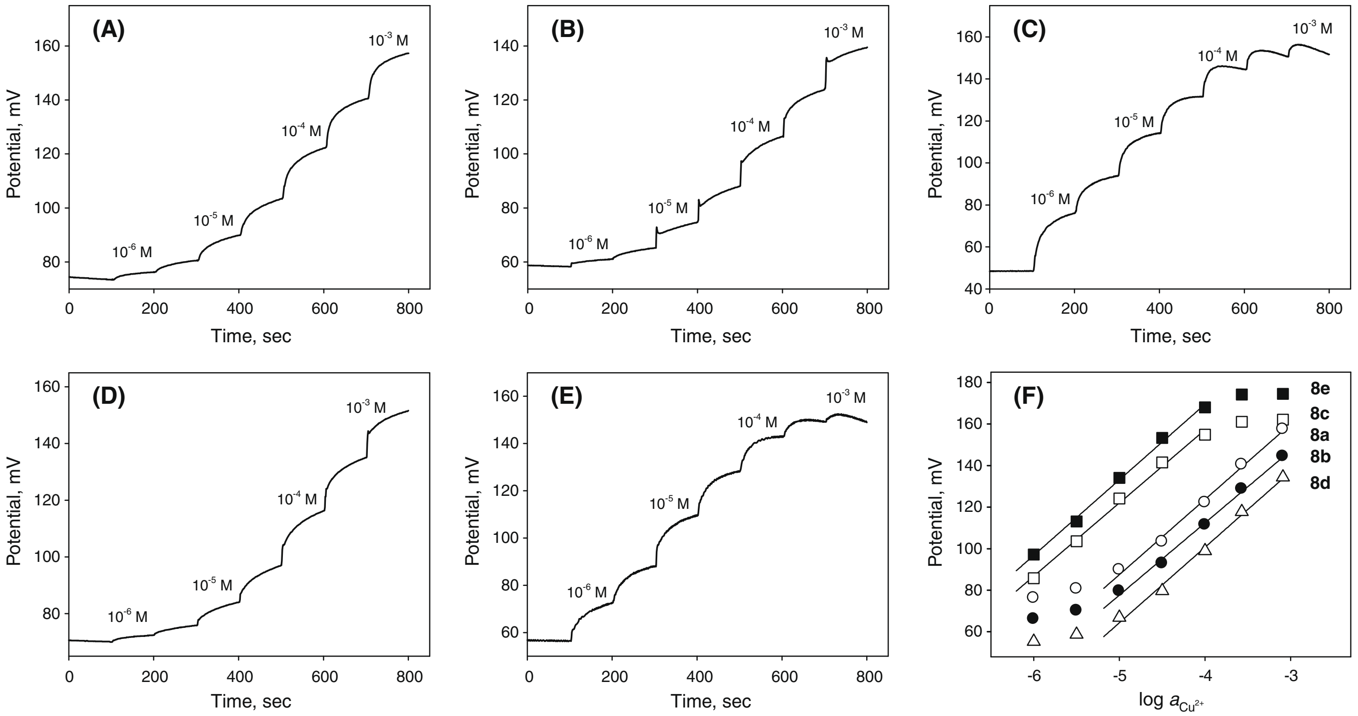


**Figure 2.** Dynamic response curves of DOA-plasticized PVC membranes containing five different tweezer-type copper(II) ionophores: (A) **8a**, (B) **8b**, (C) **8c**, (D) **8d**, and (E) **8e**. Potentiometric responses to other transition metal ions ($M^{z+} = Co^{2+}$, $Cd^{3+}$, $Fe^{2+}$, $Ni^{2+}$, $Pb^{2+}$, and $Zn^{2+}$) tested are negligible. (F) represents the calibration plots of DOA-doped membranes containing five different ionophores (**8a–e**).

**Table 1**

Potentiometric properties of copper(II) ion-selective electrodes based on tweezer-type ionophores containing 7-deoxycholic amide moiety[a]

| Compd No. | Slope, mV/decade | Detection limit ($\log a_{Cu^{2+}}$), M | Linear range, M | Linearity ($R^2$) | Selectivity coefficient[b] $\log K^{POT}_{Cu^{2+},M^{z+}}$ | | | Response time ($t_{90\%}$), s | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | $M^{z+} = Ag^+$ | $M^{z+}$ = DV[c] | $M^{z+}$ = MV[d] | $10^{-5} \to 3 \times 10^{-5}$ | $3 \times 10^{-5} \to 10^{-4}$ |
| **8a** | 36.2 | −5.41 | $10^{-5}$–$10^{-3}$ | 0.9952 | 2.1 | −2.8 | −4.2 | 70 | 58 |
| **8b** | 34.8 | −5.52 | $10^{-5}$–$10^{-3}$ | 0.9959 | 2.8 | −2.7 | −4.0 | 73 | 61 |
| **8c** | 35.2 | −6.71 | $10^{-6}$–$10^{-4}$ | 0.9951 | 1.7 | −3.6 | −4.5 | 38 | 22 |
| **8d** | 36.4 | −5.33 | $10^{-5}$–$10^{-3}$ | 0.9933 | 3.2 | −2.7 | −4.1 | 68 | 69 |
| **8e** | 36.4 | −6.83 | $10^{-6}$–$10^{-4}$ | 0.9968 | 1.3 | −3.5 | −4.6 | 35 | 24 |
| **9a** | 10.7 | — | $10^{-5}$–$10^{-3}$ | 0.9874 | — | — | — | — | — |
| **9b** | 7.6 | — | $3 \times 10^{-5}$–$10^{-3}$ | 0.9855 | — | — | — | — | — |

[a] Composition: 2 mg of ionophore, 66 mg of poly(vinyl chloride) (PVC), and 132 mg of bis(2-ethylhexyl) adipate (DOA).

[b] The values were calculated by the separate solution method at the concentrations of $10^{-3}$ M for copper(II) ion and interfering ions.

[c] DV (divalent cations) = $Co^{2+}$, $Cd^{2+}$, $Fe^{2+}$, $Ni^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $Ca^{2+}$, and $Mg^{2+}$.

[d] MV (monovalent cations) = $Li^+$, $K^+$, and $Na^+$.

$\log K^{POT}_{Cu^{2+},M^{z+}} = -4.40, -0.75, -2.25, -2.35, -2.65$, and $-3.60$; and, for copper(II) ionophore IV,[12] −3.34, −1.82, −2.67, <−4.74, <−4.61, and −4.64 for $M^{z+}$ = $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $K^+$, $Na^+$, and $Ca^{2+}$, respectively.

As described above, the length of the tweezers may affect ion capture properties (e.g., affinity and selectivity) of DCAB-based ionophores. We thus synthesized compounds **9a** and **9b** with the longer linking chain of the ion-recognition group, which are analogues corresponding to compounds **8a** and **8b**. However, the PVC membranes doped with **9a** and **9b** ionophores exhibited drastically decreased response toward copper(II) ion (i.e., slope = 10.7 and 7.6 mV/decade for **9a** and **9b**, respectively) probably due to improper cavity size for tweezing the incoming copper(II) ion (Table 1).

Figure 3 shows the response of the electrodes to pH changes varied by adding aliquots of a standard hydroxide solution to a universal buffer at room temperature.[20] The compounds **8c-** and **8e**-based electrodes exhibited the most sensitive response in the pH 6–10 range (45–50 mV/pH). Other electrodes also showed some pH response in acidic and basic regions (i.e., pH <5 and >9), but flattened sensitivity (<4 mV/pH) in neutral pH ranging from 6 to 9.

In summary, seven tweezer-type copper(II) ion-selective ionophores; that is, 3α,12α-bis[[[*N*-(*R*)thiocarboxamino]acetyl]oxy]-*N*,*N*-dioctyl-5β-cholan-24-amides (R = alkyl and phenyl) (**8a**–**e**) and 3α,12α-bis[[[*N*-alkylthio-carboxaminomethyl]acetyl]oxy]-*N*,*N*-dioctyl-5β-cholan-24-amides (**9a**, **b**), were newly designed and synthesized. Among the synthesized tweezer-type DCAB-based ionophores, **8a**–**e** showed excellent affinities and selectivities to copper(II) ions over those of other transition metal ions and alkali/alkaline earth metal ions. **9a** and **9b** ionophores that each have lengthened linking chains of the ion-recognition groups at C3 and C12 exhibited drastically decreased affinity, probably due to an inadequate cavity size for tweezing the incoming copper(II) ion. Overall, five ionophores, **8a**–**e,** exhibited super-Nernstian responses toward copper(II) ions (34–36 mV/decade) with detection limits of $10^{-6}$–$10^{-7}$ M.

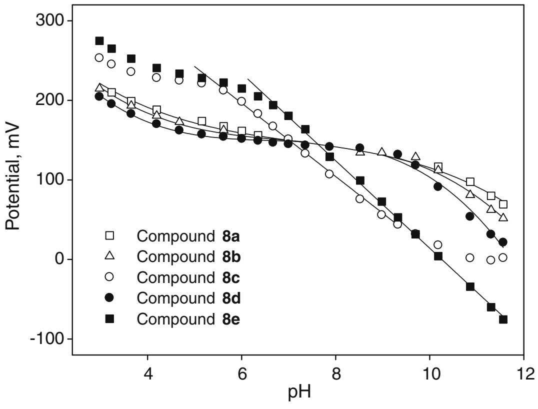


**Figure 3.** pH response of the compounds **8a** through **8e**-based membrane electrodes to varying pH scales in universal buffer.

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19. *Representative spectral data* (**8a**): A waxy solid: TLC (ethyl acetate/hexane = 4:6) $R_f$, 0.28; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.65 (br s, 1H, NH), 7.01 (br s, 1H, NH), 6.65 (br s, 2H, NH), 4.98 (s, 1H, 12β-H), 4.87 (br m, 1H, 3β-H), 4.51–4.45 (d, 2H, $OCOCH_2$), 4.35–4.29 (d, 2H, $OCOCH_2$), 3.25 (m, 4H, $CON(CH_2R)_2$), 2.35–2.05 (m, 2H, $CH_2CO$), 1.83–0.72 (m, 77H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 6.72, 8.83, 12.45, 17.31, 17.38, 17.41, 17.48, 17.62, 18.20, 19.80, 20.59, 20.78, 21.53, 21.70, 22.00, 22.29, 23.59, 23.96, 24.02, 24.07, 24.17, 24.47, 25.25, 26.26, 26.39, 26.53, 26.54, 26.56, 28.66, 28.80, 29.73, 29.75, 30.28, 36.52, 39.80, 39.98 (br), 40.50, 40.73, 40.75, 41.35 (br), 42.21, 43.12, 44.17, 70.33, 72.06, 162.79, 164.05, 169.13, 176.26, 177.34; IR (NaCl) $\nu_{max}$ 3314, 2930, 1734, 1613 $cm^{-1}$; MS (FAB) *m*/*e* 932 (M), 756 ($M-OCOCH_2NHCSNHCH\ (CH_3)_2$), 580 ($M-2OCOCH_2NHCSNHCH\ (CH_3)_2$).

20. The ion-selective membranes were prepared with a series of compositions for membrane cocktails: 2 mg of ionophore (i.e., **8a**–**e** or **9a**, **b**), 66 mg of PVC, and 132 mg of plasticizer (i.e., DOA, BBPA, *o*-NPOE, DOP, or BBP). The cocktail solutions dissolved in 1.0 mL THF were poured into a glass ring (id 22 mm) placed on a glass slide and then dried overnight under ambient conditions. After curing, 5.5 mm diameter disks were punched out of the master membrane and placed in Philips electrode bodies (IS-561; Glasbläserei Möller, Zürich, Switzerland). The inner filling solution for all electrodes was 0.1 M KCl. An Orion sleeve-type double-junction Ag/AgCl electrode (Model 90-02; Cambridge, MA, USA) was used as the external reference. The potential differences between the copper(II) ISEs and the reference electrode were measured using an IBM-compatible computer equipped with a custom-built high-impedance input 16-channel analog-to-digital converter. Dynamic response and calibration curves were obtained in the range of $10^{-6}$–$10^{-3}$ M for various transition metal ions and $10^{-6}$–$10^{-1}$ M for alkali/alkaline earth metal ions, respectively, by adding standard solutions stepwise to the background electrolyte (0.01 M magnesium acetate/$HNO_3$, pH 4.5) at room temperature under stirring. The response of the electrodes to pH changes was tested by adding aliquots of NaOH solution (ca. 0.5 M) to a solution of 11.4 mM boric acid, 6.7 mM citric acid, and 10.0 mM $NaH_2PO_4$ at room temperature. The copper(II) selectivities of all ionophores over six different transition metal ions (i.e., $Co^{2+}$, $Cd^{2+}$, $Fe^{2+}$, $Ni^{2+}$, $Pb^{2+}$, and $Zn^{2+}$; counter anion, $NO_3^-$) and five different alkali/alkaline earth metal ions (i.e., $Li^+$, $K^+$, $Na^+$, $Ca^{2+}$, and $Mg^{2+}$; counter anion, $Cl^-$) were investigated. The potentiometric selectivity coefficients ($\log K^{POT}_{Cu^{2+},M^{z+}}$) were calculated by the separate solution method (Lindner, E.; Umezawa, Y. *Pure Appl. Chem.* **2008**, *80*, 85):

$$\log K^{POT}_{Cu^{2+},M^{z+}} = \frac{(E_{M^{z+}} - E_{Cu^{2+}})}{S} + \left(1 - \frac{2}{Z_M}\right) \cdot \log a_{Cu^{2+}}$$

where $E_{Cu^{2+}}$ and $E_{M^{z+}}$ are the measured membrane potentials (mV) of the electrode in the separate solutions of the copper(II) and interfering ion at the same concentration ($10^{-3}$ M), respectively. $S$ is the slope (mV/decade) of the electrode toward copper(II) ion. $Z_M$ and $a_{Cu^{2+}}$ are the charge number of the interfering ion and the activity of copper(II) ion, respectively. The slope, detection limit, and response time for each electrode were determined by the method suggested in IUPAC recommendation (Buck, R. P.; Lindner, E. *Pure Appl. Chem.* **1994**, *66*, 2527).

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