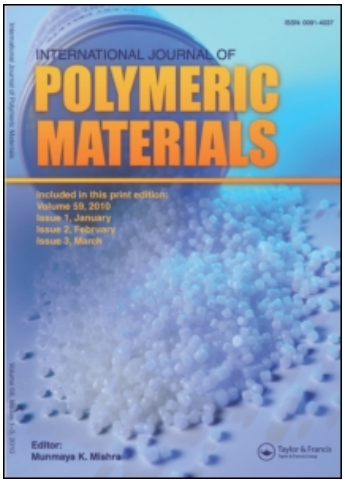

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Hydrophilic Sponges Based on 2-Hydroxyethyl Methacrylate. IV. Novel Synthetic Routes to Hydroxyl-Containing Crosslinking Agents and Their Effect on the Mechanical Strength of Sponges†

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The use of hydrophilic poly(2-hydroxyethyl methacrylate) sponges as biomaterials have diversified over recent years. Since the poor mechanical characteristics of these materials is a limiting factor to further development, an attempt was made in this study to improve the properties of sponges by using hydroxyl-containing crosslinking agents. Two such agents, 2-hydroxytrimethylene dimethacrylate (I) and 2,3-dihydroxytetramethylene dimethacrylate (II) were synthesized by novel procedures. Sponges were then produced using these agents and compared to sponges crosslinked with divinyl glycol (DVG), a hydrophilic but less reactive agent, and with ethylene dimethacrylate (EDMA), a hydrophobic but reactive agent. The use of I, II and DVG clearly improved the tensile characteristics of sponges, and tentative explanations were advanced.

Keywords: Poly(2-hydroxyethyl methacrylate); sponges; hydrophilic and hydrophobic crosslinking agents; equilibrium water content; tensile properties

INTRODUCTION

The homogeneous, transparent poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels have been widely studied and employed as

† For parts I, II and III see references 16, 17 and 18, respectively.
‡ To whom correspondence should be addressed.

polymeric biomaterials [1–6]. The macroporous, opaque PHEMA hydrogels (i.e., sponges) also raised some interest, however their biomedical applications in human patients have been limited so far to the reconstructive surgery of the breast [7–9] and nasal cartilages [10], now both abandoned.

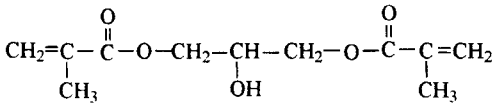
Over recent years, we have developed an artificial cornea (known also as keratoprosthesis) in which the annular skirt was made from a PHEMA sponge joining the transparent PHEMA circular core through an interpenetrating polymer network (IPN) [11–15]. The opacification of the cornea is the second major cause of blindness in the world, and the availability of a functional artificial cornea would significantly change this situation. The core-and-skirt keratoprostheses with porous skirts were introduced in the mid 1980s in the hope that the incorporation of the porous peripheral material into the host corneal tissue, through cellular invasion into the pores and growth across the polymer/tissue interface, would prevent the spontaneous expulsion of prosthesis which is the most frequent and devastating complication of this type of surgery [15]. However, a major problem with the previous such keratoprostheses was the difficulty in achieving a reliable union between the core polymer and the skirt polymer as they are quite different in their chemical structure and physical properties. Our design has obviously overcome this predicament, as both core and skirt are made from PHEMA.

The formation of PHEMA sponges is the result of phase separation during polymerization due to the presence of a large excess of water in the system. We have coined [16] for these sponges the terms "phase separation sponges" or "syneretic sponges" to differentiate them from those produced by other procedures, and studied extensively the influence of various factors on their porous morphology and swelling behaviour [16–18]. We have also demonstrated, both in cell cultures and in experimental animals, that PHEMA sponges synthesized in more than 75% water and crosslinked with hydrophobic difunctional monomers, with pores larger than 10 μm, were readily invaded by cells and tissue [19–21], and artificial cornea prototypes containing skirts made from such sponges showed promising results after implantation in animal eyes [22, 23]. However, the experiments also indicated that the mechanical strength of PHEMA sponge in the skirt is too low: during surgery, the preferable placement of structures through

the skirt usually caused tearing of the sponge and as a result they had to be passed through the transparent core polymer. Although not affecting a successful outcome of implantation, this may reduce the visual field of the patient.

In a nontrivial quest for constant improvement of the strength of PHEMA sponges some attempts have been made, including the copolymerization of HEMA with 4-*t*-butyl-2-hydroxycyclohexyl methacrylate (TBCM) [24] and the use of divinyl glycol (DVG) as a hydrophilic crosslinking agent [18]. It was reported that TBCM as a comonomer [25], of DVG as a crosslinking agent [26], both enhanced the mechanical strength of the poly(1-vinyl-2-pyrrolidinone) hydrogels. While TBCM failed to induce strengthening effects in PHEMA sponges [24], crosslinking with DVG clearly improved their elasticity [27]. However, the DVG-crosslinked PHEMA sponges displayed an anomalous swelling behaviour and macroscopic structural inhomogeneities [18]. This was attributed to a gelation rate slower than the rate of phase separation, caused by the lower free radical reactivity of DVG (an allylic difunctional monomer) as compared to dimethacrylate crosslinking agents. In preventing this undesirable effect of DVG in PHEMA sponges, the use of a more active initiating system proved successful [27]. Another possible approach is to replace DVG as a crosslinking agent with the more reactive hydrophilic methacrylate difunctional monomers which may induce a network gelation rate similar to the rate of phase separation. It is expected that this approach would result in PHEMA sponges with improved mechanical properties and lacking macroscopic inhomogeneities.

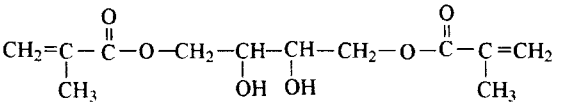
In this work, we report the synthesis of two hydroxyl-containing dimethacrylates (see Scheme I), their use as crosslinking agents, and a preliminary characterization of the resulting PHEMA sponges. The properties of sponges were compared to those of PHEMA sponges crosslinked with ethylene dimethacrylate (EDMA) or DVG. The only synthesis of compound **I** so far reported [28] consists in the ring opening reaction of glycidyl methacrylate with methacrylic acid. Compound **I** was used as a monomer in the stabilization of sandy soils [29]. Compound **II** was previously synthesized by the reaction between 1,3-butadiene diepoxide and methacrylic acid [30], and used as a crosslinking agent in the production of polymeric supports for gel permeation chromatography [31]. Closer to our time, both **I** and **II**



I

2-hydroxytrimethylene dimethacrylate

[1,3-di(2'-methyl-2'-propenoyloxy)-2-hydroxypropane]



II

2,3-dihydroxytetramethylene dimethacrylate

[1,4-di(2'-methyl-2'-propenoyloxy)-2,3-dihydroxybutane]

Scheme I

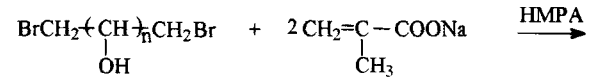
have been investigated as crosslinking agents in PHEMA compositions for contact lenses [32].

EXPERIMENTAL

Compounds **I** and **II** were synthesized by a general method based on the nucleophilic substitution undergone by the corresponding dibrominated alcohols when reacting with alkaline methacrylates (Scheme II). In an attempt to further improve the yield, compound II was also produced by a modification involving protection of the vicinal hydroxyl groups by cyclic acetalisation (Scheme III).

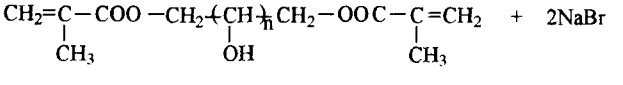
Materials

1,3-Dibromo-2-propanol (**III**) (tech., 95%), (±)-1,4-dibromo-2,3-butanediol (**IV**) (tech., 95%), sodium methacrylate (99%), hexamethylphosphoramide (HPMA) (99%), divinyl glycol (DVG) (97%)



III (n=1)

IV (n=2)



I (n=1)

II (n=2)

Scheme II

and 18-crown-6 (> 99.5%) were all supplied by Aldrich Co. and used without further purification. Ethylene dimethacrylate (EDMA) was supplied by Polysciences, Inc. and also used as such. 2-Hydroxyethyl methacrylate (HEMA) was supplied as Rocryl® 400 by Rohm and Haas and subjected to vacuum distillation prior to use. The other reagents were all supplied by local agencies.

Synthesis of 2-Hydroxytrimethylene Dimethacrylate (I)

HMPA (140 ml), **III** (8.72 g, 40 mmol), sodium methacrylate (12.97 g, 120 mmol), 18-crown-6 (0.36 g) and hydroquinone (0.4 g) were mixed together in a round-bottom flask, and stirred for 24 hours on an oil bath (60 – 80°C). After cooling, 250 ml diethyl ether were added. The precipitated sodium bromide was filtered off and washed on a filter with small amounts of ether. The combined ether phase was washed with water to remove HMPA and then with a solution of sodium hydroxide (2.5% wt) to remove the inhibitor (hydroquinone). After further washings with water, the organic phase was dried over anhydrous magnesium sulphate. Ether was removed by evaporation under vacuum, and the remaining yellow liquid was separated on a silica gel column (200–400 mesh, Aldrich Co.) using a mixture of hexane/ethyl acetate (3.5:1 vol) as a developing solvent. Compound **I** was obtained as a pale yellow liquid (3.8 g; yield 41.6%). IR (film), υ_{max}(cm^{-1}): 3483 s, br; 2960 m; 1722 v; 1636 m; 1453 m; 1298 s; 1163 s; 1018 w; 947 m. ^{13}C-NMR, δ (ppm): 165.80; 134.17; 124.84; 66.61; 63.89; 16.69.

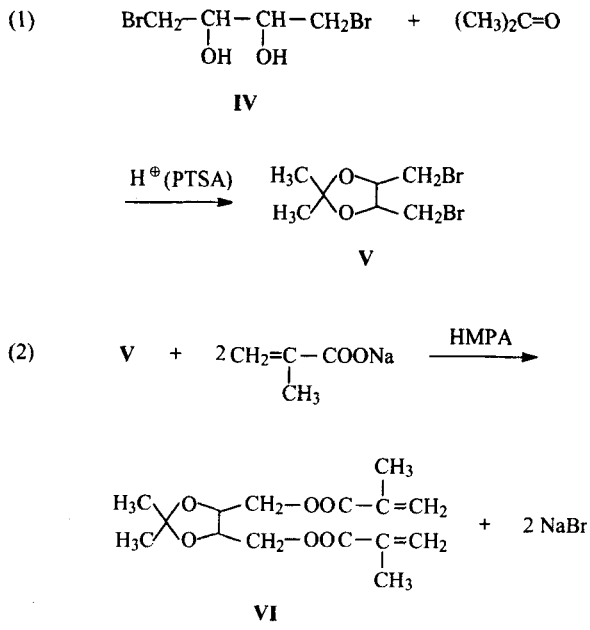
^{1}H-NMR, δ(ppm):6.10(t, 2H, H_{cis}-C = CR); 5.59(t, 2H, H_{trans} – C = CR); 4.24 (d, 4H, CH_2O); 3.78(t, 1H, CH); 2.98(s, 1H, OH); 1.93(s, 6H, CH_3).

Synthesis of 2,3-Dihydroxytetramethylene Dimethacrylate (II)

HMPA (100 ml), **IV** (5.13 g, 20.7 mmol), sodium methacrylate (6.71 g, 62.1 mmol), 18-crown-6 (0.07 g) and methyl-1, 4-benzoquinone (0.05 g) were mixed together in a round-bottom flask, and stirred for 40 hours on an oil bath (60–80°C). After cooling, the mixture was poured into 100 ml water and then extracted in a separatory funnel with four 100-ml portions of diethyl ether. The combined ether phase was washed in succession with water, sodium hydroxide solution (2.5% wt), saturated sodium chloride solution and again water. After drying over anhydrous magnesium sulphate, the ether was evaporated under vacuum until a viscous oily residue was left. A small amount of ether was added to this residue, followed by petroleum spirit (fraction 40–60°C) until white flakes precipitated. The precipitate was separated by filtration and dried under vacuum to afford **II** (2.6 g; yield 48.7%) as a white solid material with m.p. 52–54°C (lit·[30]: 53–55°C). IR (solution CCl_4), υ_{max}(cm^{-1}): 3477 s, br; 2960 m; 1722 υ; 1636 m; 1453 m; 1322 m; 1299 s; 1166 s; 1018 w; 944 m. ^{13}C-NMR, δ(ppm): 166.68; 134.21; 124.89; 67.92; 63.99; 16.68. ^{1}H-NMR, δ(ppm): 6.11 (t, 2H, H_{cis} – C = CR); 5.58(t, 2H, H_{trans} – C = CR); 4.27(m, 4H, CH_2O); 3.90(m, 2H, CH); 3.26(s, br, 2H, OH); 1.92(s, 6H, CH_3).

Synthesis of II by Using Group Protection (Scheme III)

(1) A mixture of **IV** (15 g, 60 mmol), benzene (120 ml), acetone (9 g, 160 mmol), and *p*-toluenesulphonic acid (PTSA) (0.2 g) was heated (oil bath) in a round-bottom flask provided with a Dean-Stark trap and condenser. The mixture was refluxed for 3 hours by which time 1.5 ml of water had collected in the trap. Benzene was removed through a rotary evaporator, and the brown oily residue was distilled under vacuum. 2,2-Dimethyl-4,5-dibromomethyl-1,3-dioxolane (**V**) was obtained (16.4 g; yield 94.9%) as a clear liquid (b.p. 92–94°C/0.35 mm Hg). IR (film), υ_{max}(cm^{-1}): 2988s; 2935m; 1421m; 1381s; 1372s; 1217 br; 1053s; 679m; 650m; 509m.



Scheme III

^{13}C-NMR, δ (ppm): 108.92; 77.48; 30.96; 25.80. ^{1}H-NMR, δ(ppm): 4.14(t, 2H, CH); 3.54(q, 4H, CH_2Br); 1.45(s, 6H, CH_3).

(2) **V**(14 g, 48.6 mmol) and sodium methacrylate (16 g, 148.1 mmol) were dissolved in 140 ml of HMPA. Small amounts of hydroquinone and 18-crown-6 were also added. The mixture was stirred at 80°C for 3 hours and then at room temperature for another 20 hours. The mixture was diluted with 500 ml diethyl ether and the resulting solution was washed with water (when sodium bromide dissolves in the aqueous phase), dried over anhydrous magnesium sulphate and concentrated in a rotary evaporator. The oily residue was separated on a silica gel column using a mixture of hexane/ethyl acetate (5:1 vol) as a developing solvent. 2,2-Dimethyl-4,5-dimethacryloyloxymethyl-1,3-dioxolane (**VI**) was obtained (10.9 g; yield 75.2%) as a very viscous syrup. IR (film), υ_{max}(cm^{-1}): 2988s; 2940 – 2850s, br; 1724v; 1636m; 1353m;

1320m; 1297m; 1165v; 1102s. ^{13}C-NMR, δ(ppm): 165.38; 134.71; 124.73; 108.64; 74.32; 62.26; 25.39; 16.74. ^{1}H-NMR, δ(ppm): 6.15 (t, 2H, H_{cis}–C = CR); 5.61(t, H, H_{trans}–C = CR); 4.34(m, 4H, CH_2O); 4.29(m, 2H, CH); 1.96 (s, 6H, CH_3); 1.43 (s, 6H, $C(CH_3)_2$).

(3) **VI** (4.7 g, 15.75 mmol) was dissolved in 35 ml methanol in a conical flask, and 5 ml of a hydrochloric acid 2N solution were added. The mixture was stirred at room temperature overnight. The flask was left uncovered in a fume hood during this operation. The residue in the flask was dissolved in 100 ml diethyl ether and washed with 5% sodium hydroxide and then with water. After drying the product, the ether was removed by evaporation under vacuum. The resulting pale yellow syrup was subjected to crystallization in ether/petroleum spirit (1:1 vol) to provide white flakes of **II** (3.6 g; yield 88.5%). Total yield over the three steps was 62.7%.

Spectrometric Analyses

The NMR spectra were recorded in a Varian Gemini-200 spectrometer using $CDCl_3$ as a solvent. The chemical shifts were referred to the shift of hydrogen and carbon in $CHCl_3$ contained in the deuterated solvent (7.26 ppm for ^{1}H-NMR, and 75.47 ppm for ^{13}C- NMR).

The infrared spectra were recorded in a Bruker Vector 22 FTIR spectrometer, using KBr cells.

Synthesis of Sponges

The production of PHEMA sponges was described in great detail elsewhere [11–13,16–19]. In the present study, the monomer mixtures, containing HEMA, water (80% wt), one of the crosslinking agents (EDMA, DVG, **I**, **II**), and either sodium metabisulfite/ammonium persulphate (SMBS/APS) or tetramethylethylene diamine/ammonium persulphate (TEMED/APS) as initiating systems, were cast between two Teflon® sheets separated by a silicone rubber gasket and supported by glass plates on the outer sides in order to avoid the bending of Teflon® sheets due to heating. Polymerization was carried out in an oven (50°C) for 20 hours. The code names and composition of sponges are given in Table I.

TABLE I Composition, code names, and equilibrium water content of PHEMA sponges[a]

Crosslinking agent	*I*		*II*		*EDMA*		*DVG*	
%mol	*Code name*	*EWC*	*Code name*	*EWC*	*Code name*	*EWC*	*Code name*	*EWC*
0.05	I-1	73.03 ± 0.4	II-1	72.04 ± 0.14	E-1	74.27 ± 0.86		
0.1	I-2	72.67 ± 1.35	II-2	72.23 ± 0.53	E-2	74.39 ± 0.61	D-2	74.51 ± 0.88
0.3	I-3	73.07 ± 1.34	II-3	73.37 ± 1.15	E-3	74.07 ± 0.27		
0.5	I-4	73.42 ± 0.17	II-4	70.63 ± 0.36	E-4	72.25 ± 0.24		
0.7	I-5	74.85 ± 0.65	II-5	71.26 ± 0.56	E-5	75.30 ± 1.02		
1.0	I-6	68.82 ± 0.65	II-6	66.69 ± 1.28	E-6	66.58 ± 0.94		
1.2	I-7	65.83 ± 1.18	II-7	67.85 ± 1.97	E-7	68.51 ± 0.93		
1.5	I-8	74.24 ± 0.26	II-8	73.73 ± 0.41	E-8	68.71 ± 0.17		
2.0	I-9	60.37 ± 1.09	II-9	65.51 ± 1.03	E-9	72.34 ± 1.87		
2.5	I-10	67.78 ± 0.84	II-10	68.5 ± 2.56	E-10	68.17 ± 0.81		
0.1[b]	I-11	75.49 ± 0.47	II-11	75.58 ± 0.59	E-11	75.29 ± 0.54	D-11	76.66 ± 1.06

[a]Sponges were prepared using 8g HEMA, 32g water, 100 µl of each SMBS (10%), APS (10%) and crosslinking agent.
[b]Sponges I-11, II-11, E-11 and D-11 were prepared with TEMED/APS initiator.

Equilibrium Water Content

Sponge specimens were kept in deionized water for 2 weeks with daily water exchanges. Water on the surface of specimens was removed by gently blotting and the samples were weighed. After weighing, they were dried in an oven at 50°C for 48 hours, and then reweighed. The equilibrium water content (EWC), as weight percentage, was calculated using Equation 1, where w_w and w_d are respectively the weights of a fully hydrated specimen, and of the same specimen after drying. Each specimen was evaluated in quadruplicate. The results are included in Table I.

$$EWC = 100(w_w - w_d)/w_w \quad (1)$$

Tensile Properties of Sponges

Cast sponge sheets were stamped with a dumb-bell-shaped cutting device to a size recommended by ASTM D2116 and the resulting specimens were soaked in distilled water for at least 24 hours. Using a SINTECH® 200/M Material Testing Workstation (MTS Systems Corporation, USA), with a low capacity load cell (10 N), the energy to break, elongation at break and modulus were all measured for each specimen and given in Table II as averages of six measurements. The cross head speed was 0.5 mm/s and the working length of the central part was 13 mm.

TABLE II Tensile characteristics of selected PHEMA sponges (0.1% mol crosslinking agent)

Code name	*Energy to break (N/mm)*	*Elongation at break (%)*	*Modulus (kPa)*
I-2	7.86 ± 0.2	605 ± 23	5.17 ± 2.89
II-2	8.10 ± 0.56	604 ± 52	3.92 ± 1.07
E-2	5.90 ± 0.33	483 ± 87	3.78 ± 0.32
D-2	6.54 ± 0.86	513 ± 23	6.31 ± 1.98
I-11	8.36 ± 0.57	530 ± 17	4.74 ± 1.26
II-11	10.55 ± 1.86	585 ± 47	4.76 ± 0.93
E-11	8.37 ± 0.96	502 ± 43	5.53 ± 0.95
D-11	10.58 ± 2.33	575 ± 78	5.07 ± 1.26

RESULTS AND DISCUSSION

The synthetic routes proposed here improved the yields in both crosslinking agents. In our attempts to duplicate the only published method [28] for synthesis of **I**, we have found that significant amounts of both glycidyl methacrylate (starting material) and hydroquinone (polymerization inhibitor) co-distilled with the final product. The mandatory alkaline washing and subsequent purification by column separation actually lowered the yield to values below that reported (40%[28]). By using the method described in Scheme II we assured mild synthetic conditions and a reasonable yield (41.6%) for **I**. Even better yields were obtained by using the same method for production of **II**. The yield was further improved (over 60%) by protecting the two vicinal hydroxyl groups prior to nucleophilic substitution (Scheme III), but the reason for this increase is not clear. It may be related to a possible effect of the hydroxyl groups (when unprotected) on the nucleophilic substitution. We have also noticed that the addition of a crown ether as a co-catalyst for nucleophilic substitution improved only slightly the yields, therefore its presence may not be necessary.

The swelling behavior of sponges, as illustrated by their EWC (Tab. I), revealed an irregular variation with the amount of crosslinking agent, although a general trend towards low EWC at higher concentrations of crosslinking agent may be detected. An inconsistent hydration behavior of PHEMA sponges has been found previously, [17,18] and explained by the existence of interstitial void spaces of random size leading to nonuniform water uptakes, and by macroscopic inhomogeneities probably induced by the difference in the free radical reactivities of the monomers and crosslinking agents.

For an estimation of the effect of the novel crosslinking agents on the mechanical properties of sponges, the tensile characteristics were measured in two series of sponges, each using a different initiating system, both with the same amount (0.1% mol) of crosslinking agents (Tab. II). When using the classic initiator SMBS/APS, the sponges crosslinked with **I** or **II** were stronger and more elastic than those crosslinked with EDMA or DVG. However, when a more active initiating system (TEMED/APS) was used, the measured parameters were levelled, the sponges crosslinked with EMDA and **I**, and, respectively, with DVG and **II**, displaying approximately the same mechanical characteristics.

The beneficial effect of hydrophilic crosslinking agents on the mechanical strength of PHEMA sponges is obvious and may result from delayed phase separation as compared to formulations incorporating the more hydrophobic crosslinking agent (EDMA). When added to the monomer/water mixture, EDMA remains as droplets and agitation is required to disperse them. When a hydrophilic crosslinking agent (DVG, **I**, **II**) is added, it rapidly disperses throughout the solution, even prior to agitation. EDMA promotes early phase separation in the polymerization mixture, with the result that relatively ineffective crosslinks from within the phase-separated polymer particles. Incorporation of greater than 0.1% mol EDMA leads to opaque monomer mixtures prior to polymerization, whereas mixtures incorporating DVG, **I**, or **II** remained clear even at significantly higher concentrations of crosslinking agents. Rethjen *et al.* [33] studied mechanical properties of crosslinked poly(N-isopropylacrylamide) networks as a function of polymerization temperature. When prepared at temperatures above 20°C, the polymers were opaque, while at lower temperatures transparent materials formed. The decrease in the fracture stress with temperature was attributed to the formation of inhomogeneities. Other workers [34] suggested that the inhomogeneities in poly(N-isopropylacrylamide) resulted from initially formed monomer clusters which became rigid due to crosslinks occurring within clusters. Huglin *et al.* [35–39] have used stress-strain measurements (via uniaxial compression) to estimate the effective crosslink densities in a range of hydrogels. Applying this technique to the PHEMA sponges described in the present work may enable us in the future to quantify the crosslinking efficiencies of hydrophobic and hydrophilic crosslinking agents.

Since the incorporation of hydroxyl-containing moieties into polymers promote the formation of hydrogen bonds, such a contribution to the enhancement of tensile strength in sponges crosslinked with DVG, **I** or **II** must also be taken into account.

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