

Fundamental Limitations and Advantages of Reference Electrodes based on Organic Electrolytes for Miniature Sensing Platforms and Point-of care Testing Systems

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Since the beginning of the 21st century, substantial effort in both academia and industry has been devoted to developing and commercializing sensing platforms and analytical devices for non-invasive detection and monitoring of various disease biomarkers. Potentiometric, amperometric, and other sensor types have been adapted for the quantification of various analytes in interstitial fluid, sweat, saliva, and tear fluid, driving significant advancements in electrochemical recognition mechanisms [1]. However, considerably less attention has been given to the reference electrodes (REs) used in such analytical platforms. Conventional double-junction REs, though well-established and highly stable, are challenging to miniaturize due to their reliance on large volumes of the reference solution and the bridge electrolyte. To overcome this constraint, Ag/AgCl in the form of wires or printed inks is often employed as a quasi-reference element immersed directly in the sample. However, this approach may introduce substantial measurement errors or necessitate sample modification.

In this contribution we critically assess the advantages and limitations of REs based on organic electrolytes. These REs eliminate the need for traditional liquid junctions by employing "water-immiscible salt bridges", such as free-flowing ionic liquids (ILs) or membranes doped with organic electrolytes. Upon contact with a sample, these electrolytes partition into the aqueous phase, establishing an equilibrium distribution and a phase boundary potential that remains largely unaffected by the sample composition. This approach moves away from bulky electrode compartments filled with reference and bridge electrolytes while maintaining high potential stability across a wide range of samples and thus opens broader opportunities for miniaturization and task-specific RE design. Despite these promising features, organic electrolyte-based REs have yet to gain widespread adoption, primarily due to gaps in the understanding of their functional limits [2]. Through theory and experiments, we reveal here the key limitations linked to electrolyte lipophilicity. We show that low-lipophilicity electrolytes are prone to ion-exchange interference and salt leaching, which significantly shortens RE lifetimes [3], whereas highly lipophilic electrolytes require precise cation-anion matching, as even minor impurities can cause potential deviations. To address these issues, we propose a novel approach that combines highly lipophilic electrolytes with ionophores. This combination provides stable electrode potentials with reduced electrolyte leaching, bridging the gap between the two lipophilicity ranges and offering a pathway to more robust and practical REs.

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