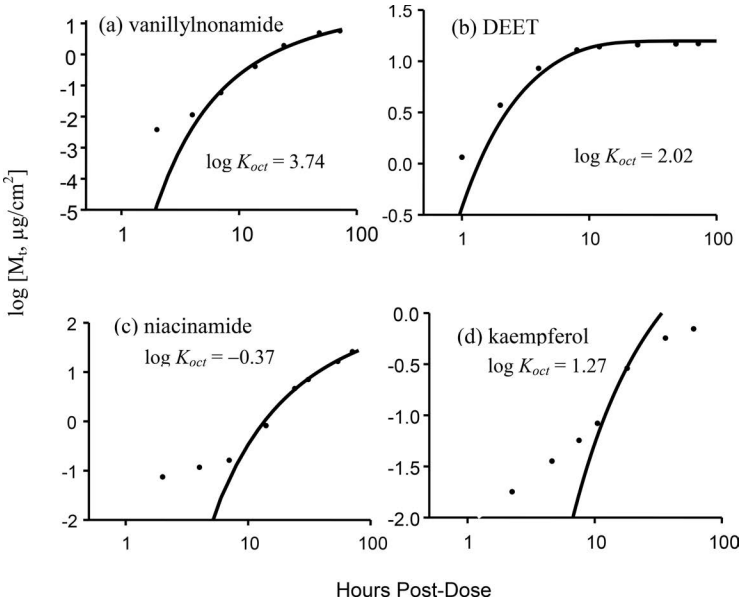

FIGURE 10.1 Permeation time course of four radiolabeled compounds through split-thickness human skin in vitro. The compounds were applied in simple solvent systems (5 µL/0.79 cm^2 cell) at doses of 10–100 µg/cm^2. (a) ^{14}C-vanillylnonanamide in propylene glycol (37); (b) ^{14}C-DEET in ethanol; (c) ^{14}C-niacinamide in 1:1 v/v ethanol/water; (d) ^{3}H-kaempferol in propylene glycol. The solid lines are theoretical curves for finite dose permeation through a homogeneous membrane (37) that have been fit to the data. The theory for DEET includes a first-order evaporative loss from the skin surface (42). The positive departures of the data from the theory suggest a second (shunt) pathway through the SC having a very short time lag.

10.3 THE ROLE OF CORNEOCYTES IN THE STRATUM CORNEUM BARRIER

Perhaps the most unfortunate consequence of the "brick-and-mortar" analogy for SC structure is the tendency to think of corneocytes as impermeable obstacles. The body of evidence to the contrary is compelling. First and foremost, immersion in water leads to swelling of the SC to several times its normal thickness in about an hour (43–46). Although a small amount of water may hydrate lipid headgroups in the lipid lamellae (47), the bulk of the water must enter the corneocytes, as the lamellar spacings do not change significantly with hydration (48). Nuclear magnetic resonance (NMR) studies have shown the diffusivity of mobile protons in partially hydrated SC (guinea pig footpad hydrated to ~43% w/w) to be 2.8×10^{-6} cm^{2}s^{-1}, only tenfold less than the self-diffusivity of water (49, 50). This signal presumably derives largely from water within the corneocytes (50). Water diffusivity in fully hydrated corneocytes is likely to be higher; an estimate from hindered diffusion theory, including keratin–water binding interaction, is 2.2×10^{-7} cm^{2}s^{-1} (51).

There is a school of thought that it is the cornified cell envelopes (CEs), rather than the keratinized interiors, that leads to corneocyte impermeability. This thinking appears to derive from a consideration of the chemical resistance of the CE, which is indeed formidable. Boiling in alkali is required to degrade these structures. It is supported by microscopic studies of heavy metal distribution in SC that show a higher fraction of metal ions or metal ion precipitates within apical corneocytes following topical administration than in the lower layers (52, 53). The published studies of Hg^{2+} distribution (52, 53) are supported by additional unpublished work with Zn^{2+} and Cu^{2+} (R. R. Warner, personal communication). Investigators have hypothesized that desmosomal degradation in the outer SC leads to breaches in the CEs, allowing ion entry (53). Although there is merit to this idea, an alternative explanation is possible to which we will return momentarily. First, we note that the impermeable CE concept is inconsistent both with spectroscopic studies of