right corner of the contour plot is seldom attainable. Most notable on these plots is the shape of the contours and changes in this shape as molecular weight is increased. Changing the physical properties of a drug in a manner that results in movement parallel to a flux contour line will result in neither an increase nor decrease in the predicted transdermal delivery of the drug. Conversely, changing the physical properties of a drug in a manner that results in movement perpendicular to a flux contour line will provide the greatest change in predicted delivery. For example, increasing the partition coefficient from 0.05 to 0.37 (lnPC = −3 to −1), while maintaining the water solubility at 2.72 mg/ml (lnS = 1) results in a 5.3-fold increase in predicted flux for a drug of molecular weight 300, but only a 2.4-fold increase in the predicted flux for a drug of molecular weight 100.

A good example of moving along a contour line is seen in the experimental transdermal flux results for the mitomycin C (MMC) analogues listed in Table 1. Note that the partition coefficient of pentyloxycarbonyl MMC is twofold greater than the partition coefficient for benzyloxycarbonyl MMC, whereas the water solubilities and molecular weights are approximately the same. The experimental results show that the in vitro percutaneous absorption of these substances are essentially the same, just as anticipated based upon the contour plot for molecular weight 500. Alternatively, benzyl MMC and propyloxycarbonyl MMC can be compared. Both compounds have essentially the same molecular weights and lipophilicity, but benzyl MMC has about fourfold greater water solubility than propyloxycarbonyl MMC. Here, the increased water solubility of the analogue increases drug flux by greater than an order of magnitude. Again, this increase in flux of the drug would have been anticipated from noting the perpendicular crossing of the contour line in Figure 2.

VI. ADDITIONAL CONSIDERATIONS

Although these contour plots are of obvious utility, it must be remembered that these computational methods provide predicted flux values that are generally within an order of magnitude of the experimental values determined using in vitro transdermal methods. It is fully expected that such computational methods may not be appropriate for topical drugs, such as steroids, that uniquely interact with the bilayer-structured epidermal lipids (see Chap. 3) (28–30), or for drugs that alter the barrier properties of the skin. This second consideration can be seen in Table 1 when considering data for the keratolytic, salicylic acid. Thus, experimental values 10,000-fold greater than the predicted values result. It is also noteworthy that each of these models assumes that diffusion is stratum corneum-controlled, rather than dermally controlled.