bilities of a drug in various vehicles, the relationship between $P_i^{s,v}$ and δ_v, and the flux of that drug from one specific vehicle it should be possible to determine the flux of that drug from other vehicles of interest, assuming that the vehicles do not damage the skin. Fourth, the parabolic nature of the relationship between δ_v and $P_i^{s,v}$ expected from regular solution theory has been confirmed for a number of drugs. Fifth, for "chameleonic" solutes (drugs) such as salicylic acid (see Fig. 3) that apparently can exhibit two different δ_i values, two different log theoretical $K_i^{s,v}$ and, hence, two different log experimental $P_i^{s,v}$ curves are generated.

In addition to the results obtained for single-component vehicles, the rates of delivery of 5-fluorouracil (5-FU) and 6-mercaptopurine (6-MP) from a binary component vehicle (oleic acid—propylene glycol) were also determined (Table 2). Here, although the log experimental $P_i^{s,v}$ values for the delivery of 5-FU and 6-MP from oleic acid and propylene glycol fell on the log theoretical $P_i^{s,v}$ versus δ_v curve, none of the log experimental $P_i^{s,v}$ values for the mixtures did. In each case, starting with mixtures that were rich in oleic acid (21,22), as the solubility of the drug in each mixture increased, its experimental $P_i^{s,v}$ value decreased. Also, in each case, there was considerably more damage to the skin observed after treatment with the binary-component solutions than after treatment with either of the single components (21,23), regardless of the δ_v of the mixture. Thus, enhanced delivery of a drug by a mixture of vehicles may be primarily the result of enhanced damage to the integrity of the skin, rather than to some thermodynamic advantage.

In the investigations of the ability of prodrugs to deliver their respective parent drugs from various vehicles through skin, there was a good correlation between the calculated solubility parameter of a series of homologous prodrugs and their ability to deliver the parent drugs through hairless mouse skin (24—26). In addition, a vehicle effect on rates of delivery was observed that was directly attributable to solubility phenomena. Generally, the results from these articles were qualitatively similar to the results of Ostrenga (9) that showed that there was a good correlation between molar attraction constants (F values) and bioactivity.

The most extensive studies of the effect of relative solubilities of a homologous series of prodrugs on their abilities to deliver a parent drug through skin are the studies of S^6,9-bis-acyloxymethyl-6-MP (6,9-bis-6-MP) and S^6-acyloxymethyl-6-MP (6-mono-6-MP) prodrugs. The acetyloxymethyl through octanoyloxymethyl along with the pivaloyloxymethyl derivatives of both the bis- and mono-series were synthesized, characterized, and the rates at which they delivered 6-MP through hairless mouse skins were measured. The solu-