Method II. (a) A solution of the sodium salt of the compound with a hydroxy group (0.1 mM) in H_2O (50 μg/mL) was extracted with an organic solvent one-half volume × 2) containing TOMAC (25 mM), and the organic solvent layer was refluxed. The reaction mixture was reextracted with 30 mM NaI/H_2O. The purification procedure was similar to that of method I (Table VIII).

(b) To a solution of **6** (144 mg) in DMF (12 mL) was added 5% TOMAC/CH_2Cl_2 (500 mL), and the mixture was refluxed for 22 h. The reaction mixture was extracted with 6% NaI/H_2O (170 mL), and the aqueous layer was treated similarly to give **17** (40.6 mg) as a freeze-dried powder.

The physicochemical properties of the derivatives are shown in Table II.

Determination of in Vitro and in Vivo Antibacterial Activity. The MIC was determined by the agar dilution method.[12] The protective effect in Slc:ICR mice was determined as described previously.[12] The 50% effective dose (ED_{50}) was calculated by the method of Reed and Muench[13] from the survival rate recorded 5 days after infection.

Determination of β-Lactamase Inhibitory Activity and Antibacterial Synergy Test. The β-lactamase inhibitory activity was determined as described previously[5] and expressed in terms of I_{50}, the concentration required to inhibit β-lactamase activity by 50%. The potentiation of the antibacterial activity of ampicillin and cefotiam by carbapenem antibiotics was examined by the 2-fold dilution method with Mueller-Hinton agar (Difco) as described previously.[6]

Determination of the Stability to Mouse Renal Enzyme(s). The carbapenem antibiotic (50 μg/mL) was incubated in a 10% mouse kidney homogenate at 30 °C. At intervals, we determined the amount of the residual carbapenem antibiotic by assaying the activity to inhibit the β-lactamase.

Acknowledgment. We are grateful to Drs. M. Yoneda, T. Kishi, and A. Imada in our Central Research Division for their encouragement throughout this work. Thanks are also due to the members of the fermentation and physical analysis sections for their support and to Y. Nohara for his skillful assistance.

Registry No. **1**, 76025-74-6; **2**, 76035-86-4; **3**, 83510-01-4; **4**, 57459-82-2; **5**, 12795-21-0; **6**, 68510-62-3; **7**, 68421-49-8; **8**, 83916-36-3; **9**, 80994-11-2; **10**, 83916-37-4; **11**, 83916-38-5; **12**, 80994-12-3; **13**, 83916-39-6; **14**, 83916-40-9; **15**, 83916-41-0; **16**, 83916-42-1; **17**, 75443-31-1; **18**, 75443-29-7; **19**, 83916-43-2; **20**, 83916-44-3; **21**, 83916-45-4; **22**, 83916-46-5; tri-*n*-octylmethylammonium chloride, 5137-55-3.

(12) K. Tsuchiya, M. Kida, M. Kondo, H. Ono, M. Takeuchi, and T. Nishi, *Antimicrob. Agents Chemother.*, **14**, 557 (1978).
(13) L. J. Reed and H. Muench, *Am. J. Hyg.*, **27**, 493 (1938).

This paper first appeared on pages 271–275. It is being reprinted due to errors introduced during the production cycle

Notes

Oscillations in Some Linear Free Energy Relationships Derived from Partition Coefficients of Phenols between Octanol and Water

A. E. Beezer and W. H. Hunter*

Departments of Chemistry and Pharmacy, Chelsea College, University of London, London, SW3 6LX United Kingdom.
Received August 5, 1982

In the partition of some resorcinol alkyl ethers between water and 1-octanol, the values of ΔG_{trs} do not increase in a regular way. Odd and even chain alkyl compounds show different, regular increases in ΔG_{trs} for addition of each methylene group. The unrecognized occurrence of this phenomenon in earlier data is pointed out, and its possible significance in medicinal chemistry is discussed.

It has long been assumed[1] that partition coefficients for the transfer of solutes, in particular drugs, between water and a nonaqueous, lipid-like phase are linearly related to the chain length for an homologous series. "Hansch" analysis[2] has been used for some years to correlate the biological activity for a series of drugs with π values (log P/P_0, where P is the partition coefficient for a member of an homologous series and P_0 is that for the "parent" member of the series). The values of P for many of these compounds are now calculated from group contributions,[3] fragmental constant,[4] or molecular connectivity schemes.[5] Clearly, the basis for such calculation schemes is that there exists a *linear* relationship between $f(P)$ and the degree of substitution; i.e., there exists a linear Gibbs energy relationship similar to the Hammett equation.[6] Thus, for the resorcinol monoethers it is assumed[2] that log P increases by 0.5 for each incremental methylene group in the side chain. Moreover, Tanford[7] has shown that the Gibbs

(1) James, K. C. *Prog. Med. Chem.* **1974**, *10*, 225–227.
(2) Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180.
(3) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–616.
(4) Nys, G. G.; Rekker, J. *Eur. J. Med. Chem.* **1974**, *9*, 361–375.
(5) For example, Boyd, J. C.; Millership, J. S.; Woolfson, A. D. *J. Pharm. Pharmacol.* **1982**, *34*, 158–161.
(6) Bowden, K.; Coombs, T. J. *Prog. Pharm. Res.* **1982**, *4*, 1–40.

0022-2623/83/1826-0757$01.50/0

Table I. Values of ΔG_{trs} and $\Delta(\Delta G_{trs})$ for Transfer of Resorcinol Monoethers from Water to 1-Octanol[a]

phenol	$-\Delta G_{trs}$	$\Delta(\Delta G_{trs})$	$\Delta G_{soln,w}$	$\Delta(\Delta G_{soln,w})$	$\Delta G_{soln,w/o}$	$\Delta(\Delta G_{soln,w/o})$
m-methoxy	9.42		13.08		13.72	
		2.35		2.85		2.75
m-ethoxy	11.77		15.93		16.47	
		3.46		3.40		3.69
m-propoxy	15.23		19.33		20.16	
		2.55		2.89		3.12
m-butoxy	17.78		22.22		23.28	
		3.41		3.41		3.74
m-pentoxy	21.19		25.63		27.02	

[a] See ref 9. Values of ΔG_{soln} for solution of resorcinol monoethers in water ($\Delta G_{soln,w}$) and in 1-octanol-saturated water ($\Delta G_{soln,w/o}$), together with the respective $\Delta(\Delta G_{soln})$ values. All values are in kJ mol^{-1}.

energies of transfer (ΔG_{trs}) of alkanes, alkenes, and alkadienes from aqueous solution to pure liquid hydrocarbon at 298 K (calculated from the solubility data of McAuliffe[8]) can also be described in terms of such linear Gibbs energy relationships. Gill and Wadso[9] have extended these data to derive a "hydrophobic interaction equation of state", which demonstrates the dependence of ΔG_{trs} upon the number of hydrogen atoms in the hydrocarbon molecule. There is nowhere a suggestion of oscillation in successive values of ΔG_{trs} or related parameters.

Not surprisingly, a wide range of lipid-like solvents has been used as the nonaqueous phase in partitioning studies, but the evidence in the literature[3] appears to suggest that the partitioning of drug molecules between water and 1-octanol is the only process that gives a good correlation with biological activity. Octanol will take up water to a concentration of 2.30 mol dm^{-3}, and water will dissolve 1-octanol to a concentration of 0.0045 mol dm^{-3}. Any discussion of the structure of the solute–solvent interactions during transfer are therefore very complex for such ternary systems. Other solvents recommended and used for partitioning studies include propylene carbonate[10] and a wide range of hydrocarbons.[3]

Aveyard and Mitchell[11,12] have calculated an average solute methylene group increment in ΔG_{trs} of −3.3 kJ mol^{-1} for distribution of a series of alkanols and alkanoic acids between water and hydrocarbon solvents, a result consistent with the Gill and Wadso[9] equation of state for transfer between water and pure liquid hydrocarbons.

We have recently reported[13] the van't Hoff derived thermodynamic parameters for the transfer of a series of resorcinol monoethers from water to 1-octanol. The data (Table I) indicate an oscillation in ΔG_{trs} values as the series is ascended. Subsequently,[14] we have reported calorimetrically derived values for the enthalpy of transfer (from measurement of enthalpies of solution of the resorcinol monoethers in both pure water and pure octanol and in the mutually saturated solvents). The Gibbs energy of solution (ΔG_{soln}) may be calculated[7,15] from:

$$\Delta G_{soln} = -RT \ln X$$

where X is the unitary (mole fraction) concentration term.

Table II. ΔG_{trs}[a] for Transfer of the Described Solute from Water to the Described Alkane and the Derived $\Delta(\Delta G_{trs})$ Values at 298 K

system	$-\Delta G_{trs}$[b]	$\Delta(\Delta G_{trs})$[b]
butanol + octane	0.80	
		3.47
pentanol + octane	4.47	
		2.62
hexanol + octane	6.89	
		3.68
heptanol + octane	10.57	
butanol + dodecane	0.80	
		3.63
pentanol + dodecane	4.43	
		2.96
hexanol + dodecane	7.39	
		3.61
heptanol + dodecane	11.00	
butanol + hexadecane	0.76	
		3.83
pentanol + hexadecane	4.59	
		2.80
hexanol + hexadecane	7.39	
		3.70
heptanol + hexadecane	11.09	
butyric acid + hexadecane	7.5	
		3.60
valeric acid + hexadecane	11.1	
		2.70
hexanoic acid + hexadecane	13.8	
		3.40
heptanoic acid + hexadecane	17.2	

[a] From refs 11 and 12. [b] Values in kJ mol^{-1}.

Table III. Gibbs Energy of Hydration (ΔG_{hyd}) of Aliphatic Alcohols at 298 K from Reference 16

alcohol	ΔG_{hyd}[a]	$\Delta(\Delta G_{hyd})$[a]
methyl	12.93	
		0.42
ethyl	13.35	
		0.79
1-propyl	14.14	
		0.46
1-butyl	14.60	
		1.00
1-pentyl	15.60	
		0.47
1-hexyl	16.07	
		0.50
1-heptyl	16.57	
		0.63
1-octyl	17.20	

[a] All values in kJ mol^{-1}.

The values so calculated for solution in water and in 1-octanol-saturated water are shown in Table I, together with the respective $\Delta(\Delta G_{soln})$ values. It can be seen that the oscillations in ΔG_{trs} originate in the values of ΔG_{soln} in water solvent systems. Our conclusion, therefore, is that the thermodynamic parameters of the partition process are controlled by the behavior of these solutes in water.[14]

These observations have an obvious bearing on the use of partition data in "Hansch" analysis in that there are scarcely any *accurately* determined partition coefficients described for homologous series and few solubility determinations of series of sparingly soluble nonelectrolytes that would permit calculation of ΔG_{soln}. Furthermore, in "Hansch" analysis little or no attention is paid to the discrepancy between the temperatures of the partition experiments and the temperature of the biological observations.

Reinspection of the partition coefficients reported by Aveyard and Mitchell[11,12] yields the results described in Table II; again an oscillation is indicated. Oscillating values of $\Delta(\Delta G_{trs})$ for the acids described were not observed for partition between water/octane and between water/dodecane. It is noteworthy that the Δ (ΔG_{trs}) values shown in Tables I and II are all approximately the same.

(7) Tanford, C. "The Hydrophobic Effect", 2nd ed.; Wiley: New York, 1980; pp 4–21.
(8) McAuliffe, C. *J. Phys. Chem.* **1966**, *70*, 1267–1275.
(9) Gill, S. J.; Wadso, I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 2955–2958.
(10) Krishnan, C. V.; Friedman, H. L. In "Solute-Solvent Interaction"; Coetzee, J. F.; Ritchie, C. D., Eds.; Dekker: New York, 1976; Vol. 2, p 52–54.
(11) Aveyard, R.; Mitchell, R. W. *Trans. Faraday Soc.* **1969**, 2645–2653.
(12) Aveyard, R.; Mitchell, R. W. *Trans. Faraday Soc.* **1970**, 37–42.
(13) Beezer, A. E.; Hunter, W. H.; Storey, D. E. *J. Pharm. Pharmacol.* **1980**, *32*, 815–891.
(14) Beezer, A. E.; Hunter, W. H.; Storey, D. E. *J. Pharm. Pharmacol.*, in press.
(15) Reynolds, J. A.; Gilbert, D. B.; Tanford, C. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 2925–2927.

Moreover the mean of the values shown is not far from the 3.3 kJ mol^{-1} reported by Tanford[7], Gill and Wadso,[9] and Aveyard and Mitchell,[11,12] whose data have, of course, been used here.

Values for the Gibbs energy of hydration (ΔG_{hyd}) of some aliphatic alcohols (a closely related term to ΔG_{soln} through the Gibbs energy of vaporization) have been reported by Butler[16] and are shown in Table III. Given the difficulties inherent in the methods adopted and, hence, the errors associated with ΔG_{hyd} it is tempting to see an oscillation in the values of ΔG_{hyd} too, especially for the lower members of the series. Irregularity of behavior in solution with steady increase in chain length has been reported also by Mukerjee, Mysels, and Kapauan[18] for micelle formation in a series of long-chain alkyl ammonium salts.

It therefore appears that for some, though not all, systems the assumption of a monotonous increase in ΔG_{trs} per methylene group, and thus P, may not be valid. Indeed, if the oscillation in $\Delta(\Delta G_{trs})$ is confirmed, then the linear relationships normally described between $f(P)$ and chain length may be the mean of two other linear relationships, one relating to the substances of odd-numbered chain length and the other to the even-numbered members. If these results are confirmed by studies on other systems (in progress in our laboratory) and by other workers, then the methods for calculation of P, cited earlier, may need to be revised, as will the general application of "Hansch" analysis. These observations may therefore have a significance for such empirically based analyses as QSAR studies or the empirical solubility estimation of Amidon et al.,[17] which depends upon calculated values of P.

We are as yet uncertain about the origin of this phenomenon, but it must lie in the solute–solute or solute–solvent interactions. Since the phenols and the solutes of Tables II and III are all liquids, the kind of irregularities encountered amongst solids cannot provide an explanation, but it is perhaps significant that all the solutes showing oscillations in $\Delta(\Delta G_{trs})$ contain hydroxy groups. It is therefore conceivable that the separate contributions made to ΔG_{soln} in water by the hydroxy function and by the hydrocarbon part of the molecule vary according to some unknown interaction occurring either in the liquid solute or some conformational effect in the solvated molecule. It may also be significant that in the series so far examined, oscillation in these values is confined to the lower members, that is, to those members where ΔG_{trs} and ΔS_{trs} both vary;[13,14] for the higher members whose partition is increasingly "entropy driven", the large ΔS_{trs} contributions to ΔG_{trs}, which are linearly related to chain length, tend to obscure the ΔH_{trs} contribution.[13,14]

Only more detailed experiments on partitioning, performed under carefully controlled conditions, will reveal the general or particular nature of these observations.

Registry No. *m*-Methoxyphenol, 150-19-6; *m*-ethoxyphenol, 621-34-1; *m*-propoxyphenol, 16533-50-9; *m*-butoxyphenol, 18979-72-1; *m*-pentoxyphenol, 18979-73-2; butanol, 71-36-3; pentanol, 71-41-0; hexanol, 111-27-3; heptanol, 111-70-6; butyric acid, 107-92-6; valeric acid, 109-52-4; hexanoic acid, 142-62-1; heptanoic acid, 111-14-8; hexadecane, 544-76-3; dodecane, 112-40-3; octane, 111-65-9; 1-octanol, 111-87-5; water, 7732-18-5.

(16) Butler, J. A. V. *J. Chem. Soc.* **1936**, 1171–1173.
(17) Amidon, G. L.; Yalkowsky, S. H.; Anik, S. T.; Valvani, S. C. *J. Phys. Chem.* **1976**, *79*, 2239–2245.
(18) Mukerjee, P.; Mysels, K. J.; Kapauan, P. *J. Phys. Chem.* **1967**, *71*, 4166–4175.

9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine: A New Potent and Selective Antiherpes Agent[1]

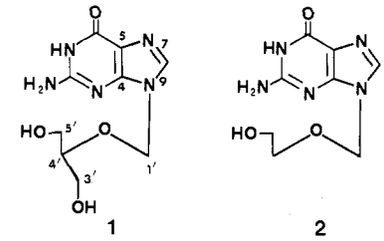
John C. Martin,* Charles A. Dvorak, Donald F. Smee, Thomas R. Matthews, and Julien P. H. Verheyden

Syntex Research, Palo Alto, California 94304. Received January 17, 1983

The synthesis of a new acyclic analogue of deoxyguanosine, 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **1**), is described starting from epichlorohydrin via condensation of 2-*O*-(acetoxymethyl)-1,3-di-*O*-benzylglycerol (**5**) with N^2,9-diacetylguanine (**6**). In vitro studies indicate that DHPG is a potent and broad-acting (herpes simplex virus types 1 and 2, cytomegalovirus, and Epstein-Barr virus) antiherpetic agent. In vivo studies indicate its lack of toxicity [LD_{50} (mice) = 1–2 g/kg, ip] and its superiority over acyclovir [oral ED_{50} = 7 (mg/kg)/day vs. 550 (mg/kg)/day in HSV-2 infected mice].

Much effort has been devoted to the synthesis of novel nucleoside analogues as antiherpetic agents,[2] many of which are also toxic to the host. Recently, a few less toxic nucleoside analogues have been shown to be good substrates for the viral-specified thymidine kinase while being poorly phosphorylated by host enzymes.[3] The resulting nucleoside monophosphates are then converted to the triphosphates, which in turn inhibit virus replication by interfering with the viral DNA synthesis while not disrupting uninfected cell DNA synthesis.

This note reports the synthesis and the physical and biological properties of DHPG (**1**),[4,5] an acyclic deoxy-



1 **2**

(1) Contributions 162 and 639 from the Institutes of Bio-Organic Chemistry and Organic Chemistry, Syntex Research.
(2) DeClercq, E. *Biochem. J.* **1982**, *205*, 1.
(3) (a) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B. *Nature (London)* **1978**, *272*, 583. (b) DeClercq, E.; Deschamps, J.; DeSomer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947. (c) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.
(4) Verheyden, J. P. H.; Martin, J. C. U.S. Patent 4 355 032.

0022-2623/83/1826-0759$01.50/0