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Characterisation of the water–isopropyl myristate system

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Abstract

Partition coefficients for compounds (solutes) from water to isopropyl myristate, IPM, have been obtained from the literature, either as directly determined partition coefficients or from solubilities in water and in IPM. The general solvation equation of Abraham has been applied to 141 such partition coefficients, as log Pipm, and it is shown that the main solute factors that influence partition are dipolarity/polarisability, hydrogen bond acidity and hydrogen bond basicity that reduce partition, and volume that increases partition. These factors are quantitatively very similar to those that influence partition in the water to olive oil system, and indicate that IPM has the expected behaviour of a long chain, hydrophobic ester. It is shown that the water to IPM system is a poor model for partition between water and human *stratum corneum* and for permeation from water through human skin.

Keywords: Isopropyl myristate; Partition; Solvation equation; Hydrogen bonding

1. Introduction

Isopropyl myristate (IPM) is an important solvent in studies of permeation of solutes through skin. First, it has been suggested as a model for the *stratum corneum* and partitions from water to IPM, Pipm, have been compared to partitions from water to the *stratum corneum* or to permeation rates through skin (Saket et al., 1984, 1985; Hadgraft and Ridout, 1987; Surber et al., 1990a,b). Second, IPM has been used a vehicle for permeation through skin, usually hairless mouse skin. Much of the work in this area is due to Sloan, and has been summarized in a detailed and valuable review (Sloan and Wasdo, 2003). In both areas, values of Pipm have been determined for a large range of solutes, either directly, or through solubilities in water, Sw, and isopropyl myristate, Sipm:

$$\log \text{Pipm} = \log \text{Sipm} - \log \text{Sw} \quad (1)$$

In spite of the above investigations into IPM as a model for percutaneous absorption, it is difficult to reach any

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general conclusions, mostly because of the restricted number and range of compounds used. A good correlation between partition into the *stratum corneum* and partition into IPM was found (Saket et al., 1985), but this was limited to cortisone, hydrocortisone, and their esters, a total of only 11 solutes. Studies on transport across an IPM impregnated membrane indicated that permeation of human skin from water could be predicted in this way, but the number of solutes used was only eight, and two of these had to be omitted in the correlation (Hadgraft and Ridout, 1987).

It is the aim of the present work, to set up a linear free energy relationship (LFER) for log Pipm and to compare this to previous LFERs that we have constructed for permeation from water through human skin, as log kp, and for partition from water to *stratum corneum*, as log Ksc (Abraham and Martins, 2004). In this way, we hope to overcome the difficulty of a limited number of solutes common to the different systems. We aimed also to compare partition from water to IPM with partition to various other solvents, in order to ascertain if there is any unusual physicochemical property of IPM that may explain its use as a permeation vehicle.

2. Methods

Our method is based on the general LFER (Abraham, 1993; Abraham et al., 2004)

$$\mathrm{SP} = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + v\mathbf{V} \quad (2)$$

where SP is the dependent variable such as values of log Pipm for a series of compounds. The independent variables are solute properties or descriptors as follows (Abraham et al., 2004). **E** is the solute excess molar refractivity in units of $(\mathrm{cm}^3\,\mathrm{mol}^{-1})/10$, **S** is the solute dipolarity/polarisability, **A** and **B** are the overall or summation hydrogen bond acidity and basicity, and **V** is the McGowan characteristic volume in units of $(\mathrm{cm}^3\,\mathrm{mol}^{-1})/100$.

Although we have determined descriptors for a large number of solutes from experimental data, most of the solutes used in permeation from IPM are novel prodrugs (Sloan and Wasdo, 2003) for which descriptors had to be obtained. We used the method of Pharma Algorithms (2002) to calculate descriptors from structure, and also assigned descriptors by analogy to compounds that had the same, or similar, fragments and functional groups. The descriptors obtained in this way were used to calculate water to octanol partition coefficients, and these were compared to recorded values, as log Poct. The latter were experimental values if available (MedChem, 2003), or were otherwise calculated values (Pharma Algorithms, 2002; Leo, 2001). If the log Poct values calculated from the assigned descriptors were considerably different from the recorded values, either or both of the **S** and **B** descriptors were adjusted appropriately, whilst still bearing in mind the values assigned by analogy. Since the LFER for log Poct has an almost zero a-coefficient (Abraham, 1993), the **A** descriptor cannot be checked in this way, and has to be assigned from experimental log P values, if available, or by analogy or by the method of Pharma Algorithms (2002).

3. Results and discussion

The values of log Pipm, that we have collected are in Table 1, together with the solute descriptors shown in Eq. (2). Most of the data is from the work of Sloan and Wasdo (2003) measured at room temperature, 23 °C. We omitted a small number of compounds. For hydrocortisone, reported values are 1.63 (Saket et al., 1984, 1985) and −0.20 (Hadgraft and Ridout, 1987); the former seems improbably high and was left out. A value of −1.46 has been reported for log Pipm for nicotine (Dal Pozzo et al., 1991) but no details as to pH were given, and so the species present in the aqueous solution is not known. Values of log Pipm have been determined for four phenols (Surber et al., 1990b), together with partition coefficients for water to *stratum corneum*, as log Psc, and for *stratum corneum* to IPM, as log P(sc/ipm). The three sets of log P values are mutually inconsistent, and so we decided not to use any of this data.

We have a total of 141 values of log Pipm, enough to divide into a training set and a separate test set. In order that the predictive (test set) data space should be the same as that of the training set, we divided the 141 compounds into a training set of 71 compounds and a test set of 70 compounds by the Kennard–Stone method (Kennard and Stone, 1969). For the training set we obtained the equation

Table 1
Compounds, their descriptors, and observed values of log Pipm

Compound name	**E**	**S**	**A**	**B**	**V**	Observed	Ref.
Hydrocortisone	2.030	3.49	0.71	1.90	2.7976	−0.20	Hadgraft and Ridout (1987)
5,5-Diethylbarbituric acid	1.030	1.14	0.47	1.18	1.3739	−0.54	Hadgraft and Ridout (1987)
5-Ethyl-5-phenylbarbital	1.630	1.80	0.73	1.15	1.6999	0.32	Hadgraft and Ridout (1987)
5-Ethyl-5-*sec*-butylbarbituric acid	1.030	1.11	0.47	1.23	1.6557	0.50	Hadgraft and Ridout (1987)
5-Ethyl-5-(1-methylbutyl)barbituric acid	1.030	1.11	0.47	1.23	1.7966	0.97	Hadgraft and Ridout (1987)
Nicotine	0.865	0.92	0.00	1.08	1.3710	0.30	Hadgraft and Ridout (1987)
Isoquinoline	1.211	1.00	0.00	0.54	1.0443	1.44	Hadgraft and Ridout (1987)
Hydrocortisone-21-acetate	1.890	2.88	0.46	2.16	3.0951	1.84	Saket et al. (1985)
Hydrocortisone-21-propanoate	1.870	2.90	0.46	2.16	3.2360	2.42	Saket et al. (1985)
Hydrocortisone-21-pentanoate	1.830	2.98	0.46	2.16	3.5178	3.08	Saket et al. (1985)
Hydrocortisone-21-hexanoate	1.810	3.02	0.46	2.16	3.6587	3.56	Saket et al. (1985)
Hydrocortisone-21-octanoate	1.770	3.05	0.46	2.16	3.9405	4.28	Saket et al. (1985)
Cortisone	1.960	3.50	0.36	1.87	2.7546	1.42	Saket et al. (1985)
Cortisone-21-acetate	1.820	3.11	0.21	2.13	3.0521	1.77	Saket et al. (1985)
Cortisone-21-butanoate	1.780	3.45	0.21	2.13	3.3339	2.55	Saket et al. (1985)
Cortisone-21-hexanoate	1.740	3.86	0.21	2.13	3.6157	3.40	Saket et al. (1985)
Cortisone-21-octanoate	1.700	4.00	0.21	2.13	3.8975	4.12	Saket et al. (1985)
Estradiol	1.800	1.77	0.86	1.10	2.1988	2.30	Surber et al. (1990a)
Corticosterone	1.860	3.43	0.40	1.63	2.7389	0.81	Johnson et al. (1996)
Methyl 3-pyridinecarboxylate	0.710	1.13	0.00	0.71	1.0315	0.36	Dal Pozzo et al. (1991)
Ethyl nicotinate	0.667	1.10	0.00	0.73	1.1724	0.92	Dal Pozzo et al. (1991)
Butyl nicotinate	0.658	1.07	0.00	0.73	1.4542	2.12	Dal Pozzo et al. (1991)
Hexyl nicotinate	0.628	1.07	0.00	0.73	1.7360	3.32	Dal Pozzo et al. (1991)
Benzyl nicotinate	1.262	1.60	0.00	0.80	1.6393	2.42	Dal Pozzo et al. (1991)
2-Hydroxypropyl nicotinate	0.840	1.38	0.35	1.19	1.3720	−1.20	Dal Pozzo et al. (1991)
Triglycol nicotinate	0.950	1.58	0.37	1.78	1.9121	−1.72	Dal Pozzo et al. (1991)
2-Methoxyethyl nicotinate	0.690	1.20	0.00	1.14	1.3720	0.24	Dal Pozzo et al. (1991)
Methyltriglycol nicotinate	0.730	1.42	0.00	1.79	2.0530	−0.64	Dal Pozzo et al. (1991)
2-Hydroxybenzoic acid	0.890	0.84	0.71	0.38	0.9904	1.10	Fang et al. (2003) and Irwin and Smith (1991)
Acetylsalicylic acid	0.781	0.80	0.49	1.00	1.2879	0.20	Fang et al. (2003)
Ketoprofen	1.650	2.26	0.55	0.89	1.9779	1.88	Fang et al. (2003)
Naproxen	1.510	1.98	0.60	0.68	1.7821	2.37	Fang et al. (2003)
Diclofenac	2.275	1.22	0.63	0.96	2.0250	3.25	Fang et al. (2003)
Flurbiprofen	1.440	1.45	0.62	0.76	1.8389	2.83	Fang et al. (2003)
6-Mercaptopurine	1.750	1.70	0.40	1.00	0.9866	−1.71	Sloan and Wasdo (2003)
5-Fluorouracil	0.720	0.84	0.57	1.02	0.7693	−3.24	Sloan and Wasdo (2003)
Theophylline	1.500	1.60	0.54	1.34	1.2223	−2.13	Sloan and Wasdo (2003)
7-Methylcarbonyloxymethyltheophylline	1.930	2.34	0.00	1.65	1.7194	−0.85	Sloan and Wasdo (2003)
7-Ethylcarbonyloxymethyltheophylline	1.930	2.34	0.00	1.65	1.8603	−0.20	Sloan and Wasdo (2003)
7-Propylcarbonyloxymethyltheophylline	1.930	2.34	0.00	1.66	2.0012	0.38	Sloan and Wasdo (2003)
7-Butylcarbonyloxymethyltheophylline	1.930	2.34	0.00	1.68	2.1421	0.93	Sloan and Wasdo (2003)
7-Pentylcarbonyloxymethyltheophylline	1.930	2.34	0.00	1.69	2.2830	1.45	Sloan and Wasdo (2003)
7-*t*-Butylcarbonyloxymethyltheophylline	1.930	2.29	0.00	1.73	2.1421	0.75	Sloan and Wasdo (2003)
1-Methylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.18	1.2664	−1.74	Sloan and Wasdo (2003)
1-Ethylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.17	1.4073	−1.23	Sloan and Wasdo (2003)
1-Propylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.16	1.5482	−0.47	Sloan and Wasdo (2003)
1-Butylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.16	1.6891	0.08	Sloan and Wasdo (2003)
1-Pentylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.15	1.8300	0.82	Sloan and Wasdo (2003)
1-Heptylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.15	2.1118	1.77	Sloan and Wasdo (2003)
1-Nonylcarbonyloxymethyl-5-F-uracil	0.860	1.60	0.28	1.15	2.3936	3.14	Sloan and Wasdo (2003)
1-*t*-Butylcarbonyloxymethyl-5-F-uracil	0.860	1.55	0.28	1.22	1.6891	−0.01	Sloan and Wasdo (2003)
6-Methylcarbonyloxymethylmercaptopurine	1.834	2.00	0.16	1.40	1.4837	−0.83	Sloan and Wasdo (2003)

Table 1 (*Continued*)

Compound name	**E**	**S**	**A**	**B**	**V**	Observed	Ref.
6-Ethylcarbonyloxymethylmercaptopurine	1.830	2.00	0.16	1.40	1.6246	−0.25	Sloan and Wasdo (2003)
6-Propylcarbonyloxymethylmercaptopurine	1.830	2.00	0.14	1.42	1.7655	0.21	Sloan and Wasdo (2003)
6-Butylcarbonyloxymethylmercaptopurine	1.830	2.00	0.14	1.43	1.9064	0.73	Sloan and Wasdo (2003)
6-Pentylcarbonyloxymethylmercaptopurine	1.830	2.00	0.12	1.45	2.0473	1.19	Sloan and Wasdo (2003)
6-Heptylcarbonyloxymethylmercaptopurine	1.830	2.00	0.10	1.48	2.3291	2.23	Sloan and Wasdo (2003)
6,9-Bis(methylcarbonyloxymethymecaptopurine)	1.900	2.50	0.00	1.64	1.9808	0.26	Sloan and Wasdo (2003)
6,9-Bis(ethylcarbonyloxymethylmercaptopurine)	1.900	2.50	0.00	1.64	2.2626	1.30	Sloan and Wasdo (2003)
6,9-Bis(propylcarbonyloxymethymercaptopurine)	1.900	2.50	0.00	1.65	2.5444	2.67	Sloan and Wasdo (2003)
6,9-Bis(butylcarbonyloxymethylmercaptopurine)	1.900	2.50	0.00	1.68	2.8262	3.57	Sloan and Wasdo (2003)
6,9-Bis(pentylcarbonyloxymethymercaptopurine)	1.900	2.50	0.00	1.69	3.1080	4.67	Sloan and Wasdo (2003)
1-Methylaminocarbonyl-5-fluorouracil	1.130	1.85	0.39	0.94	1.1666	−1.09	Sloan and Wasdo (2003)
1-Ethylaminocarbonyl-5-fluorouracil	1.130	1.85	0.37	0.94	1.3075	−0.44	Sloan and Wasdo (2003)
1-Propylaminocarbonyl-5-fluorouracil	1.130	1.85	0.37	0.94	1.4484	0.14	Sloan and Wasdo (2003)
1-Butylaminocarbonyl-5-fluorouracil	1.130	1.85	0.37	0.94	1.5893	0.68	Sloan and Wasdo (2003)
1-Hexylaminocarbonyl-5-fluorouracil	1.130	1.85	0.37	0.92	1.8711	2.09	Sloan and Wasdo (2003)
1-Octylaminocarbonyl-5-fluorouracil	1.130	1.85	0.38	0.90	2.1529	3.19	Sloan and Wasdo (2003)
1-Methyloxycarbonyl-5-fluorouracil	0.870	1.65	0.18	1.09	1.1255	−1.72	Sloan and Wasdo (2003)
1-Ethyloxycarbonyl-5-fluorouracil	0.870	1.65	0.18	1.09	1.2664	−1.12	Sloan and Wasdo (2003)
1-Propyloxycarbonyl-5-fluorouracil	0.870	1.65	0.17	1.09	1.4073	−0.45	Sloan and Wasdo (2003)
1-Butyloxycarbonyl-5-fluorouraacil	0.870	1.65	0.16	1.09	1.5482	0.16	Sloan and Wasdo (2003)
1-Hexyloxycarbonyl-5-fluorouracil	0.870	1.65	0.14	1.09	1.8300	1.48	Sloan and Wasdo (2003)
1-Octyloxycarbonyl-5-fluorouracil	0.870	1.65	0.13	1.09	2.1118	2.46	Sloan and Wasdo (2003)
1-Methylcarbonyl-5-fluorouracil	0.870	1.55	0.11	0.89	1.0668	−0.73	Sloan and Wasdo (2003)
1-Ethylcarbonyl-5-fluorouracil	0.870	1.55	0.09	0.89	1.2077	−0.12	Sloan and Wasdo (2003)
1-Propyloxy-5-fluorouracil	0.870	1.55	0.07	0.90	1.3486	0.43	Sloan and Wasdo (2003)
1-Butyloxy-5-fluorouracil	0.870	1.55	0.05	0.91	1.4895	1.05	Sloan and Wasdo (2003)
1-Pentyloxy-5-fluorouracil	0.870	1.55	0.03	0.92	1.6304	1.58	Sloan and Wasdo (2003)
1-Heptyloxy-5-fluorouracil	0.870	1.55	0.00	0.94	1.9122	2.88	Sloan and Wasdo (2003)
3-Methylcarbonyl-5-fluorouracil	0.870	1.72	0.14	0.92	1.0668	−1.39	Sloan and Wasdo (2003)
3-Ethylcarbonyl-5-fluorouracil	0.870	1.72	0.13	0.93	1.2077	−0.97	Sloan and Wasdo (2003)
3-Propylcarbonyl-5-fluorouraci	0.870	1.72	0.12	0.92	1.3486	−0.01	Sloan and Wasdo (2003)
3-Butylcarbonyl-5-fluorouracil	0.870	1.72	0.11	0.93	1.4895	0.22	Sloan and Wasdo (2003)
3-Methylcarbonyloxymethyl-5-fluorouracil	0.863	1.70	0.30	1.10	1.2664	−1.62	Sloan and Wasdo (2003)
3-Ethylcarbonyloxymethyl-5-fluorouracil	0.860	1.70	0.30	1.10	1.4072	−1.03	Sloan and Wasdo (2003)
3-Propylcarbonyloxymethyl-5-fluorouracil	0.860	1.70	0.30	1.10	1.5481	−0.45	Sloan and Wasdo (2003)
3-Butylcarbonyloxymethyl-5-fluorouracil	0.860	1.70	0.29	1.11	1.6890	0.13	Sloan and Wasdo (2003)
3-Pentylcarbonyloxymethyl-5-fluorouracil	0.860	1.70	0.28	1.12	1.8299	0.74	Sloan and Wasdo (2003)
3-Heptylcarbonyloxymethyl-5-flurouracil	0.860	1.70	0.25	1.14	2.1117	1.90	Sloan and Wasdo (2003)
7-Methyloxycarbonyltheophylline	1.430	2.46	0.00	1.36	1.5785	−1.21	Sloan et al. (2000)
7-Ethyloxycarbonyltheophylline	1.430	2.46	0.00	1.36	1.7194	−0.52	Sloan et al. (2000)
7-Propyloxycarbonyltheophylline	1.430	2.46	0.00	1.36	1.8603	0.11	Sloan et al. (2000)
7-Butyloxycarbonyltheophylline	1.430	2.46	0.00	1.35	2.0012	0.74	Sloan et al. (2000)
7-Hexyloxycarbonyltheophylline	1.430	2.46	0.00	1.36	2.2830	1.76	Sloan et al. (2000)
7-Methylcarbonyltheophylline	1.500	2.41	0.00	1.36	1.5198	−0.80	Sloan et al. (2000)
7-Ethylcarbonyltheophylline	1.500	2.41	0.00	1.36	1.6607	−0.50	Sloan et al. (2000)
7-Propylcarbonyltheophylline	1.500	2.41	0.00	1.34	1.8016	0.38	Sloan et al. (2000)
7-Butylcarbonyltheophylline	1.500	2.41	0.00	1.35	1.9425	0.67	Sloan et al. (2000)
Fluoranthene	2.377	1.55	0.00	0.24	1.5846	5.50	MacLeod and Daugulis (2003)
Pyrene	2.808	1.71	0.00	0.28	1.5846	5.55	MacLeod and Daugulis (2003)
Acetic acid	0.265	0.64	0.62	0.44	0.4648	−1.41	Simonin and Hendrawan (2000)
2-Hydroxy-4-methoxybenzophenone	1.650	1.60	0.00	0.53	1.7391	4.45	Jiang et al. (1998)
Zidovudine	1.830	1.70	0.47	1.83	1.8192	−1.87	Seki et al. (1990)
O-Acetylzidovudine	1.740	1.80	0.28	2.01	2.1167	−0.65	Seki et al. (1990)
O-Butanoylzidovudine	1.740	1.81	0.30	2.01	2.3985	0.25	Seki et al. (1990)

Table 1 (*Continued*)

Compound name	**E**	**S**	**A**	**B**	**V**	Observed	Ref.
Arildone	1.390	2.30	0.00	1.22	2.9602	5.70	Baker and Hadgraft (1995)
N,*N*-Diethylpropanamide	0.304	1.27	0.00	0.80	1.2104	−0.40	Hayton et al. (1972)
Testosterone	1.540	2.59	0.32	1.19	2.3827	2.61	Roberts (1969) and James and Roberts (1968)
Prednisolone	2.210	3.10	0.71	1.92	2.7546	−0.08	Hayton et al. (1972)
Prednisone	2.140	3.58	0.36	1.89	2.7116	−0.42	Hayton et al. (1972)
Testosterone formate	1.500	2.45	0.00	1.16	2.5593	4.02	Roberts (1969) and James and Roberts (1968)
Testosterone acetate	1.450	2.21	0.00	1.28	2.6802	4.05	Roberts (1969) and James and Roberts (1968)
Testosterone propanoate	1.450	2.23	0.00	1.33	2.8211	4.53	Roberts (1969) and James and Roberts (1968)
Testosterone butanoate	1.450	2.28	0.00	1.35	2.9620	5.30	Roberts (1969) and James and Roberts (1968)
Testosterone pentanoate	1.450	2.28	0.00	1.35	3.1029	5.08	Roberts (1969) and James and Roberts (1968)
Melatonin	1.600	2.33	0.84	1.23	1.8251	−0.72	Kikwai et al. (2002)
Fluocinonide	2.000	2.55	0.29	2.50	3.4603	2.42	Ostrenga and Steinmetz (1970)
Fluocinolone acetonide	2.090	2.45	0.55	2.35	3.1626	1.58	Ostrenga and Steinmetz (1970)
4-Hydroxyacetanilide	1.060	1.63	1.04	0.86	1.1724	−1.69	Wadso and Sloan (2004)
4-Methoxycarbonyloxyacetanilide	0.970	1.75	0.27	1.15	1.5286	−0.16	Wadso and Sloan (2004)
4-Ethyloxycarbonyloxyacetanilide	0.970	1.75	0.25	1.17	1.6695	0.32	Wadso and Sloan (2004)
4-Propyloxycarbonyloxyacetanilide	0.970	1.75	0.23	1.18	1.8104	0.90	Wadso and Sloan (2004)
4-Butyloxycarbonyloxyacetanilide	0.970	1.75	0.20	1.18	1.9513	1.50	Wadso and Sloan (2004)
4-Hexyloxycarbonyloxyacetanilide	0.970	1.75	0.18	1.18	2.2231	2.71	Wadso and Sloan (2004)
4-Methoxyethyloxycarbonyloxyacetanilide	0.970	2.20	0.06	1.47	1.8691	−0.30	Wadso and Sloan (2004)
4-Methoxyisopropyloxycarbonyloxyacetanilide	0.970	2.17	0.06	1.47	2.0100	0.13	Wadso and Sloan (2004)
4-Methoxybenzoic acid	0.899	0.96	0.58	0.48	1.1313	0.94	Armstrong et al. (1979)
4-Ethoxybenzoic acid	0.880	1.00	0.56	0.52	1.2722	1.45	Armstrong et al. (1979)
4-Butoxybenzoic acid	0.880	0.97	0.56	0.53	1.5540	2.61	Armstrong et al. (1979)
4-Hydroxyphenylacetic acid	1.030	1.44	0.94	0.74	1.1313	−0.90	Armstrong et al. (1979)
4-Methoxyphenylacetic acid	0.880	1.21	0.56	0.73	1.2722	0.47	Armstrong et al. (1979)
4-Ethoxyphenylacetic acid	0.880	1.22	0.56	0.74	1.4131	0.98	Armstrong et al. (1979)
4-Hydroxyphenylpropanoic acid	1.030	1.41	0.94	0.76	1.2722	−0.36	Armstrong et al. (1979)
4-Methoxyphenylpropanoic acid	0.880	1.18	0.56	0.75	1.4131	1.02	Armstrong et al. (1979)
4-Methoxyphenylbutanoic acid	0.880	1.21	0.56	0.77	1.5540	1.44	Armstrong et al. (1979)
4-Hydroxybenzoic acid	0.930	0.90	0.81	0.56	0.9904	−0.26	Armstrong et al. (1979)
Trans-stilbene	1.450	1.05	0.00	0.34	1.5630	5.11	From solubilities determined in this work
Anthracene	2.290	1.34	0.00	0.28	1.4544	4.93	From solubilities determined in this work
Progesterone	1.450	3.29	0.00	1.14	2.6215	3.38	Nandi et al. (2003)
Indomethacin	2.236	1.35	0.57	1.57	2.5299	3.26	Nandi et al. (2003)

$$\log \text{Pipm} = -0.421 + 0.844\mathbf{E} - 1.200\mathbf{S} - 1.758\mathbf{A} - 4.165\mathbf{B} + 4.314\mathbf{V} \quad (3)$$

$N = 71$, $R = 0.991$, S.D. = 0.288, $F = 703$.

We then used Eq. (3) to predict log Pipm values for the 70 compounds in the test set, not used to obtain Eq. (3). Results are in Table 2. There is almost no bias in the predicted values, with AE = −0.001 only. The

Table 2
Predictions for the 70 compound test set from Eq. (3)

Average error, AE	−0.001
Average absolute error, AAE	0.197
Standard deviation, S.D.	0.259

Table 3
Coefficients in Eq. (2) for partitions from water to various solvents

Solvent	*e*	*s*	*a*	*b*	*v*
IPM	0.930	−1.153	−1.682	−4.093	4.249
Octanol	0.562	−1.054	0.034	−3.460	3.814
Isobutanol	0.514	−0.693	0.020	−2.258	2.776
Pentanol	0.575	−0.787	0.020	−2.837	3.249
Oleyl alcohol	−0.270	−0.528	−0.035	−4.042	4.204
Trichloromethane	0.157	−0.391	−3.191	−3.437	4.191
Hexane	0.579	−1.723	−3.599	−4.764	4.344
Hexadecane	0.667	−1.617	−3.587	−4.869	4.433
Cyclohexane	0.784	−1.678	−3.740	−4.929	4.577
Toluene	0.527	−0.720	−3.010	−4.824	4.545
Diethyl ether	0.561	−1.016	−0.226	−4.553	4.075
Ethyl acetate	1.157	−1.397	−0.054	−3.755	3.726
PGDP	0.501	−0.828	−1.022	−4.640	4.033
Olive oil	0.574	−0.798	−1.422	−4.984	4.210
Skin permeation	−0.106	−0.473	−0.473	−3.000	2.296
Skin partition	0.341	−0.206	−0.024	−2.178	1.850

AAE = 0.197 and the S.D. = 0.259 show that Eq. (3) can be used to predict further values of log Pipm to around 0.25 log unit. The observed values of log Pipm have been obtained in various laboratories, using different experimental methods, on different specimens. This will lead to increased errors in any correlations of data, and so it is not surprising that the predictive error of around 0.25 log units is larger than predictive errors for other water–solvent partitions.

The training and test sets can then be combined into one general equation, that we suggest should be used for predictions. The combined equation is:

$$\log \text{Pipm} = -0.605 + 0.930\mathbf{E} - 1.153\mathbf{S} - 1.682\mathbf{A} - 4.093\mathbf{B} + 4.249\mathbf{V} \quad (4)$$

$N = 141$, $R = 0.990$, S.D. = 0.265, $F = 1393$.

Note that the S.D. calculated for Eq. (3), 0.265, is not quite compatible with the S.D. calculated for the observed and predicted test, 0.259. The former has $N - p - 1$ degrees of freedom and the latter $N - 1$ degrees of freedom; p is the number of descriptors and N is the number of data points.

We can also use the coefficients in Table 2 to compare the water–IPM system with partitions in other water–solvent systems, as log P values. In Table 3 are given the coefficients in the general Eq. (2) for regressions of log P against the five descriptors; that is log P = SP in Eq. (2). Values of the coefficients in Eq. (2) are given for a number of water to solvent partitions (Abraham et al., 1994, 2004; Acree and Abraham, 2002; Zissimos et al., 2002). Also in Table 3 are coefficients for partition in the water–*stratum corneum* system, SP = log Psc or log Ksc, and coefficients for the rate of permeation of human skin from water, SP = log kp (Abraham and Martins, 2004).

Table 4
Comparison of the water–IPM system with other water to solvent systems, in terms of the distance parameter, *D*

Solvent	*D*	*D*
IPM	0	3.66
Olive oil	1.08	4.15
Ether	1.59	3.37
Toluene	1.65	4.85
Ethyl acetate	1.78	2.84
Octanol	1.92	2.50
Chloroform	1.97	4.14
Hexane	2.11	5.30
Hexadecane	2.13	5.36
Pentanol	2.40	1.67
Isobutanol	2.97	1.06
Skin partition, log Ksc	3.66	0.00
Skin permeation, log kp	2.83	1.16

By inspection of Table 3, it appears that the coefficients for the water to IPM system are reasonably close to those for the water to olive oil system. We can put the comparison of coefficients on a quantitative scale by a method previously described (Abraham and Martins, 2004). We regard the five coefficients for a given system as a point in five-dimensional space. The distance between the point for the given system and the point for any other system, *D*, can simply be calculated by Euclidean geometry. The smaller the distance between the points, the nearer are the sets of coefficients, and the closer the systems resemble each other chemically. Distances from the point for the water–IPM system are in Table 4. The very lipophilic ester, olive oil, is the nearest to IPM, not surprising, given that olive oil and IPM are both esters with long hydrocarbon chains.

There seems to be nothing exceptional about the solution chemistry of IPM. The coefficients in Eq. (4) reflect the chemical properties of IPM by comparison to those for water. As a solvent, it has a small dipolarity/polarisability ($s = -1.180$), it has moderate hydrogen bond basicity ($a = -1.711$), almost zero hydrogen bond acidity ($b = -4.029$), and is very hydrophobic ($v = 4.243$). These are just the properties

expected for a long chain ester, and are reasonably close to the corresponding coefficients for olive oil. The coefficients in Eq. (4) show exactly the solute factors that influence partition. Any polar factor, such as dipolarity/polarisability, hydrogen bond acidity and hydrogen bond basicity reduces partition into IPM, and any non-polar factor such as excess molar refraction and, especially, volume increases partition into IPM.

We can also compare the coefficients in Eq. (4) with those for partition between water and the *stratum corneum*, log Ksc or log Psc, and those for the rate of permeation from water through human skin, log kp, obtained previously (Abraham and Martins, 2004). There is very little connection between the coefficients for log Pipm, and those for partition between water and human *stratum corneum*, log Psc or log Ksc (Abraham and Martins, 2004) so that in chemical terms IPM is a very poor model for the *stratum corneum*. In Table 4 are the Euclidean distances, *D*, from the point for log Psc, on an arbitrary scale. The water–IPM system can be seen to be a very poor model, in chemical terms, for the water–*stratum corneum* system. Indeed, it seems to be difficult to select any partitioning system between water and common solvents as a suitable model for the water–*stratum corneum* system. Water to wet isobutanol is the nearest system to the water–*stratum corneum* system. As pointed out before (Abraham and Martins, 2004), one reason may be that wet isobutanol contains a considerable amount of water; and so appears to be chemically nearer to the *stratum corneum*, which, in contact with water, is heavily hydrated. There is also little connection between the coefficients for the water–IPM partition system and those for log kp, so that the former system is a poor chemical model for the rate of permeation through human skin. Whether or not the water–IPM system is a better model for partition from neat IPM into skin, or for permeation from neat IPM through skin, is another matter on which, at the moment, we cannot comment.

For the water–IPM system and partition from water into the *stratum corneum*, there is not enough common data to assess our predictions. For log Pipm and for log kp there are 28 common compounds, quite enough to test our prediction that the water–IPM system will be a poor model. We use the log kp data already available (Abraham and Martins, 2004), where kp is in units of cm s^{-1} at 37 °C, and refers to permeation of the neutral species. For the 28 common compounds we find:

$$\log \mathrm{kp} = -6.427 + 0.403 \log \mathrm{Pipm} \quad (5)$$

$N = 28$, $R = 0.800$, S.D. = 0.576, $F = 46.2$.

Eq. (5) is quite poor, as, indeed, we had predicted. A referee has instructed us to include a double regression with log Pipm and compound molecular weight, MW, for which we find:

$$\log \mathrm{kp} = -5.427 + 0.563 \log \mathrm{Pipm} - 0.00465\,\mathrm{MW} \quad (6)$$

$N = 28$, $R = 0.923$, S.D. = 0.378, $F = 71.6$.

There is a very significant improvement of Eq. (6) over Eq. (5). However, in our view it is much more informative to use a coherent set of descriptors, as in Eqs. (2) and (4), to analyse free energy related processes such as transfer and rates of transfer between phases. Only in this way can processes be compared on the lines illustrated by the data in Table 4.

4. Conclusion

The water–IPM system is shown to be a poor chemical model for partition from water to the *stratum corneum* and for permeation from water through human skin. The solute factors that influence partition into IPM are quantitatively not the same as those that control partition into the *stratum corneum*. The solution properties of IPM are quite normal, and are those expected for a long chain hydrophobic ester.

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