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Modeling Free Energies of Solvation in Olive Oil

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Abstract: Olive oil partition coefficients are useful for modeling the bioavailability of drug-like compounds. We have recently developed an accurate solvation model called SM8 for aqueous and organic solvents (Marenich, A. V.; Olson, R. M.; Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2007**, *3*, 2011) and a temperature-dependent solvation model called SM8T for aqueous solution (Chamberlin, A. C.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2008**, *112*, 3024). Here we describe an extension of SM8T to predict air−olive oil and water−olive oil partitioning for drug-like solutes as functions of temperature. We also describe the database of experimental partition coefficients used to parametrize the model; this database includes 371 entries for 304 compounds spanning the 291−310 K temperature range.

Keywords: Bioavailability; membrane partitioning; continuum model; lipid−water partitioning

1. Introduction

Computation is increasingly used to predict absorption, distribution, permeability, and other measures of bioavailability and uptake for drug candidates, in some cases prior to synthesis.[1−13] Bioavailability is often predicted using some measure of the lipophilicity of the drug; traditionally octanol−water partition coefficients are used.[14] However, in cases where the drug molecules have not yet been synthesized, the partition coefficients (or, alternatively, the solubilities and vapor pressures) must be estimated. One class of solvation models, called implicit or continuum solvation models,[15−18] has proven particularly useful for prediction or estimation of a number of solute properties including free

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energies of partitioning between different phases (most commonly the gas phase and liquid solution). Currently, implicit solvation models based on quantum mechanical (QM) solute models can reproduce free energies of solvation for organic molecules in aqueous solution at room temperature and pressure to within ~0.6 kcal/mol.[19]

Past research has shown that water−olive oil[20−22] and air−olive oil[23−26] partition coefficients exhibit a correlation with drug efficacy. In particular, it has been shown that these partition coefficients correlate with the partitioning of the drugs into rat and human tissue.[27−32] As noted above, octanol/water partition measurements can also provide useful and well-characterized correlates with bioavailability and absorption. However, Poulin et al.[28b] have shown that olive/oil−water partition measurements are clearly superior to octanol/water for the prediction of adipose tissue plasma partition coefficients. This is not surprising since adipose tissue is primarily triglyceride. Adipose tissue partition is a pharmacologically important parameter because it can dominate the volume of distribution of lipid soluble drugs. The availability of an accurate *theoretical* means to estimate olive oil/water partitioning is particularly important because of the very limited experimental data that is available for this parameter.

Modeling pharmacokinetic properties like bioavailability is not the only reason for interest in solubility and partitioning in olive oil; not only are olive oil formulations prime examples of lipid-based drug delivery systems, which are often advantageous,[33−38] but bioderived oils are also receiv-

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ing attention as green solvents for liquid–liquid extractions[39] and nanoparticle synthesis.[40]

Data on olive oil partitioning are sparser than octanol partitioning data, and thus a predictive model can be very useful. The earliest attempts to model olive oil partitioning were based on linear free energy relations.[29,41–45] (These methods have also been applied to general triglyceride solvents.[46]) Although linear free energy modeling is very powerful,[14,47] it suffers from difficulties in modeling cross terms in multifunctional solutes. For this reason QM-based models are expected to provide higher accuracy for general solutes. Applying an implicit solvent model to olive oil is particularly challenging because most implicit solvent models are developed for 298 K, but the most useful partition coefficients are those for basal body temperature (310 K). The variation of the free energy of solvation as a function of temperature has been included in only a few implicit solvation models.[48–50] Also, since olive oil is a mixed solvent containing both triglycerides and fatty acids, it is not straightforward to relate its solvating properties to those of pure solvents.

Table 1. Composition of Olive Oil

component	% of total composition	ref
triglycerides	98–99%	114
fatty acids	0.6–1.4%	115
squalene, triterpene alcohols, steroid tocopherols, polyphenols, trace aromatic compounds	1–2%	116

Table 2. Experimental Determinations of Olive Oil Descriptors

temp (K)	value	conditions	ref
	Dielectric Constant (ε)		
295	3.029	fresh	84
295	3.99	air and light	84
295	3.47	moisture and light	84
298	3.11		83
298	3.15		85
298	3.098	unrefined	117
298	3.093	refined	117
308	3.036	unrefined	117
308	3.048	refined	117
	Refractive Index (n)		
293	1.468		86
298	1.465		85
298	1.467	unrefined	117
298	1.467	refined	117
a	1.469–1.484		115
	Surface Tension (γ)		
288.65	32.2		87
293–320	$S_\gamma = 33.377 - 0.057(T - 273.15)$		92
295	33		93
300	34.2		88
309	33.6		88
303	25.8	refined	91
a	33		90
a	33		89

[a] Temperature not given.

Water–olive oil partitioning is thus an interesting subject for the application of solvation model 8 with temperature

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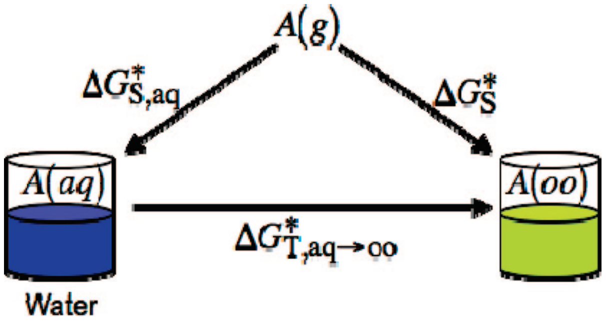

Figure 1. Hess's cycle for the calculation of free energies of solvation in olive oil.

Table 3. Coefficients of Temperature Dependence (ccal Å^{-2} mol^{-1} K^{-1}) in SM8T-OO[a]

	C	O	F	S
B-coefficient	24.03	24.03	−47.23	−24.43
C-coefficient	−168.04	−168.04	7.02	−3.66

	Cl	Br	HC	HN
B-coefficient	−47.23	−47.23	0.26	−335.28
C-coefficient	7.02	7.02	−167.95	0

	HO	CC	CC2	NC
B-coefficient	214.95	24.03	24.03	74.66
C-coefficient	−67.79	−167.95	5.50	0

	NC2	OC	OS
B-coefficient	−18.28	24.03	81.47
C-coefficient	0	−67.79	0

[a] See Supporting Information for explanation of SM8T atom types.

dependence[50] (SM8T), which was developed to predict aqueous free energies of solvation of neutral compounds containing the atoms H, C, N, O, F, S, Cl, or Br and was trained to the temperature range 273 to 373 K. The present article provides the first extension of SM8T to a nonaqueous solvent, namely, olive oil. A necessary first step for this development is to extend the earlier solvation model 8[19] (SM8), defined only at 298 K but including organic solvents as well as aqueous solution, to olive oil.

2. SM8 and SM8T

To accurately predict the partition coefficients of solutes in olive oil it is necessary to use a slightly modified version of SM8T, the explanation of which first requires a brief summary of SM8[19] and SM8T.[50] For a more detailed explanation of SM8 and SM8T see the original publications.[19,50]

2.A. SM8. Solvation model 8 (SM8) is the most recent version of the SM*x* series.[19,51−57] In SM8 the standard-state free energy of solvation is computed as the sum of three contributions,[19]

$$\Delta G_S^* = \Delta G_{ENP} + G_{CDS} + \Delta G_{conc}^* \qquad (1)$$

where ΔG_{ENP} is the free energy contribution due to a well-defined model of the electrostatic interactions between the solute and the bulk solvent, G_{CDS} is a parametrized term designed to account for first-solvation-shell effects and for approximations used in the calculation of ΔG_{ENP}, and ΔG_{conc}^* is the contribution due to any change in the standard-state solute concentration in solution as compared to the gas phase.

In implicit solvation models, such as the SM*x* series, the bulk electrostatic contribution to the free energy of solvation is computed by approximating the solvent as a homogeneous continuous dielectric medium characterized by its experimental temperature-dependent bulk dielectric constant, ε. SM8 employs the generalized Born equation,[51,58−61] wherein the solute charge distribution is approximated by a set of atom-centered partial atomic charges, computed using charge model 4[56,62,63] (CM4), and the solute is distinguished from

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Table 4. Olive Oil Model for Entire Data Set of Free Energies of Solvation[a]

data set	no. of points	α	MSE	MUE	RMSE
entire data set: no temperature coefficients	335	0.19	−0.30	0.93	1.29
310 K: no temperature coefficients	227	0.28	−0.23	0.81	1.16
298 K: no temperature coefficients	24	0.02	−0.15	0.56	0.70
293 K: no temperature coefficients	70	0.07	−0.81	1.31	1.70
entire data set: with temperature coefficients	335	0.10	−0.28	0.87	1.21

[a] Errors in kcal/mol.

Table 5. Comparison of the Internal Errors to the Temperature Dependence of the Experimental Free Energies of Solvation (kcal/mol)

variation between exptl points for a compd at:	mean unsigned deviation	root mean squared deviation
the same temperature	0.26	0.34
different temperatures	0.27	0.33

the surrounding solvent by a series of atom-centered spherical cavities depending upon an atomic radius called the intrinsic Coulomb radius. In SM8 the intrinsic Coulomb radius for each atom depends upon atomic number and Abraham's hydrogen bond acidity, α, of the solvent (vide infra).

G_{CDS} is an empirical term designed to minimize the deviation between experimental and calculated values of ΔG_{ENP}; it accounts for all solvation phenomena not included in the bulk electrostatic term or ΔG^*_{conc}. Previous studies[53,64−69] have shown that the free energies associated with these phenomena closely correlate with the solvent accessible surface areas[70−73] (SASAs) of the solute atoms. The atomic radii used to define the SASA for the G_{CDS} term are determined using the atomic radii of Bondi[74] for the atoms of the solute and a solvent radius of 0.4 Å. G_{CDS} accounts for the specific non-bulk-electrostatic effects of various functional groups upon the free energy of solvation by using functions of the solute geometry. For nonaqueous solvents, the SM8 surface tensions of atoms, $\tilde{\sigma}_{Z_k}$, and of functional groups, $\tilde{\sigma}_{Z_k Z_m \tau}$, are functions of solvent properties including the following: the hydrogen bond acidity, α, and basicity β, of the solvent, which are modeled by the $\Sigma\alpha_2$ and $\Sigma\beta_2$ descriptors of Abraham;[75−78] the macroscopic surface tension (in units of cal mol^{-1} Å^{-2}), γ; the solvent refractive index at 293 K at the wavelength

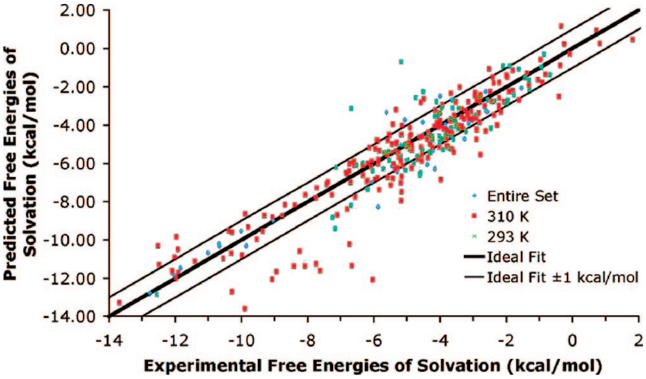

Figure 2. Comparison of the predicted and experimental free energies of solvation in olive oil over the entire data set and for the two largest single-temperature subsets.

Table 6. Errors (kcal/mol) in SM8T-OO and the Temperature Independent Model, α = 0.19, Compared to Abraham and Ibrahim[45] for Free Energies of Solvation (kcal/mol) for Abraham's Data Set for Compounds in Olive Oil at 310 K

	SM8T-OO	α = 0.19	ref 45
MSE	−0.13	−0.21	0.04
MUE	0.62	0.65	0.21
RMSE	0.76	0.81	0.32

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Table 7. Comparison of SM8T-OO and the Temperature Independent Model, $\alpha = 0.19$, to Average Experimental Free Energies of Solvation (kcal/mol) for Compounds of Pharmacologic Interest in Olive Oil at Various Temperatures (K)

	$\alpha = 0.19$	SM8T-OO	expt	temp
Alcohols				
thymol	−7.54	−7.80	−7.76	293.00
propofol	−7.21	−6.54	−6.32	310.00
Amines				
procaine	−11.63	−11.17	−7.75	310.00
morphine	−13.65	−11.93	−11.98	310.00
codeine	−−12.07	−10.72	−9.98	310.00
imipramine	−12.72	−11.26	−6.66	310.00
Heterocycles Containing N				
nicotine	−8.09	−6.70	−5.89	310.00
Compounds Containing Both OH and Amide Functionality				
salicylamide	−10.76	−10.48	−11.92	293.00
Compounds Containing Both Ether and Amide Functionality				
phenacetin	−10.71	−11.10	−11.41	293.00
Heterocycles Containing N with Amide Functional Groups (i.e., Barbitals and Xanthines)				
caffeine	−12.78	−12.65	−10.28	310.00
veronal	−11.17	−11.36	−8.08	292.00
veronal	−11.16	−11.35	−8.41	293.00
probarbital	−10.41	−10.59	−8.24	293.00
amobarbital	−11.83	−12.04	−9.07	293.00
antipyrine	−10.90	−10.16	−6.74	310.00
pentobarbital	−11.47	−11.65	−8.94	293.00
phenobarbital	−13.81	−14.26	−10.92	293.00
phenobarbital	−13.63	−13.53	−9.90	310.00
phenytoin	−15.11	−15.06	−12.66	310.00
Compounds Containing Both F and Ether Functionality				
desflurane	−0.65	−1.09	−1.80	310.00
sevoflurane	−0.99	−1.44	−2.41	310.00
Compounds Containing Both Cl and OH Functionality				
chloralhydrate	−7.42	−7.44	−5.15	309.00
chloralhydrate	−7.48	−7.37	−5.84	291.00
Compounds Containing F, Cl, and Ether Functionality				
methoxyflurane	−3.56	−4.05	−4.05	310.00
isoflurane	−1.81	−2.37	−2.78	310.00
enflurane	−2.02	−2.57	−2.85	310.00
Compounds Containing Both F and Br				
teflurane	−2.17	−2.74	−2.07	310.00
halopropane	−3.13	−3.53	−3.56	310.00
Compounds Containing F, Cl, and Br				
halothane	−3.31	−4.00	−3.35	310.00

Table 8. Errors in SM8T-OO and the Temperature Independent Model, $\alpha = 0.19$, for Compounds of Pharmacologic Interest in Olive Oil

	error of SM8T-OO		error of $\alpha = 0.19$	
	ΔG_S (kcal/mol)	log K	ΔG_S (kcal/mol)	log K
MSE	−1.03	−0.76	−1.46	−1.07
MUE	1.25	0.91	1.97	1.45
RMSE	1.86	1.36	2.40	1.76

of the Na D line, n; the fraction of the nonhydrogenic atoms in the solvent that are aromatic carbon atoms, ϕ; and the fraction of the nonhydrogenic atoms in the solvent molecules that are electronegative halogens, ψ.

2.B. SM8T. Solvation model 8 with temperature dependence (SM8T)[49,50] is designed to account for the temperature dependence of free energies of solvation for compounds containing H, C, N, O, F, S, Cl, or Br in the range 273 to 373 K. The change in the solvation free energy relative to the reference temperature (T_0) of 298 K is computed as

$$\Delta\Delta G^*_{S} = \Delta\Delta G_{ENP}(T) + \Delta G_{CDS}(T) + \Delta\Delta G^*_{conc} \qquad (2)$$

where $\Delta\Delta G_{ENP}$ is the temperature dependence associated with ΔG_{ENP}, ΔG_{CDS} is the temperature dependence of first-solvation-shell phenomena (and other approximations associated with use of the generalized Born equation), and $\Delta\Delta G^*_{conc}$ is the temperature dependence of the free energy contribution due to any change in standard-state concentration on going from the gas phase into solution.

As noted above, ΔG_{ENP} depends on the partial atomic charges of the solute, the intrinsic Coulomb radii of the solute atoms, the solute geometry, and the dielectric constant of the solvent, all of which might in principle depend on temperature. In SM8T, the temperature dependence of $\Delta\Delta G_{ENP}$ is restricted to only the dielectric constant, $\varepsilon(T)$.

The ΔG_{CDS} term is computed using parameters designed to reproduce the effects of the entropy of solvation and the heat capacity of solvation as well as all residual effects (for example, systematic errors in the modeled charges or the temperature dependence of the solute−solvent boundary) beyond those accounted for by $\Delta\Delta G_{ENP}$. A subset of the same functions[16,79,80] and solvent accessible surface areas that are used in SM8 to compute G_{CDS} are used to calculate ΔG_{CDS}.

3. Olive Oil Model Development

Olive oil is a mixed solvent with a variable composition; see Table 1. Furthermore, its properties can vary significantly depending on the source and the storage conditions, as shown in Table 2. Olive oil is not necessarily well approximated as a homogeneous continuum; there may be preferential

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Table 9. Comparison of Predictions of SM8T-OO and the Temperature Independent Model, $\alpha = 0.19$, to Average Experimental Free Energies of Transfer from Olive Oil to Water, $\Delta G_{\mathrm{aq}\rightarrow\mathrm{oo}}$ (kcal/mol) at Various Temperatures (K)

	$\alpha = 0.19$	SM8T-OO	expt	temp
Hydrocarbons				
ethene	−1.47	−1.33	−1.62	310
cyclopropane	−3.03	−2.83	−2.45	310
benzene	−3.36	−3.68	−3.15	293
phenanthrene	−5.78	−6.43	−6.52	293
Alcohols				
methanol	1.90	1.90	2.88	293
ethanol	0.61	0.61	2.11	293
ethanol	0.32	0.87	1.89	310
ethanol	0.32	0.87	1.89	310
1,2-ethanediol	2.68	2.97	4.71	298
1-propanol	−0.16	−0.18	1.23	293
2-propanol	−0.11	−0.16	1.87	293
1,2-propanediol	1.83	1.75	3.93	293
glycerol	3.59	3.51	5.88	293
1-butanol	−0.68	−0.69	0.40	293
2-butanol	−0.96	−0.97	0.51	293
1,3-butanediol	1.32	1.34	3.36	293
1,4-butanediol	1.35	1.38	3.80	293
2,3-butanediol	0.59	0.57	3.50	293
1,5-pentanediol	0.84	0.83	3.13	293
phenol	−1.19	−1.47	−1.11	293
1,6-hexanediol	−0.05	−0.03	3.08	293
thymol	−4.20	−4.47	−3.95	293
menthol	−4.56	−4.61	−3.31	293
propofol	−6.17	−5.50	−5.20	310
Ethers				
ethyl vinyl ether	−1.68	−1.85	0.43	293
diethyl ether	−1.55	−1.57	−0.52	293
paraldehyde	0.26	0.20	−0.40	293
1,1-diethoxyethane	−1.40	−1.41	−1.28	293
1,4-dimethoxybenzene	−1.82	−2.20	−3.09	293
Compounds Containing Both OH and Ether Functionality				
2-methoxyethanol	2.09	2.11	3.19	293
2-ethoxyethanol	0.30	0.30	2.44	293
diethylene glycol monomethyl ether	1.08	−0.01	3.37	293
diethylene glycol monoethyl ether	−0.01	1.08	3.15	293
piperonal	0.71	0.09	−2.08	293
Aldehydes and Ketones				
acetone	0.50	0.27	0.95	293
2,5-hexanedione	−0.59	−0.97	1.55	293
Compounds Containing OH, Ether, and Aldehyde Functionality				
vanillin	2.16	1.70	−0.64	293
Carboxylic Acids				
acetic acid	1.26	1.16	2.15	298
acetic acid	1.26	1.16	1.84	298
propanoic acid	−0.02	−0.10	1.13	298
butanoic acid	−0.66	−0.74	0.50	298
butanoic acid	−0.66	−0.74	0.30	298
pentanoic acid	−1.44	−1.53	−0.58	298
pentanoic acid	−1.44	−1.53	−0.68	298
3-pentanoic acid	−1.48	−1.54	−0.38	298
hexanoic acid	−2.27	−2.36	−1.18	298

Table 9. continued

	$\alpha = 0.19$	SM8T-OO	expt	temp
salicylic acid	0.77	0.34	−1.42	293
heptanoic acid	−2.97	−3.14	−2.40	296
Esters				
methylacetate	0.51	0.20	0.52	293
ethylacetate	−0.30	−0.61	−0.71	293
ethylacetoacetate	0.61	0.15	−0.06	293
coumarin	0.25	−0.45	−1.72	293
triacetin	5.06	4.26	0.74	293
triacetin	5.06	4.26	0.51	293
Amines				
procaine	−2.88	−2.43	0.66	310
morphine	0.09	1.81	1.50	310
codeine	−1.07	0.28	0.08	310
imipramine	−8.68	−7.22	−2.75	310
Heterocycles Containing N				
pyridine	−0.39	−0.81	0.03	293
nicotine	−2.19	−0.81	−0.47	310
acridine	−3.48	−2.48	−3.26	309
1-aminoacridine	−1.39	−1.79	−2.54	293
2-aminoacridine	−1.64	−1.99	−2.79	293
3-aminoacridine	−0.90	−1.25	−2.65	293
4-aminoacridine	−2.46	−2.84	−4.37	293
aminopyrine	−1.99	−2.71	0.84	293
Amides, Ureas, and Thioureas				
formamide	4.90	5.23	4.44	293
urea	5.81	6.59	5.41	293
thiourea	3.26	3.81	4.14	293
acetamide	3.74	4.16	4.37	293
methylurea	4.25	4.60	4.76	293
acrylamide	2.80	3.18	3.46	293
butylamide	1.94	2.36	2.86	293
pentanamide	1.17	1.57	1.63	293
benzamide	1.20	1.01	0.62	293
benzamide	0.92	1.30	0.51	309
acetanilide	0.58	0.20	−0.21	293
Carbamates				
methylcarbamate	4.88	5.45	1.98	293
methylcarbamate	4.88	5.45	2.13	293
urethane	4.08	4.65	1.20	293
urethane	4.08	4.65	1.45	293
N-phenylurethane	−1.04	−1.34	−2.96	293
Compounds Containing Both OH and Amide Functionality				
salicylamide	1.64	1.92	−0.61	293
Compounds Containing Both Ether and Amide Functionality				
phenacetin	0.80	0.41	−0.73	293
Heterocycles Containing N with Amide Functional Groups (i.e., Barbitals and Xanthines)				
caffeine	−1.96	−1.83	1.52	310
veronal	−1.17	−1.36	1.36	293
veronal	−1.17	−1.36	0.99	293
probarbital	−1.21	−1.38	0.20	293
amobarbital	−2.72	−2.93	−0.65	293
antipyrine	−1.58	−0.84	1.97	310
pentobarbital	−2.98	−3.16	−0.91	293

Table 9. continued

	α = 0.19	SM8T-OO	expt	temp
phenobarbital	−2.76	−3.21	−0.26	293
phenobarbital	−3.27	−3.18	0.08	310
phenytoin	−4.01	−3.97	−2.36	310
Cyanides				
dimethylcyanamide	−1.07	−2.02	1.62	293
cyanoguanidine	−0.76	−1.79	4.72	293
Compounds Containing Cl				
carbon tetrachloride	−4.25	−3.91	−3.77	293
chloroethane	−1.95	−1.85	−2.18	293
2-chlorobiphenyl	−6.32	−6.51	−6.95	298
2,4′-dichlorobiphenyl	−7.07	−7.22	−8.08	298
2,3,4,5-tetrachlorobiphenyl	−8.29	−8.45	−9.13	298
2,2′,5,5′-tetrachlorobiphenyl	−8.22	−8.32	−8.09	298
2,2′,6,6′-tetrachlorobiphenyl	−8.10	−8.22	−8.46	298
3,3′,4,4′-tetrachlorobiphenyl	−8.52	−8.67	−10.01	298
3,3′,4,4′,5-pentachlorobiphenyl	−9.25	−9.39	−10.77	298
2,2′,3,3′,4,4′-hexachlorobiphenyl	−9.73	−9.87	−10.26	298
2,2′,4,4′,6,6′-hexachlorobiphenyl	−9.77	−9.82	−10.06	298
3,3′,4,4′,5,5′-hexachlorobiphenyl	−10.19	−10.32	−10.84	298
2,2′,3,3′,4,4′,5,5′-octachlorobiphenyl	−11.19	−11.29	−11.48	298
decachlorobiphenyl	−11.76	−11.85	−11.77	298
Compounds Containing Both Cl and OH Functionality				
chloralhydrate	−0.90	−1.39	0.94	291
chloralhydrate	−1.37	−0.80	1.09	309
Compounds Containing Both Cl and Carboxylic Acid Functionality				
chloroacetic acid	0.07	0.05	1.56	298
dichloroacetic acid	−1.16	−1.18	0.43	298
3-chloroproprionic acid	−0.71	−0.74	0.75	298
Compounds Containing Both Cl and Nitro Functionality				
chloropicrin	−1.79	−1.80	−3.43	293
Compounds Containing F, Cl, and Ether Functionality				
methoxyflurane	−3.18	−3.67	−3.29	310
Compounds Containing Br				
bromoethane	−2.51	−2.45	−2.47	293
Compounds Containing Both Br and Carboxylic Acid Functionality				
bromoacetic acid	−0.09	−0.19	1.02	298
2-bromopropanoic acid	−1.04	−1.14	0.26	298
2-bromobutanoic acid	−1.56	−1.78	−0.20	293

solvation of certain functionalities by one or another component of the solvent. The primary difference between the two major components of the solvent, fatty acids and triglycerides, is the presence or absence of a hydroxyl group, which is a hydrogen-bond donor. By using Abraham's hydrogen-bond acidity and basicity terms to characterize first-solvation-shell interactions, the SMx models account for hydrogen bonding not only in the bulk electrostatic component of the solvation free energy but also in the non-bulk-electrostatic term.

3.A. Database Development. We first developed a database of experimental free energies of solvation in olive oil. These were obtained from air−olive oil partition coefficients and from combinations of water−olive oil partition coefficients with air−water partition coefficients. The free energy of solvation dictates the equilibrium of a solute (A) between the gas phase (g) and olive oil (oo):

$$A(\mathrm{g}) \xrightarrow{\Delta G_{\mathrm{S}}^{*}} A(\mathrm{oo}) \qquad (3)$$

All the free energies of solvation reported here correspond to a 1 M ideal gas and a 1 M ideal solution; such free energies of solvation are denoted as $\Delta G_{\mathrm{S}}^{*}$. This choice of standard states eliminates any change in the translational entropy (called librational entropy in solution) upon solvation, as discussed by Ben-Naim,[81] and therefore $\Delta G_{\mathrm{conc}}^{*}$ and $\Delta\Delta G_{\mathrm{conc}}^{*}$ in eqs 1 and 2 are both zero. Experimentally determined standard-state free energies of solvation are

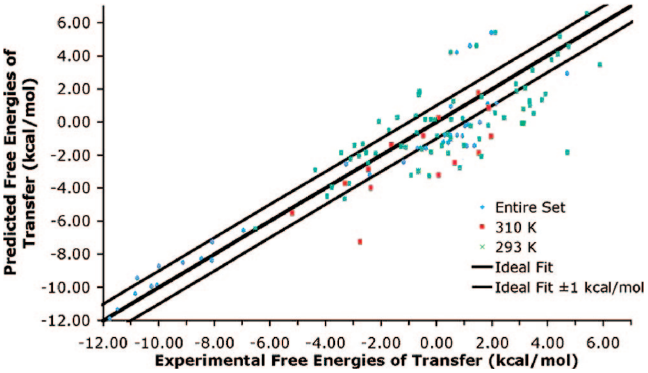

Figure 3. Comparison of the predicted and experimental free energies of transfer from water to olive oil over the entire data set and for the two largest single-temperature subsets.

Table 10. Errors in SM8T-OO and the Temperature Independent Model, α = 0.19, for Free Energies of Transfer from Olive Oil to Water, ΔG_T (kcal/mol)

	SM8T-OO		α = 0.19	
	ΔG_T (kcal/mol)	log *K*	ΔG_T (kcal/mol)	log *K*
MSE	−0.57	−0.41	−0.56	−0.41
MUE	1.45	1.06	1.51	1.11
RMSE	1.85	1.36	1.88	1.38

usually reported for a 1 bar ideal gas and a 1 M ideal solution. The standard-state free energy of solvation for a gas-phase standard state of 1 bar is

$$\Delta G_S^\circ = \Delta G_S^* + RT\ln(RTC^*/P^\circ) \tag{4}$$

where *R* is the gas constant, C^* is 1 M, P° is 1 bar, and *T* is the temperature in kelvins. The second term on the right-hand side of eq 4 equals 1.89 kcal/mol at 298 K and 2.00 kcal/mol at 310 K.

For an infinitely dilute solution, the partition coefficient for process 3 is the Henry's law constant, K_H^*, and ΔG_S^* is computed as

$$\Delta G_S^* = RT\ln(K_H^*/K^*) \tag{5}$$

where $K^* = 1$ since we use 1 M as the concentration in both phases. and *T* is the temperature at which the measurement was taken. Henry's law constants are tabulated using a variety of units,[82] each of which corresponds to a different standard state; all Henry's law constants used in this work were converted to K_H^*, that is, molarity units.

Alternatively, the free energies of solvation in olive oil may be computed from a combination of the free energy of solvation in aqueous solution, $\Delta G_{S,aq}$, and the free energy of transfer from water to olive oil, $\Delta G_{T,aq\to oo}$. (See Figure 1.) The free energy of solvation in aqueous solution was computed either by using experimental data[49] or by using SM6[56] to compute free energies in aqueous solution. (SM6 is very similar to SM8 for aqueous solutions.) The free energy of transfer, $\Delta G_{T,aq\to oo}$, for various solutes was computed from the water−olive oil partition coefficients, $K^*_{aq\to oo}$, as

$$\Delta G^*_{T,aq\to oo} = RT\ln(K^*_{aq\to oo}/K^*) \tag{6}$$

Using a combination of experimental and computed free energies of solvation, we developed a database based on 371 free energies of solvation, each of which corresponds to an experimental value for a particular solute at a given temperature. Prior to training, multiple measurements for the same solute at the same temperature were averaged, yielding 335 energies in olive oil for 304 compounds. (See Supporting Information for a list of all of the compounds in the data set, the temperatures at which the free energies of solvation were determined, and the experimental sources.)

3.B. Fitting the Data. SM8 has been developed for a wide range of organic solvents for which the necessary solvent descriptors are available. Three of the solvent properties required for a prediction using SM8 are available for olive oil from experiment, namely, ε, γ, and *n*. In the case of ε, it is possible to fit those data[83−85] that do not involve degradation of the oil from exposure to air and/or light using linear functions of temperature:

$$\varepsilon = 3.109 - 0.0074(T - 298) \tag{7}$$

In the case of *n* and γ, in the spirit of SM8 and SM8T the experimental measurements at 298 K were used throughout, and hence we used the constant value of 1.468[86] for *n* and 32.80 for γ.[87−93] The SM8 descriptors ϕ and ψ were set to zero since olive oil is primarily composed of triglycerides and fatty acids having neither halogens nor aromatic carbon atoms. Given these major components of olive oil, we set β equal to 0.45, which is characteristic of both types of compounds.[76,94−96] The α descriptor, however, cannot be

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Table 11. Breakdown of the Contributions to the Free Energy of Solvation in Olive Oil Based upon Functional Group at 298 K (kcal/mol)

	F	Cl	Br	ether	remainder	total
Bulk Electrostatic						
desflurane	0.70			0.43	−2.03	−0.90
enflurane	0.73	0.08		0.37	−2.06	−0.88
halopropane	1.03		0.04		−2.05	−0.98
halothane	0.13	0.05	0.04		−0.71	−0.49
sevoflurane	0.85			0.59	−2.76	−1.32
Non-Bulk Electrostatic						
desflurane	0.98			−0.64	0.08	0.43
enflurane	0.82	−1.13		−0.56	−0.09	−0.96
halopropane	0.63		−2.01		−0.53	−1.91
halothane	0.48	−1.10	−1.93		−0.20	−2.75
sevoflurane	1.07			−0.66	0.15	0.56
Total						
desflurane	1.68	0.00	0.00	−0.21	−1.95	−0.47
enflurane	1.55	−1.05	0.00	−0.19	−2.15	−1.84
halopropane	1.66	0.00	−1.97	0.00	−2.58	−2.89
halothane	0.61	−1.05	−1.89	0.00	−0.91	−3.24
sevoflurane	1.92	0.00	0.00	−0.07	−2.61	−0.76

Table 12. Breakdown of the Contributions to the Free Energy of Solvation in Water Based upon Functional Group at 298 K (kcal/mol)

	F	Cl	Br	ether	remainder	total
Bulk Electrostatic						
desflurane	0.39			0.91	−5.33	−4.02
enflurane	0.42	0.11		0.81	−5.09	−3.75
halopropane	0.84		−0.01		−4.25	−3.42
halothane	−0.18	0.08	0.06		−1.33	−1.37
sevoflurane	0.04			0.90	−5.63	−4.68
Non-Bulk Electrostatic						
desflurane	4.28			−0.50	0.57	4.35
enflurane	3.56	0.00		−0.40	0.44	3.60
halopropane	2.73		−0.83		0.43	2.33
halothane	2.09	0.00	−0.80		0.14	1.43
sevoflurane	4.66			−0.69	0.81	4.78
Total						
desflurane	4.67	0.00	0.00	0.41	−4.76	0.33
enflurane	3.98	0.11	0.00	0.41	−4.65	−0.15
halopropane	3.57	0.00	−0.84	0.00	−3.82	−1.09
halothane	1.91	0.08	−0.74	0.00	−1.19	0.06
sevoflurane	4.70	0.00	0.00	0.21	−4.82	0.10

as easily defined, since for long chain esters a value of 0.00 is appropriate,[76,94,95] while for fatty acids a value of 0.60 would be expected.[76,96] If a weighted value of α were to be assigned based upon composition, it would be $\sim$0.01, which is insignificant; however, our investigation, as well as that of Abraham and Ibrahim,[45] suggests that olive oil does exhibit significant hydrogen bond acidity. Thus a practical alternative is to optimize a value for α such that SM8T best reproduces the free energies of solvation in the olive oil database.

The free energy of solvation computed using SM8 or SM8T depends on α both through the bulk electrostatic term

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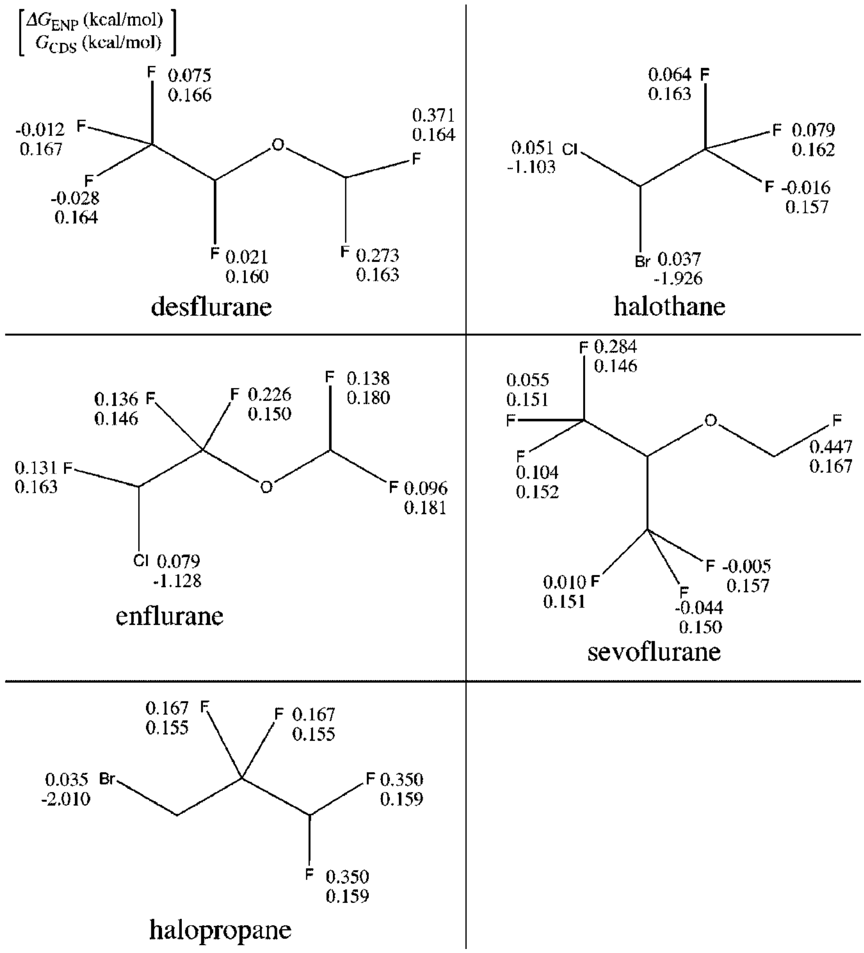

Figure 4. Bulk electrostatic and non-bulk electrostatic contributions to the free energy of solvation for halogen-containing compounds in olive oil.

and through the CDS term. The bulk electrostatic contribution to the free energy of solvation, ΔG_{ENP}, depends in nonlinear fashion on α through the radii;[19] therefore, to efficiently optimize α, we fit ΔG_{ENP} as a function of α for a constant value of the dielectric constant, $\varepsilon = 3.10$, using

$$\Delta G_{\mathrm{ENP}}[\alpha, \varepsilon = 3.10] = a\alpha^2 + b\alpha + c \tag{8}$$

where a, b, and c are coefficients, and α was varied from 0.00 to 0.43. To account for the effect of the temperature dependent dielectric constant, $\varepsilon(T)$, upon the bulk electrostatic contribution to the free energy of solvation the following ratio was used:

$$\frac{\Delta G_{\mathrm{ENP}}[\alpha, \varepsilon(T)]}{\Delta G_{\mathrm{ENP}}[\alpha, \varepsilon = 3.10]} = \left\{\frac{1 - [1/\varepsilon(T)]}{1 - (1/3.10)}\right\} \tag{9}$$

where $\varepsilon(T)$ is given by eq 7. Equation 9 is can be derived from the generalized Born equation if the intrinsic Coulomb radii and partial atomic charges of the solute are held constant. We found that this approximation is adequate for the small changes in the dielectric constant that occur in olive oil in the temperature range 293−310 K. Combining eqs 8 and 9 results in the following equation for the bulk electrostatic contribution to the free energy of solvation as a function of α and $\varepsilon(T)$:

$$\Delta G_{\mathrm{ENP}}[\alpha, \varepsilon(T)] = \left\{\frac{1 - [1/\varepsilon(T)]}{1 - (1/3.10)}\right\}(a\alpha^2 + b\alpha + c) \tag{10}$$

The $\Delta G_{\mathrm{CDS}}(T)$ term of eq 2 in SM8T was parametrized for olive oil (SM8T-OO) by using the same choices of which parameters to optimize as those identified in the development of SM8T for water, but for olive oil we also include an additional term for the HS group in thiols, $\sigma^{B}_{1(16)1}$. Thus, at any temperature T, we have

$$G_{\mathrm{CDS}} = G_{\gamma n\beta}(T_0) + \sum_k \left(\alpha\tilde{\sigma}_{Z_k\alpha} + \sum_{m\neq k}\sum_{\tau}(\alpha\tilde{\sigma}_{Z_kZ_m\tau\alpha})F_{Z_kZ_m\tau}\right)A_k + \sum_k \sigma^B_k A_k(T - T_0) + \sum_k \sigma^C_k A_k[(T - T_0) - T\ln(T/T_0)] \tag{11}$$

where Z_k is the atomic number of atom k; τ is a label for a geometry-dependent function, $F_{Z_kZ_m\tau}$; A_k is the SASA of atom k; $G_{\gamma n\beta}(T_0)$ is the sum of the contribution dependent on γ, n, and β at the reference temperature; and the other contributions are indicated explicitly. The fitting parameters are α plus the sets of σ^B_k and σ^C_k. These parameters were optimized simultaneously to minimize the mean unsigned error (MUE).

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$$D=\left[\frac{1}{335}\sum_{i}^{335}|\Delta G_{\text{S}}^{*}(\text{Exp};i)-\Delta G_{\text{ENP}}(i)-\Delta G_{\text{CDS}}(\text{Calc};i)|\right] \tag{12}$$

During the optimization, the magnitudes of the σ_k^B and σ_k^C were restricted to be no greater than 534 ccal Å^{-2} mol^{-1} K^{-1}, which is twice the largest such coefficient in SM8T.[49,50] This was done to ensure that we did not introduce unstable parameters into the new model associated with data sparsity in olive oil compared to the prior aqueous parametrization over a more diverse training set. Additionally α was constrained to be between 0 and 1, these being the limits on this quantity defined by Abraham.[76]

The calculations were carried out using MN-GSM[97] (a locally developed module of the *Gaussian*[98] computer program), and SM8T is also available in GAMESSPLUS,[99] in SMXGAUSS[100] (a code that was developed within our group to allow use of our solvation models with *Gaussian*-style input), and in HONDOPLUS.[101] The electronic structure of each compound was optimized in the gas phase with the mPW1[102] density functional using the 6-31+G(d,p)[103,104] basis set.

4. Results

Solvation model 8 with temperature dependence for olive oil (SM8T-OO) was developed by optimizing α, σ_k^B, and σ_k^C parameters with all temperatures considered simultaneously and using the values given in section 3.B for the remaining solvent descriptors. We find that the optimum α is 0.10; the optimized coefficients for the temperature-dependent CDS term are shown in Table 3. As the coefficients in Table 3 are determined from a test set spanning a relatively narrow temperature range, we recommend using SM8T-OO only for the temperature over which we had data, which is 291 to 310 K.

Table 4 shows the MUE, along with the mean signed error (MSE), and the root mean squared error (RMSE) for both SM8T-OO (last row) and the 1-parameter model using only Abraham's hydrogen bond acidity, α, as a free parameter (first row). It also shows the results of single-temperature fits for the three temperatures at which we had the most data. SM8T-OO has a MUE of 0.87 kcal/mol and a RMSE of 1.21 kcal/mol.

Including the temperature-dependent coefficients gives only a small improvement for SM8T-OO compared to the 1-parameter model. Moreover, the experimental error as-

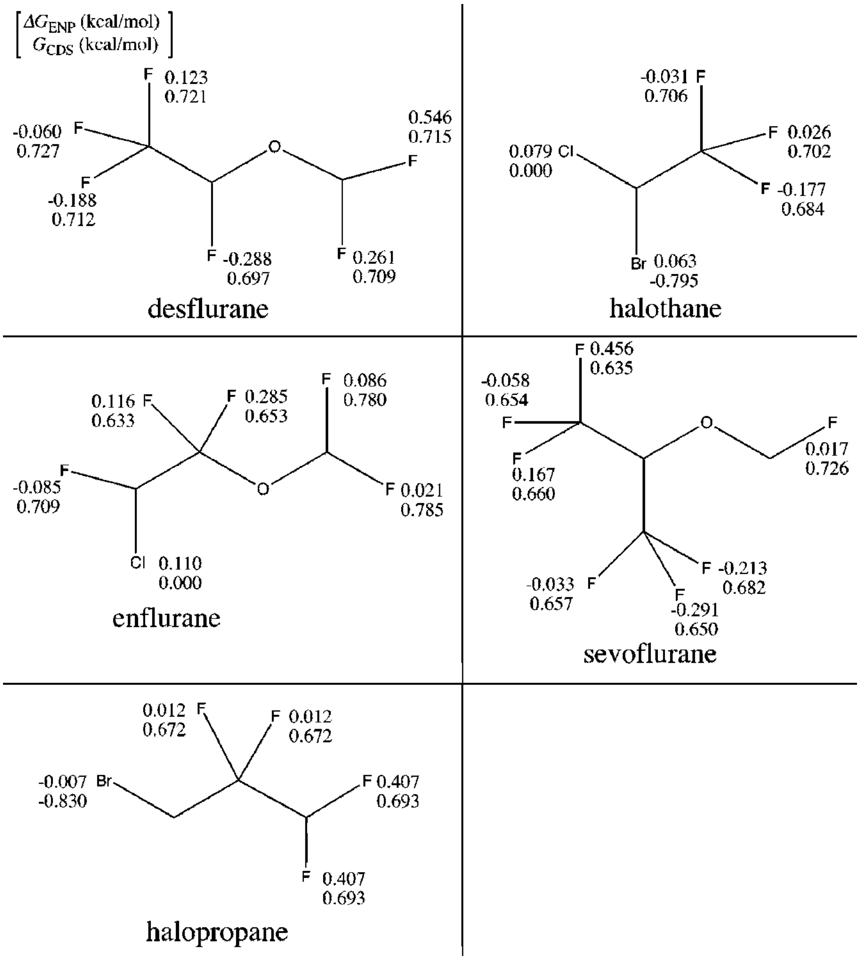

Figure 5. Bulk electrostatic and non-bulk electrostatic contributions to the free energy of solvation for halogen-containing compounds in water.

sociated with different measurements at the same temperature is on the order of reported variations in the free energy of solvation measured at different temperatures (Table 5), consistent with the comment of Leo et al.[105] that the effect of temperature upon solvation in olive oil is negligible. Nevertheless the free energy of solvation *is* a function of *T*, and so we include temperature dependence in SM8T-OO to the extent that the data properly reflect it.

Figure 2 shows the full performance of the model. There are a number of points whose errors are greater than twice the RMSE of the model. Removal of these points does not significantly change the model and merely decreases the error of the model against the data set. The outlying solutes do not possess a recognizable common property, and so they have been retained in the interest of reporting a realistic estimate of the error of the model. SM8T-OO errors are larger than those reported by Abraham and Ibrahim[45] over their 310 K data set (Table 6). However, SM8T-OO has been trained on a broader range of temperatures and solutes than are contained in their data set, which is a subset of ours.

One of the primary objectives of this project was to derive a model that could be usefully applied to drug-like compounds, and so we further investigated the accuracy of the model for a small collection of compounds with known anesthetic, analgesic, or other bioactive properties (Table 7). The MUE of SM8T-OO for these molecules is 1.25 kcal/mol (Table 8); while these molecules were included in the SM8T-OO parametrization in order to deliver as robust a parametrization as possible, their removal led to very small changes in optimized parameter values, so our results would be little changed had we employed them as an external test set. The average spread of errors for these drug-like molecules is larger than the error for the remainder of the data set. One point of particular interest is that the model serves quite well for a variety of functionalities, and the error in the model correlates only weakly with increasing size of solutes: the average molecular weight of drug-like compounds having errors greater than the MUE of 1.25 kcal/mol is 215 g/mol, while the average molecular weight of the remaining compounds is 189 g/mol.

The SM8T-OO model does exhibit some trends in its error with regard to types of compounds. The most notable example is the barbitals which have a mean unsigned error of 3.00 kcal/mol, whereas the fluranes have a mean unsigned error of 0.50 kcal/mol. Barbitals include amides in N-heterocyclic rings (see Table S3 of the Supporting Information for a list of the functional groups present in each drug-like compound), and we observe that 100% of the ketone-containing compounds, 79% of the N-heterocyclic compounds, and 71% of the amide-containing compounds in the drug set possess errors greater than the MUE (Table 7). Further investigation of the effect of different functional groups on the error of SM8T-OO across the entire data set reveals that 81% of the ketone-containing compounds in the data set and 54% of the N-heterocycles have RMSEs greater than the overall RMSE of SM8T-OO. Other functional groups exhibit smaller errors.

So far we have focused on air−water partitioning, but water−olive oil partitioning is of special interest in most bioavailability studies. To test whether SM8T-OO is applicable to water−olive oil partitioning, we used the SM8T and SM8T-OO models to predict water−olive oil free energies of transfer, $\Delta G_{\mathrm{T,aq}\rightarrow\mathrm{oo}}$. For this purpose, we only considered that subset of our database for which experimental water−olive oil partition coefficients were available; these are listed in Table 9 and shown in Figure 3. The mean unsigned error of SM8T-OO for predicting *air*−olive oil partitioning for the compounds in this data subset is 1.15

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kcal/mol. The predicted *water*−olive oil free energies of transfer have a mean unsigned error of 1.45 kcal/mol (about one log unit at 303 K; see Table 10), which is thus less accurate than either SM8T for air−water or SM8T-OO for air−olive oil. This increase in the MUE is disappointing, but reflects to some extent the increased weight of outliers identified previously, including salicylamide, salicylic acid, and cyanoguanidine.

It is also interesting to investigate the effect of various functional groups on the solvation of drug-like molecules. (Tables 11 and 12). The method for partitioning SM*x* solvation free energies into group contributions has been explained elsewhere.[106] One salient example in the current data set is the positive contribution fluorine atoms make to the total free energy of solvation of fluorinated compounds in olive oil (Figure 4). It is evident that the increasing fluorination of drug molecules *decreases* the solubility of the compounds in olive oil relative to the gas phase. For instance, compare the significantly positive contributions of fluorine to the free energy of solvation in enflurane and desflurane (Figure 4). Initially, this observation appears to contradict the conventional wisdom that greater fluorination increases a solute's bioavailability by increasing its lipophilicity.[107−111] However, when we consider the same effect of fluorination upon the solvation free energy of these solutes in water (Figure 5), we see that it makes an even larger positive free energy contribution to aqueous solvation. Hence, the observed preferential partitioning of fluorinated compounds from blood into cell membranes is not so much due to more favorable interaction with the membranes, i.e., lipophilicity, as it is to *unfavorable* interactions with water, i.e., hydrophobicity.

Investigation of the effect of different halogens upon the free energy of solvation in olive oil reveals that the contributions to the free energy of solvation for F, Cl, and Br in halothane in olive oil, which are 0.20 kcal/mol (average), −1.05 kcal/mol, and −1.89 kcal/mol, respectively, become more and more favorable with the increasing atomic number of the halogen (Figure 4 and Table 11; cf. the free energy contributions of F and Cl in enflurane, 0.31 kcal/mol (average), and −1.05 kcal/mol, respectively). In olive oil, fluorine alone among the halogens makes a positive contribution to the free energy of solvation. The free energy contributions of F, Cl, and Br to solvation of halothane in water, by contrast, are 0.64 kcal/mol (average), 0.08 kcal/mol, and −0.74 kcal/mol respectively. For the case of enflurane in water, the contributions of F and Cl are 0.80 and 0.11 kcal/mol respectively. In each of these cases, it is apparent that solvation of all of the halogens in olive oil is more favorable than in water. However, the free energy of transfer from water to olive oil for F, Cl, and Br varies significantly. For instance, for enflurane the free energy contributions for F, Cl, and Br to the free energy of transfer from water to olive oil are −0.44, −1.13, and −1.15 kcal/mol, respectively. While the individual free energy contributions of F, Cl, and Br vary from compound to compound, the contribution of each atom to the free energy of transfer does not vary much. The contributions to the free energy of transfer from water to olive oil by F and Cl in enflurane are −0.49 and −1.16 kcal/mol respectively, and in halothane the contributions of F and Br are −0.48 and −1.13 kcal/mol, respectively. These results agree with prior observations[106] that group free energies of transfer are highly transferable for substituted nucleic acids partitioning between water and chloroform. The difference in the effect of F upon the transfer free energy compared to the effect of chlorine is quite large, ~0.7 kcal/mol, while the difference between the energetically more favorable Cl and Br is very small. This result agrees with the experimental observation that substitution of F for Cl in halogenated compounds can significantly reduce the bioavailability/lipophilicity of the compound.[110,112,113]

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5. Conclusion

We developed and investigated a solvation model, called solvation model 8 with temperature dependence for olive oil (SM8T-OO), for predicting olive oil partition coefficients. SM8T-OO reproduces the temperature-dependent air−olive oil partition coefficients over a range of 291 to 310 K for 304 compounds with a mean signed error of 0.87 kcal/mol, which corresponds to 0.64 log unit in base 10. SM8T-OO involves only 15 parameters to account for temperature dependence and one optimized descriptor to account for a wide range of functionality including compounds of pharmacologic interest. SM8T-OO was then used to investigate the preferential solvation of halogenated compounds in olive oil. The driving force for the preferential solvation of such compounds in olive oil is the more unfavorable interactions halogens such as F or Cl have with water rather than the favorable interactions that they have with olive oil.

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Supporting Information Available: All parametrization data and complete details on SM8 and SM8T. This material is available free of charge via the Internet at http://pubs.acs.org.

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