Supporting Information

Anisotropic solvent model of the lipid bilayer. 2. Energetics of insertion of small molecules, peptides and proteins in membranes

AUTHOR NAMES: Andrei L. Lomize*, Irina Pogozheva, Henry I Mosberg

AUTHOR ADDRESS**:** Department of Medicinal Chemistry, College of Pharmacy, University of Michigan, 428 Church St., Ann Arbor, MI, 48109-1065, USA

AUTHOR EMAIL ADDRESS: almz@umich.edu; irinap@umich.edu; him@umich.edu

TITLE RUNNING HEAD: Anisotropic Solvent Model of Lipid Bilayer

*CORRESPONDING AUTHOR FOOTNOTE

Andrei L. Lomize, Ph.D. Associate Research Scientist

Department of Medicinal Chemistry, College of Pharmacy,

University of Michigan,428 Church St., Ann Arbor, MI, 48109-1965

Tel: 734-615-7194; Fax:734-763-5595

Email: almz@umich.edu

Table S1. Parameters of lipid groups and water used for calculation of polarity profiles for DOPC bilayers: partial volumes (V_i), locations and widths of Gauss functions (Z_i and s_i), and polarity parameters of the groups .

	Structural fragment					
Parameter	**CH=CH**	**Glycerol + carbonyls**	**Phosphate + CH_2-CH_2N**	**CH_3 of choline**	**CH_2**	**H_20**
V_i Å^3 [a]	44	139	86	106	27.7	18
Z_i Å [a]	9.6	14.8	19.1	20.6	14.4 [b]	-
s_i Å [a]	3.05	2.05	2.41	2.98	2.48 [b]	-
α	0.0	0.0	0.0	0.82 [c]	0.0	0.82 [d]
β	0.07[e]	0.86 [f]	1.74 [g]	0.0	0.0	0.35 [d]
π^*	0.34[h]	0.55[i]	0.73[j]	0.73 [j]	0.0	1.09 [j]
ε [k]	2.0	6.02	21.3	2.45	2.0	78.4

[a] From Kucherka et al. (2008)[1].

[b] Parameters of Gauss error function

[c] Value for NMe_4^{+2}. Parameters α and β were modified for DOPS bilayer: α was taken as 0.87 (value for ammonium[2] and β was taken as a sum of values for charged phosphate and acetate[2].

[d] From Abraham (1993)[3, 4].

[e] Value for -C=CH_2 fragment[5].

[f] Value for -CH2-C(O)OMe fragment[5], multiplied by two.

[g] We used β of methylsulfonate ion, due to lack of data for phosphate ion. The β of methylsulfonate was estimated as $\beta_{acetate}(pK^{HB}_{methylsulfonate}/pK^{HB}_{acetate})$, where pK_{HB} values define strength of 1:1 hydrogen bonding complexes by methylsulfonate and acetate ions (3.9 and 5.6, respectively)[6], and $\beta_{acetate}$ is 2.50[2]. This estimate is based on the linear correlation between pK^{HB} of hydrogen bonding complexes and the hydrogen bonding basicity of the corresponding groups, $\Sigma\beta_2$[4].

[h] Average value for dienes[7].

[i] Value for methyl acetate[8]

[j] Value for trimethylphosphate[7].

[k] Dielectric constants of glycerol/carbonyl phosphate, and choline fragments were taken as for uncharged methyl acetate, trimethyl-phosphate and triethylamine, respectively.

Table S2. Parameters of DOPS bilayer used for the calculations.

Parameters	**DOPS**[a]	**DOPC**
V_{CG} Å^3	132	139
V_{HGR} Å^3	132	192
A, Å^2	64.1	67.7
½ $D_{c,}$ Å	15.4	14.4
½ D_{HH} Å	19.5	18.4
Z_{CG} Å	15.9	14.8
Z_{HGR} Å	20.2	19.1

[a]The cross-sectional area, hydrophobic thickness, and D_{HH} distance of fluid DOPS bilayer were taken from Petrache et al. (2004)[9]. The positions of peaks for carbonyl-glycerol groups (Z_{CG}) and for the remainder of lipid head groups (Z_{HGR}) in DOPS bilayer were calculated by assuming that the peaks are identically shifted in DOPS and DOPC bilayers with respect to the main peak determined by X-ray scattering (D_{HH} distance). Semi-widths of the group distributions were taken as for DOPC. V_{CG} and V_{CG} parameters of DOPS were estimated from standard volumes of the component groups[10].

Table S3. Linear regression coefficients (cal mol^{-1} $Å^{-2}$) applied for calculation of atomic solvation parameters in combination with Block-Walker dielectric model in the present work. The parameters are taken from the accompanying publication.

Parameter	σ_i^0	e_i (1/ε term)	a_i (α term)	b_i (β term)
σ_{Csp3}	17	8±2	0	0
$\sigma_{Csp3pol}$	-1	0	0	0
σ_{Csp2}	13	0	10	0
σ_{Csp1}	2	0	0	0
σ_{NH}	0	-88	0	0
σ_{N}	0	-124	0	0
$\sigma_{N\equiv}$	-8	0	0	0
σ_{OH}	0	-28	-27	-63
σ_{O}	0	-44	-19	0
σ_{S}	-2	0	10	0
σ_{F}	7	0	10	0
σ_{Cl}	10	0	10	0
σ_{Br}	13	0	10	0
σ_{I}	12	0	10	0
σ_{NO2}	16	0	10	0
σ_{NH4+}	0	0	0	-23
σ_{O-}	0	0	-221	0

The coefficient for dipolar energy $e_{dip,BW}$ was -1.865± 0.094 kcal mol^{-1} D^{-1}, e_{Born} was -0.198.

Table S4. Water distribution parameters determined by fitting of theoretically calculated transfer energy curves to statistical energy profiles of Trp and Tyr residues (symmetric membrane model).

Membrane	**$C_{H2O,HG}$[1], M**	**$C_{H2O,mid}$[1], M**	**z_0[2], Å**	**Z_{CG}[3], Å**	**$Z_{CG} - z_0$[4], Å**	**λ[5], Å**	**rmsd (kcal/mol)**
DOPC[11]	2.05	0.39	8.2	14.8	6.6	0.5	n.a.
Inner bacterial, archaeal, eukaryotic (α-helical proteins)	3.66	0.55	9.0	15.0	6.0	1.1	0.21
Outer bacterial (β-barrel proteins)	5.33	0.55	7.5	11.8	4.3	1.9	0.33

[1] molar concentrations of water in the center of membrane ($C_{H2O, mid}$) and in the mid-polar region ($C_{H2O,HG}$) calculated from volume fractions of water in eq. (5)

[2] z_0 from eq. (5), semi-width of central non polar region;

[3] semi-width of acyl chain region (corresponding to the position of lipid carbonyls);

[4] width of "mid-polar" region;

[5] decay rate from eq. (5)

Table S5. Comparison of calculated and experimental membrane binding free energies of small molecules. Experimental values are obtained from partition coefficients of these molecules between water and phospholipid vesicles[12-16].

Small molecule	ΔG_{exp} (kcal/mol)	ΔG_{calc} (kcal/mol)
Ibuprofen	-5.26	-5.7
Morphine	-2.57	-3.0
Phenol	-2.68	-3.4
3-Me-phenol	-3.18	-3.8
4-Et-phenol	-3.92	-4.3
Acetylsalicylic acid (Hb)	-3.26	-2.9
Aniline	-2.2	-3.2
3,4-dimethylaniline	-3.06	-3.5
2,4,6-trimethylaniline	-3.76	-3.6
p-xylene	-4.06	-4.9
N,N-dimethylaniline	-3.18	-2.9
2-allylphenol	-4.17	-5.1
2-phenylphenol	-4.72	-5.8
4-amino-3-methylphenol	-2.88	-2.4
9-anthracenomethanol	-4.77	-5.7
benzocaine	-3.09	-2.6
4-biphenylcarboxaldehyde	-4.28	-5.6
cinnamamide	-2.54	-3.8
1,5-dihydroxynaphthalene	-3.70	-2.6
1-naphtaldehyde	-3.82	-4.9
Indole	-3.77	-4.1
3-Me-indole	-4.46	-4.4
N-Me-indole	-3.88	-4.0

Table S6. Comparison of calculated transfer energies of N-methyl acetamides of nonpolar amino acids with Wimley-White and Jacobs-White hydrophobicity scales.

Residue	**ΔG_{calc}[a] (kcal/mol)**	**ΔG_{calc}(-Ala)[a] (kcal/mol)**	**ΔG_{WW} (-Ala)[b] (kcal/mol)**	**ΔG_{JW} (-Ala)[c] (kcal/mol)**
Ala	-0.6	0	0	0
Ile	-1.7	-1.1	-0.48	
Leu	-1.7	-1.1	-0.73	-1.09
Val	-1.3	-0.7	-0.10	
Met	-1.2	-0.6	-0.40	
Phe	-2.6	-2.0	-1.13	-1.23
Thr	-0.7	-0.1	-0.03	
Trp	-2.5	-1.9	-2.02	-2.11
Tyr	-1.7	-1.1	-1.11	

[a] Calculated values for N-methyl-acetamides of amino acids (lowest energy for two main-chain conformers: -120, 120 and -60, -40 and three χ^1 conformers).

[b] Results for hydrophobic pentapeptide Ac-WL-X-LL[17]

[c] Results for shorter tripeptde A-X-A-O-*t*-Bu[18]

Table S7. Comparison of experimental membrane binding affinity (ΔG_{exper}) of 16 peripheral proteins and their transfer free energies calculated with PPM 1.0 (ΔG_{PPM1}) and PPM 2.0 (ΔG_{PPM2}) methods.

Protein	**ΔG_{exp}[a](kcal/mol)**	**ΔG_{PPM2} (kcal/mol)**	**ΔG_{PPM1}[a](kcal/mol)**
1coy	-5.9	-6.8	-4.1
1b4v	-7.5[a]	-8.4	-7.1
1zq4	-6.8	-7.4	-5.0
1poa	-11.4	-10.8	-5.4
1vap	-10.6	-10.3	-10.2
1n28	-6.4	-7.0	-6.3
1s6x	-6.8	-6.3	-5.6
1nbl	-6.4	-7.4	-6.4
2ptd	-5.6	-8.3	-6.0
1poc	-8.2	-9.5	-10.3
1soc	-5.4	-6.9	-5.6
1eth(A)	-11.0	-12.3	-16.1
1tgx	-9.6	-10.0	-12.1
1faq	-5.5	-7.3	-6.3
1tk2	-8.3	-8.4	-14.1
2crd	-3.6	-3.2	-1.6
R^2		0.78	0.47
Rmse (kcal/mol)		1.13	2.73

[a] Data were taken from[19]

List of 119 α-helical and 53 β-barrel transmembrane proteins used for calculation of statistical energy profiles (PDB codes):

α-helical proteins 1afo, 1bcc, 1e12, 1ehk, 1fft, 1gzm, 1h2s, 1j4n, 1jdm, 1kb9, 1kf6, 1kqf, 1l0l, 1l7v, 1ldf, 1m56, 1nek, 1okc, 1ots, 1p49, 1p7b, 1pw4, 1q16, 1qm8, 1r3j, 1rc2, 1rh5, 1u7g, 1v55, 1wpg, 1wu0, 1xio, 1xl6, 1yew, 1z98, 1zcd, 1zll, 1zoy, 2a65, 2ahy, 2b2f, 2b6o, 2bbj, 2bg9, 2bs2, 2cfq, 2ei4, 2f2b, 2fyn, 2gfp, 2gif, 2h8a, 2hac, 2hyd, 2ic8, 2j7a, 2jln, 2jp3, 2jwa, 2k1k, 2k9j, 2k9y, 2ka1, 2klu, 2nq2, 2nwl, 2oar, 2onk, 2qjp, 2qks, 2qts, 2r6g, 2r9r, 2rh1, 2rlf, 2uuh, 2v50, 2vl0, 2vpz, 2vt4, 2w2e, 2w8a, 2yvx, 2z73, 2zbd, 2zjs, 2zw3, 2zxe, 2zz9, 3b4r, 3b60, 3b8c, 3b8c, 3b8e, 3b9w, 3beh, 3c02, 3chx, 3d9s, 3ddl, 3dh4, 3din, 3dww, 3eam, 3eml, 3g5u, 3gd8, 3gia, 3h90, 3hd6, 3hd7, 3hfx, 3jyc, 3k3f, 3kcu, 3kg2, 3kly, 3kp9, 3l1l,

β-barrel proteins: 1a0s, 1af6, 1e54, 1ek9, 1fep, 1hxx, 1i78, 1k24, 1kmp, 1osm, 1p4t, 1pho, 1qd6, 1qj8, 1qjp, 1t16, 1thq, 1tly, 1uyo, 1wp1, 1xkw, 1yc9, 2erv, 2f1c, 2f1v, 2gr7, 2grx, 2gsk, 2hdi, 2iah, 2iwv, 2j1n, 2k0l, 2mpr, 2o4v, 2odj, 2por, 2qdz, 2qom, 2qtk, 2vqi, 2wjr, 3bry, 3bs0, 3csl, 3dwo, 3dzm, 3efm, 3fhh, 3fid, 3jty, 3kvn, 3prn

FIGURES

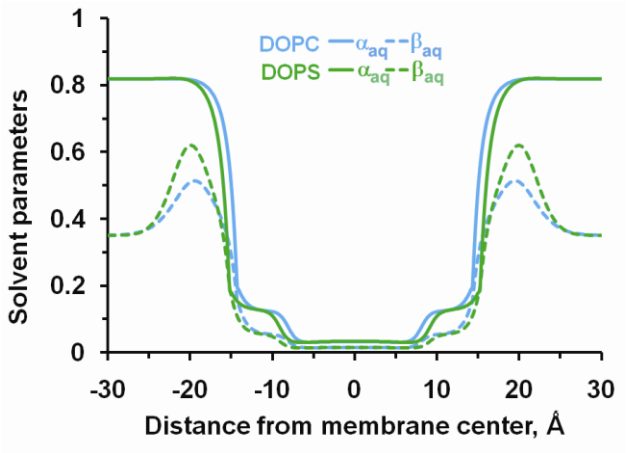

Figure S1. Profiles of hydrogen bonding donor and acceptor parameters (α_{aq} and β_{aq}) in DOPC and DOPS bilayers.

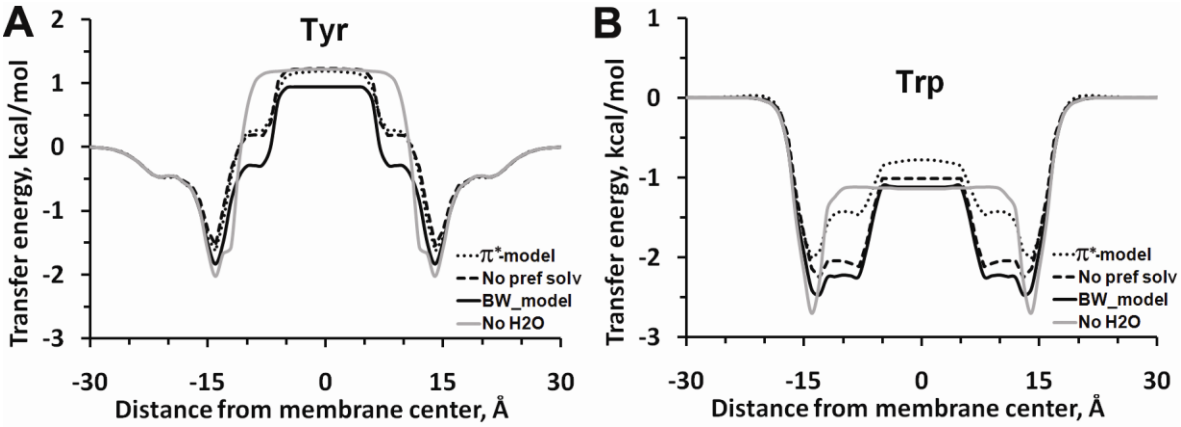

Figure S2. Transfer energy profiles of Tyr (A) and Trp (B) residues calculated with alternative physical models. Comparison of energy profiles obtained with the finally selected model, which combines Block-Walker dielectric functions and preferential solvation (solid black line), with π*-based electrostatic model (doted black line), Block-Walker model without preferential solvation (dashed black line), or model ignoring water in the "mid-polar" region (solid gray line).

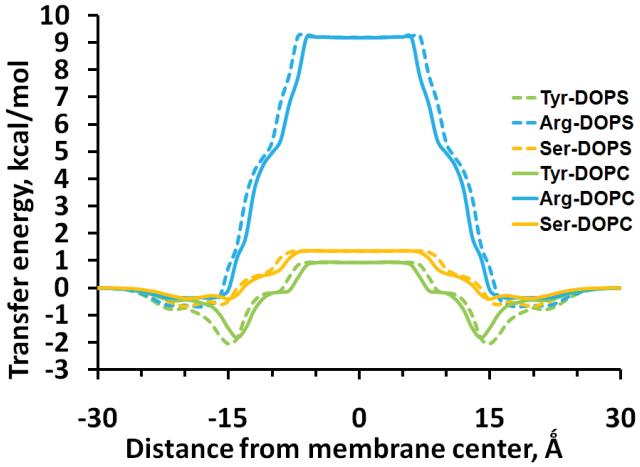

Figure S3. Transfer energies from water to the DOPC or DOPS of amino-acid residues (Ser, Arg, Tyr) in transmembrane α-helix that moves across the lipid bilayer.

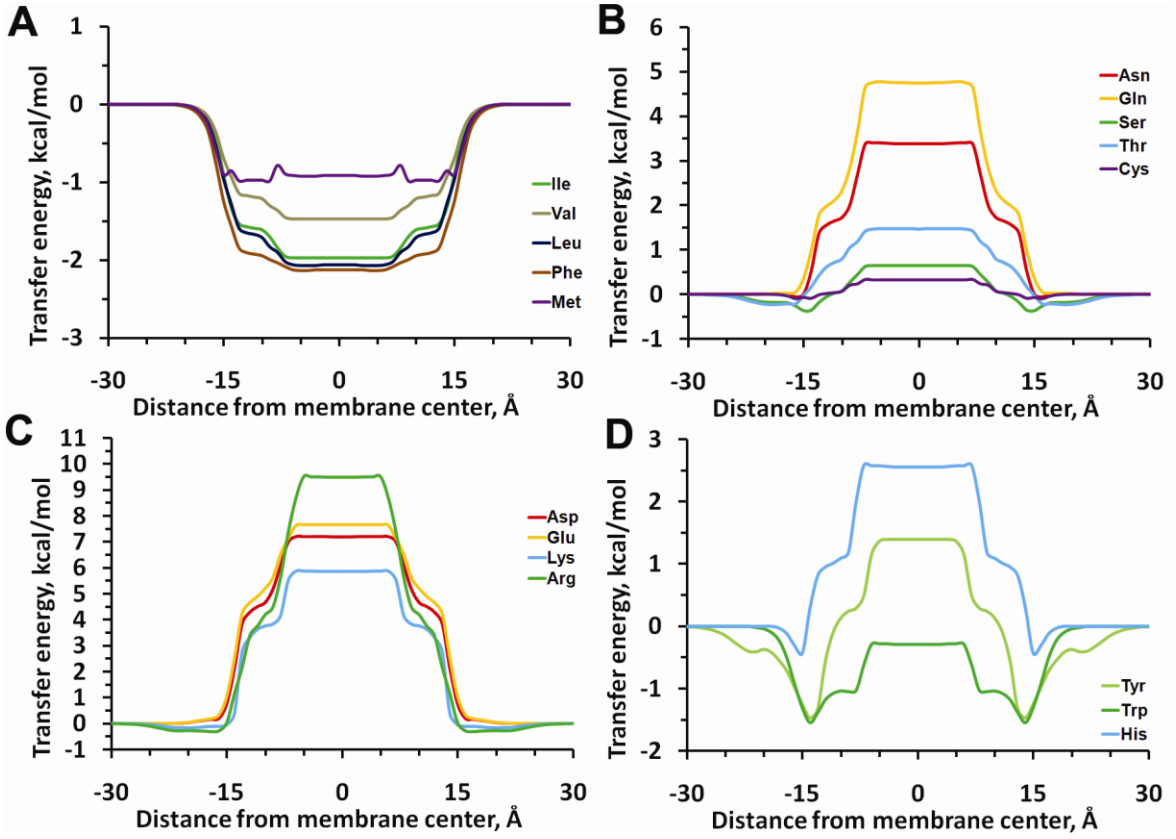

Figure S4. Profiles of transfer energy of amino-acid residues incorporated into β-barrel moving across the DOPC bilayer.

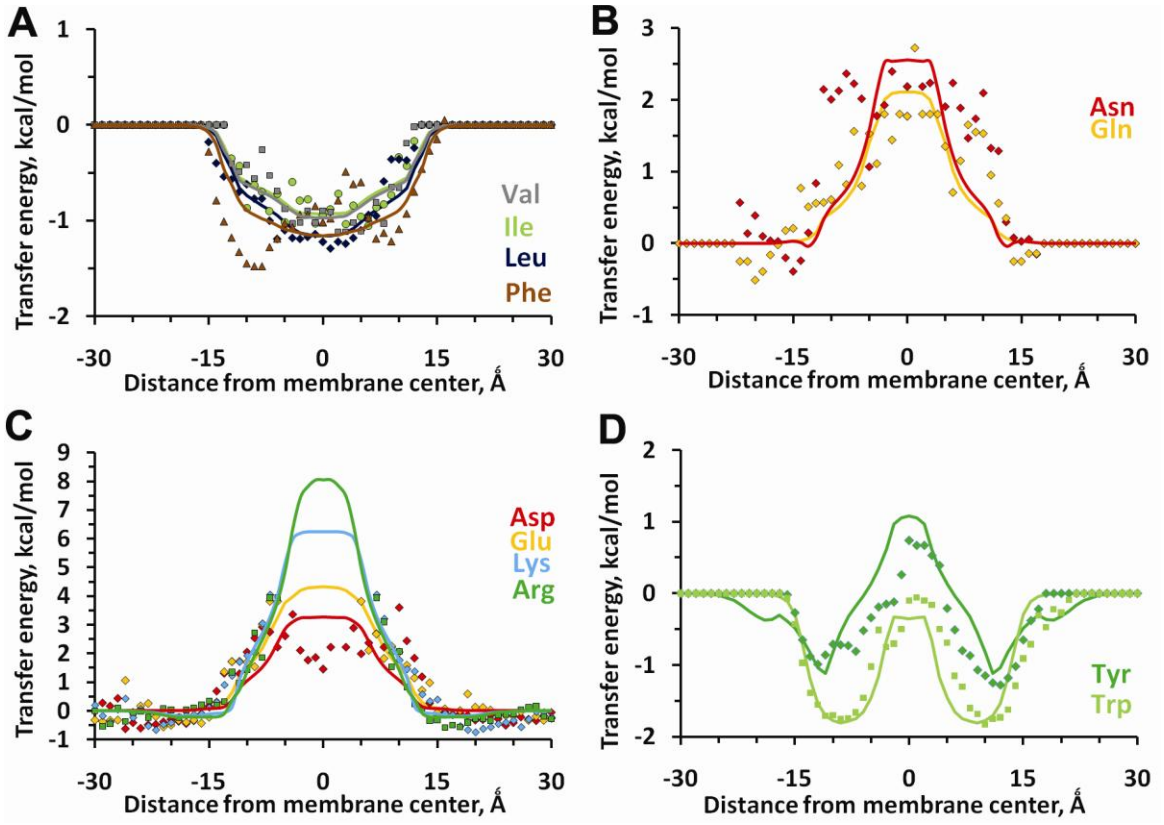

Figure S5. Comparison of theoretical (solid lines) and statistical energies (triangles, squares, circles, diamonds) for surface residues in transmembrane β-barrel. The statistical energies were obtained for lipid-facing residues in 53 β-barrel proteins from outer bacterial membranes. Theoretical energies were calculated after optimization of parameters for water in outer bacterial membrane (C_{wHG},= 0.55 M; C_{wmid},= 5.33 M; z_o,= 7.5 Å; and λ=1.9 Å). The calculated energies were normalized to account for the difference of ASA for the residue in the set of proteins and in isolated β-barrel.

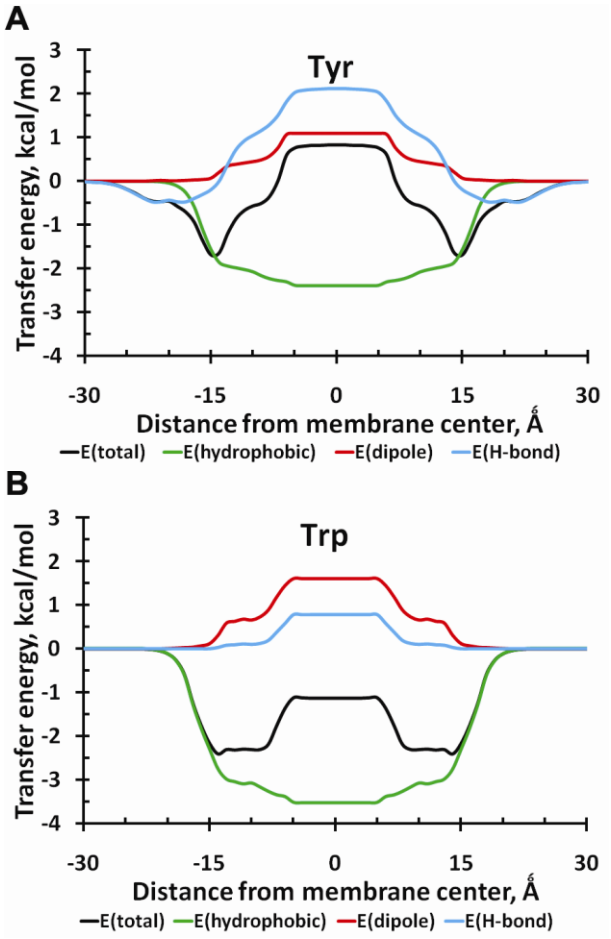

Figure S6. Contributions to total transfer energy (black) from water to the lipid bilayer of Tyr and Trp residues in α-helix: energy of hydrophobic interactions (green), electrostatic energy of dipole transfer (red), and dehydration energy originating from loss of hydrogen-bonds of polar atoms (OH in Tyr and NH in Trp) with water (blue).

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