Supporting Information for:

The transmembrane helix tilt may be determined by the balance between precession entropy and lipid perturbation

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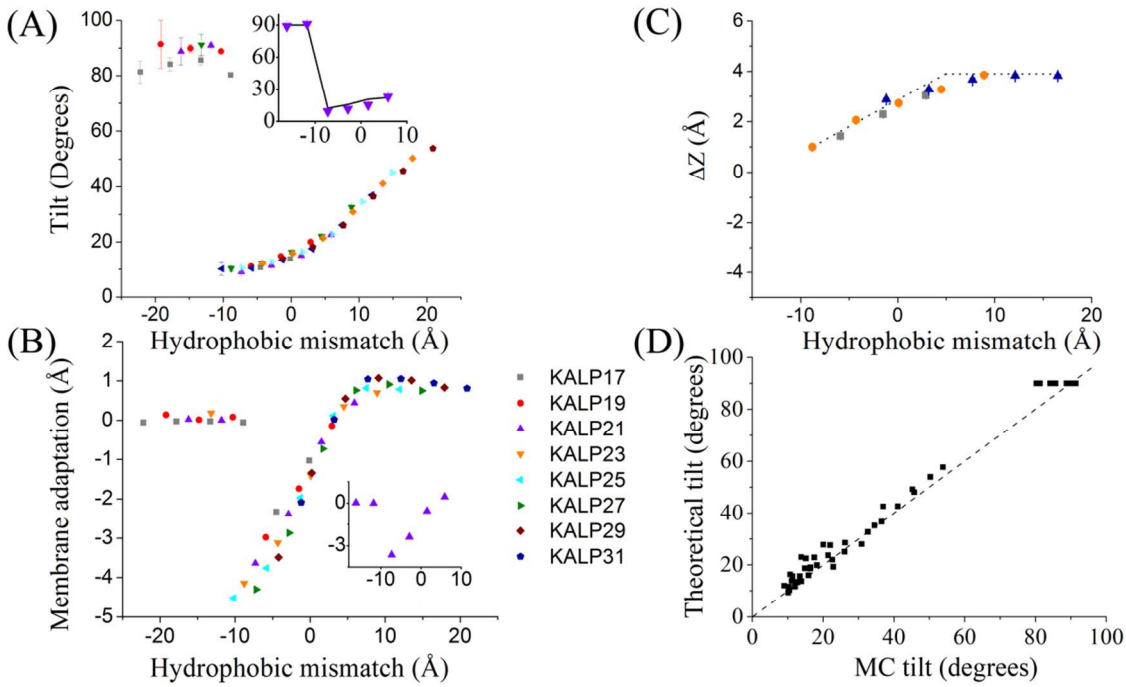

FIGURE S1 (equivalent of Figure 2 but with peptides of the KALP series). MC simulations with KALPs. The standard errors are marked; in many cases the error bars are smaller than the symbols. (A) Tilt angle vs. hydrophobic mismatch. A tilt angle of zero corresponds to a helix with the principal axis perpendicular to the membrane plane; a tilt angle of 90° corresponds to a helix with its principal axis parallel to the membrane plane. The inset shows the theoretical dependence of the tilt angle of KALP21 on the hydrophobic mismatch (solid curve) in comparison to the values obtained from the MC simulations (triangles). (B) Dependence of the membrane adaptation on the hydrophobic mismatch. The inset demonstrates the results for KALP21. (C) Location of the flanking residues in the membrane vs. hydrophobic mismatch. For clarity, the data for only three peptides are shown. ΔZ is the shortest distance between the average position of the α-carbon of the flanking residue and the boundary of the hydrocarbon region of the membrane. The dotted lines were added to guide the eye. (D) Correlation between

the theoretically predicted tilt angles of KALPs and the values estimated from the MC simulations; $Theoretical\_tilt = 0.97 \times MC\_tilt + 2.7$, R^2=0.99. The dashed line represents the ideal fit, i.e., $Theoretical\_tilt = MC\_tilt$. The theoretical tilts from the membrane normal were calculated using Eq. 6. The values based on the MC simulations were reproduced from (A).

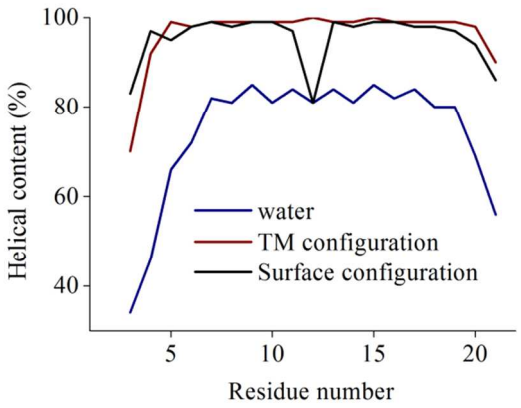

FIGURE S2. The average helical content of WALP23 in the aqueous phase and in association with a DMPC membrane, in surface and TM configurations. The peptide is, in essence, helical regardless of the environment.

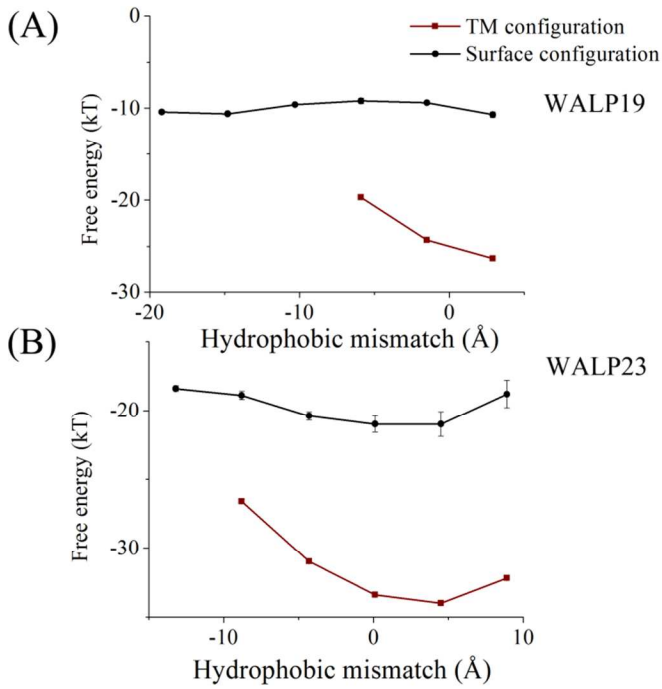

FIGURE S3. The free energy of association of WALP19 (A) and WALP23 (B) with membranes of various thicknesses in TM and surface configurations, as a function of the hydrophobic mismatch. Helix adsorption on the membrane surface (i.e., surface configuration) is energetically favorable always, while the stability of the TM configurations depends on the hydrophobic mismatch. The results were obtained from MC simulations as described in the "Methods" section. The error bars represent standard error; in some cases the error bars are smaller than the symbols.

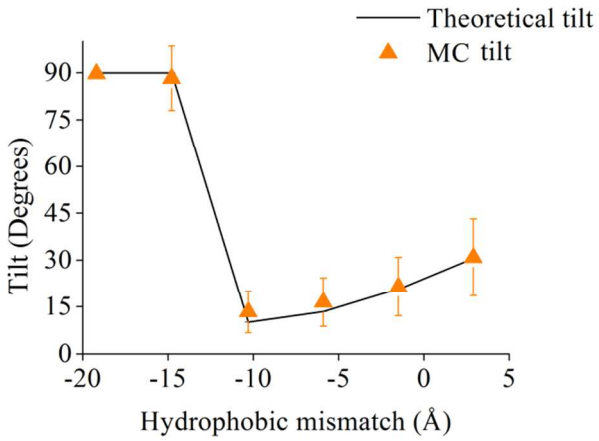

FIGURE S4. Tilt angle vs. hydrophobic mismatch of GWALP23 in various membrane types. The theoretical dependence of the tilt angle of GWALP23 on the hydrophobic mismatch (solid curve) is compared to the values obtained from the MC simulations (triangles). A tilt angle of 0° corresponds to a helix with its principal axis perpendicular to the membrane plane; a tilt angle of 90° corresponds to a helix with its principal axis parallel to the membrane plane.

TABLE S1 (equivalent of Table 3, but with peptides of the KALP series). Comparison of α (degrees), calculated using the theoretical model, to the MC simulations and previous data; the method used is listed in parentheses. Where possible, the values are shown as average ± standard deviation. NMR, nuclear magnetic resonance; MD, molecular dynamics.

Peptide	Membrane	Theoretical model	MC	Previous data
KALP19	DLPC	19	14.8±7.2	~12 (MD)[1]
	DMPC	14	11.2±6.6	~7 (MD)[1]
KALP23	DLPC	28	22.0±8.6	6.6 (NMR)[2*]
				23 (NMR)[3]
				~28 (MD)[1]

	DMPC	19	16.4±7.8	3 (NMR)[2*] 11±11 (MD)[4] 18 (NMR)[3]
	DPPC	13	12.2±7.2	~13 (MD)[1] 20.7 (MD)[5]
KALP27	DLPC	39	34.5±8.5	~42 (MD)[1]
	DMPC	19	22.9±8.9	~38 (MD)[1]
	DPPC	17	16.4±8.0	~12 (MD)[1]
KALP31	DLPC	50	45.6±7.2	~48 (MD)[1]
	DMPC	39	36.5±7.4	~40 (MD)[1]
	DPPC	25	26.1±9.0	~35 (MD)[1]

[*]calculated from ^{2}H-NMR data without considering the peptide' dynamics

TABLE S2. Comparison of the tilt angles of GWALP23 in different membrane types with previous data; the method used is listed in parentheses. All tilts are shown in degrees (°). Where possible, the previous data is presented as average ± standard deviation. NMR, nuclear magnetic resonance; MD, molecular dynamics.

Lipid type	Previous data	MC	Theoretical model
DLPC	10.8 (NMR)[6]	21.5±9.4	23
	12.6 (NMR)[6]		
	15.5±7.5 (MD)[7]		
	20.8 (NMR)[8]		
DMPC	9.1(NMR)[8]	16.5±7.8	16
	18 (NMR)[9]		
DOPC	5.9-7.5 (NMR)[10]	15.8±8.9	13
	6.1(NMR)[8]		
	6.5±5.3 (MD)[7]		
	13(MD)[10]		
DPPC	15(MD)[10]	13.4±6.7	12

TABLE S3. P_{eff} (Å) in different membrane types. When the preferred state of the (helical) peptide in a certain membrane type is a surface orientation, the P_{eff} value is shown in *italics*. The value of P (Å) of each helical peptide, estimated assuming a translation of 1.5Å per residue, Ala or Leu, along the helix axis as in a perfect α-helix, is listed in parentheses.

Membrane thickness	KALP17 (16.5)	KALP19 (19.5)	KALP21 (22.5)	KALP23 (25.5)	KALP25 (28.5)	KALP27 (31.5)	KALP29 (34.5)	KALP31 (37.5)
16.6	15.14	16.94	17.90	20.90	23.90	26.90	29.90	32.90
21	16.90	18.70	20.50	22.30	23.90	26.90	29.90	32.90
25.4	*18.66*	20.46	22.26	24.06	25.86	26.90	29.90	32.90
29.8	*20.42*	*22.22*	24.02	25.82	27.62	29.42	31.22	32.90
34.3	*22.22*	*24.02*	*25.82*	27.62	29.42	31.22	33.02	34.82
38.7	*23.98*	*25.78*	*27.58*	*29.38*	31.18	32.98	34.78	36.58

Membrane thickness	WALP17 (16.5)	WALP19 (19.5)	WALP21 (22.5)	WALP23 (25.5)	WALP25 (28.5)	WALP27 (31.5)	WALP29 (34.5)	WALP31 (37.5)
16.6	15.30	17.16	19.30	22.30	25.30	28.30	31.30	34.30
21	16.97	18.83	20.69	22.55	25.30	28.30	31.30	34.30
25.4	*18.64*	20.50	22.36	24.22	26.08	28.30	31.30	34.30
29.8	*20.31*	*22.17*	24.03	25.89	27.75	29.61	31.47	34.30
34.3	*22.02*	*23.88*	*25.74*	27.60	29.46	31.32	33.18	35.04
38.7	*23.70*	*25.56*	*27.42*	*29.28*	31.14	33.00	34.86	36.72

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