Supporting Information

Modeling Temperature Dependency of Ionization Constants of Amino Acids and Carboxylic Acids.

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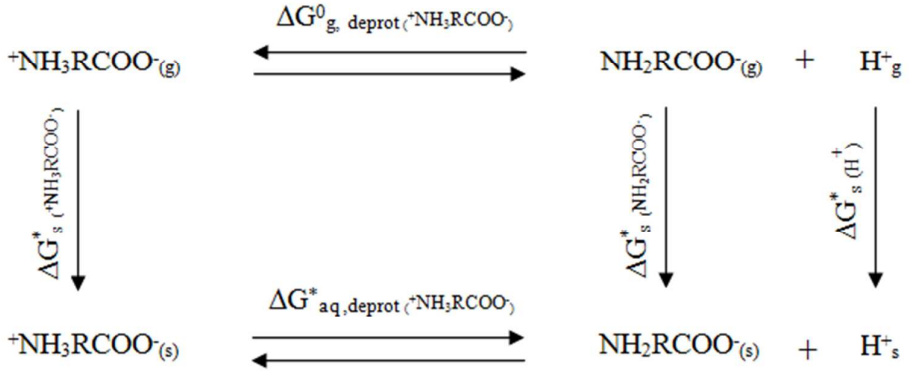

Fig S1: Thermodynamical cycle employed for calculation of pKa_2 values

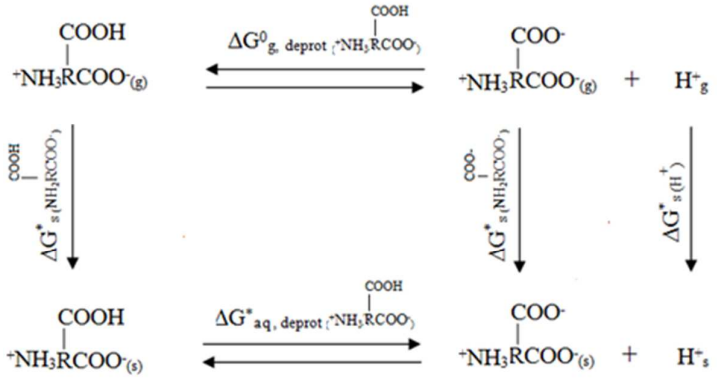

Fig S2: Thermodynamical cycle employed for calculation of pKa_3 values

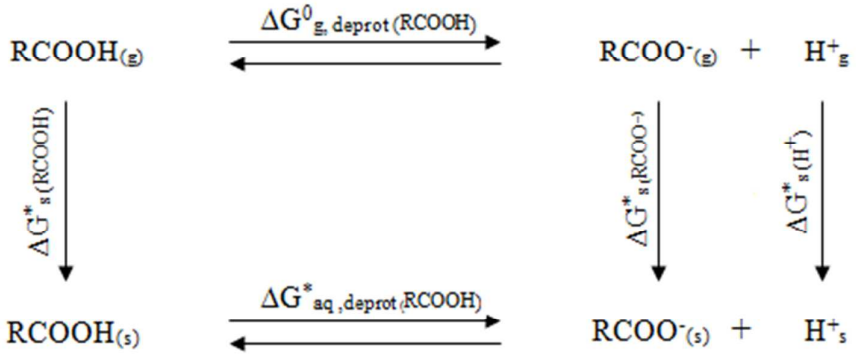

Fig S3: Thermodynamical cycle employed for calculation of pKa values of carboxylic acids

Table S1: Electrostatic and Non Electrostatic Contributions to Solvation free energy (kcal/mol) in PCM model as a function of Temperature for Propionate ion.

Temp (K)	PCM solvation energy contributions				Total non elec (Dis + Rep + Cav)	Gsolv(A) (Elec - Non elec)
	Electrostatic	Dispersion	Repulsion	Cavitation		
273	-72.61	-13.86	3.36	10.27	-0.23	-72.84
293	-72.61	-13.86	3.36	11.02	0.52	-72.09
298	-72.61	-13.86	3.36	11.21	0.71	-71.9
313	-72.61	-13.86	3.36	11.77	1.27	-71.34
333	-72.61	-13.86	3.36	12.52	2.02	-70.59
353	-72.61	-13.86	3.36	13.27	2.77	-69.84
373	-72.61	-13.86	3.36	14.03	3.53	-69.08
393	-72.61	-13.86	3.36	14.78	4.28	-68.33

*From the table we can see that it is only cavitation energy which is changing with temperature, so there is a scope of improvement in cavitation energy calculation for ions in PCM model.

Table S2: Temperature dependency of Cavitation Energies (kcal/mol) of Carboxylic acid ions.

Temp (K)	Cavitation Energies (kcal/mol)				
	Formate	Acetate	Propanoate	Benzoate	Oxalate
273	6.17	8.4	10.27	14.89	10.47
293	6.63	9.02	11.02	15.98	11.24
298	6.74	9.18	11.21	16.26	11.44
313	7.08	9.64	11.77	17.07	12.01
333	7.53	10.25	12.52	18.16	12.77
353	7.98	10.87	13.27	19.25	13.54
373	8.44	11.48	14.03	20.34	14.31
393	8.89	12.1	14.78	21.43	15.07

Table S3: pKa of propionic acid by using PCM solvation energy (equation 17) and the modified equations for the PCM solvation energy (equation 18).

Temp (K)	PCM equation 17		PCM modified equation 18	
	ΔG_{solv}	pKa	ΔG_{solv}	pKa
273	-72.85	8.69	-71.96	9.41
293	-72.1	8.15	-72.05	8.18
298	-71.9	8.03	-71.90	8.03
313	-71.35	7.67	-71.02	7.91
333	-70.59	7.26	-68.85	8.41
353	-69.84	6.89	-65.55	9.56
373	-69.09	6.56	-61.12	11.25
393	-68.34	6.27	-55.56	13.40

*By using solvation energies given by equation 17, we get a decrease in pKa values with increase in temperature, but on using equation 18, we obtain increase in pKa w.r.t temperature as observed experimentally at higher temperatures. Still there is a need to improve the model, to get accurate temperature dependency of pKa values of carboxylic acids from continuum solvation models.

Table S4: -d (pKa)/ dT for common carboxylic acids using pKa and standard state entropy data in equation 20.

S. No	RCOOH	pKa (at 298 K)	ΔS^0	-d(pKa)/dT
1.	Acetic Acid	4.76	-73.6	0.0031
2.	Butanoic Acid	4.82	-102	-0.0016
3.	Benzoic Acid	4.20	-79.1	0.0003

*Data from Perrin, D. D. Dissociation constants of organic bases in aqueous solution; Butterworth's: London, 1965.

Table S5: Absolute pKa values for amino acid pK_1 with PCM solvation model

Temp (K)	Gly	β-ala	Tau	Sar	Meth	Pro	Phe-ala	6-AHA	Glu	Asp
273	15.36	16.96	1.03	15.90	9.58	13.29	13.38	21.17	10.70	11.26
293	14.41	15.85	1.07	14.92	9.04	12.47	12.58	19.81	10.06	10.57
298	14.19	15.60	1.07	14.69	8.91	12.28	12.39	19.50	9.91	10.41
313	13.59	14.88	1.11	14.08	8.58	11.76	11.88	18.64	9.50	9.97
333	12.86	14.03	1.15	13.33	8.17	11.14	11.26	17.61	9.02	9.45
353	12.21	13.26	1.19	12.66	7.82	10.59	10.73	16.69	8.58	8.98
373	11.64	12.59	1.22	12.07	7.49	10.10	10.25	15.88	8.20	8.57
393	11.12	11.98	1.26	11.54	7.20	9.66	9.82	15.14	7.85	8.19

Table S6: Absolute pKa values for amino acid pK_1 with SM8T solvation model

Temp (K)	Gly	β-ala	Tau	Sar	Meth	Pro	Phe-ala	6-AHA	Glu	Asp
273	17.90	13.18	-1.13	15.79	11.34	13.15	14.09	21.32	10.77	10.86
293	16.67	12.23	-1.04	14.71	10.56	12.25	13.13	19.86	10.00	10.07
298	16.39	12.01	-1.01	14.46	10.38	12.05	12.91	19.53	9.83	9.89
313	15.60	11.40	-0.94	13.77	9.88	11.47	12.29	18.59	9.35	9.39
333	14.66	10.67	-0.85	12.95	9.29	10.79	11.56	17.47	8.78	8.80
353	13.82	10.03	-0.75	12.23	8.76	10.18	10.91	16.49	8.28	8.28
373	13.08	9.47	-0.65	11.58	8.30	9.65	10.34	15.62	7.84	7.82

Table S7: Absolute pKa values for amino acid pK_2 with PCM solvation model

Temp (K)	Gly	β-ala	Tau	Sar	Meth	Pro	Phe-ala	6-AHA	Glu	Asp
273	6.87	5.11	1.25	9.24	6.51	12.28	9.18	-1.77	13.58	9.31
293	6.51	4.87	1.24	8.67	6.11	11.50	8.60	-1.69	12.53	8.67
298	6.44	4.81	1.25	8.54	6.02	11.32	8.47	-1.67	12.29	8.53
313	6.21	4.66	1.24	8.17	5.76	10.82	8.09	-1.64	11.60	8.11
333	5.94	4.47	1.23	7.74	5.45	10.22	7.64	-1.58	10.79	7.61
353	5.70	4.31	1.22	7.36	5.18	9.69	7.24	-1.54	10.07	7.18
373	5.49	4.17	1.21	7.01	4.94	9.22	6.88	-1.49	9.41	6.78
393	5.30	4.05	1.21	6.70	4.73	8.79	6.56	-1.46	8.83	6.43

Table S8: Absolute pKa values for amino acid pK_2 with SM8T solvation model

Temp (K)	Gly	β-ala	Tau	Sar	Meth	Pro	Phe-ala	6-AHA	Glu	Asp
273	6.26	9.96	1.92	5.73	6.56	8.43	10.04	-1.24	4.70	-3.06
293	5.98	9.42	1.91	5.52	6.20	8.01	9.42	-1.16	4.31	-2.80
298	5.92	9.29	1.91	5.48	6.12	7.91	9.28	-1.15	4.22	-2.74
313	5.75	8.95	1.91	5.35	5.89	7.65	8.89	-1.09	3.98	-2.55
333	5.55	8.55	1.92	5.20	5.61	7.34	8.43	-1.02	3.72	-2.31
353	5.39	8.20	1.94	5.08	5.37	7.07	8.02	-0.95	3.50	-2.07
373	5.25	7.89	1.97	4.97	5.16	6.83	7.67	-0.88	3.32	-1.84

Table S9: Absolute pKa values for amino acid pK_3 with PCM and SM8T solvation model

Temp (K)	Glu		Asp	
	PCM	SM8T	PCM	SM8T
273	10.52	12.41	8.84	9.76
293	9.94	11.70	8.28	9.17
298	9.79	11.54	8.15	9.04
313	9.41	11.09	7.79	8.66
333	8.96	10.55	7.37	8.21
353	8.57	10.08	7.00	7.82
373	8.22	9.66	6.67	7.47
393	7.90		6.37	

Table S10: Absolute pKa values for carboxylic acid pK_a with PCM and SM8T solvation model

Temp (K)	Form		Ace		Prop		Oxa		Benz	
	PCM	SM8T	PCM	SM8T	PCM	SM8T	PCM	SM8T	PCM	SM8T
273	6.03	-0.04	8.52	4.66	8.69	5.11	-1.44	-6.42	7.33	4.51
293	5.70	0.05	8.06	4.47	8.15	4.81	-1.20	-5.89	6.91	4.27
298	5.62	0.08	7.95	4.42	8.03	4.74	-1.15	-5.76	6.81	4.22
313	5.41	0.15	7.66	4.31	7.67	4.56	-1.00	-5.40	6.54	4.08
333	5.16	0.24	7.32	4.19	7.26	4.35	-0.82	-4.95	6.23	3.92
353	4.94	0.34	7.01	4.10	6.89	4.18	-0.65	-4.53	5.94	3.80
373	4.75	0.44	6.74	4.03	6.56	4.04	-0.51	-4.14	5.69	3.69
393	4.58		6.49		6.27		-0.37		5.47	

Table S11: Correction factors applied to PCM and SM8T ΔG^*_{aq} for pKa_1 results compared with experimental ΔG^*_{aq} for pKa_1

S. No.	Amino acid	ΔG^*_{aq} (298 K)			Correction	
		Exp*	PCM	SM8T	PCM	SM8T
1.	Gly	3.19	19.28	22.27	16.09	19.08
2.	β-ala	4.83	21.20	16.32	16.37	11.49
3.	Tau	2.04	1.46	-1.38	-0.58	-3.42
4.	Sar	3.00	19.97	19.65	16.96	16.65
5.	Meth	2.89	12.11	14.11	9.22	11.22
6.	Pro	2.65	16.69	16.37	14.04	13.72
7.	Phe-ala	2.99	16.83	17.54	13.84	14.55
8.	6-AHA	5.94	26.50	26.53	20.56	20.59
9.	Glu	2.98	13.47	13.36	10.50	10.38
10.	Asp	2.71	14.14	13.44	11.44	10.74

*Exp ΔG^*_{aq} values are from pKa values given in Table 1. ** All Values are in kcal/mol.

Table S12: Correction factors applied to PCM and SM8T ΔG^*_{aq} for pKa_2 results compared with experimental ΔG^*_{aq} for pKa_2

S. No.	Amino acid	ΔG^*_{aq} (298 K)			Correction	
		Exp*	PCM	SM8T	PCM	SM8T
1.	Gly	13.28	8.75	8.04	-4.52	-5.23
2.	β-ala	14.04	6.54	12.63	-7.50	-1.41
3.	Tau	12.31	1.69	2.59	-10.62	-9.72
4.	Sar	13.87	11.61	7.44	-2.27	-6.43
5.	Meth	12.64	8.19	8.31	-4.45	-4.33
6.	Pro	14.62	15.39	10.75	0.77	-3.87
7.	Phe-ala	12.65	11.51	12.61	-1.14	-0.04
8.	6-AHA	14.68	-2.27	-1.56	-16.95	-16.24
9.	Glu	13.73	16.70	5.74	2.97	-7.99
10.	Asp	13.60	11.59	-3.72	-2.01	-17.32

*Exp ΔG^*_{aq} values are from pKa values given in Table 1. ** All Values are in kcal/mol.

Table S13: Correction factors applied to PCM and SM8T ΔG^*_{aq} for pKa_3 results compared with experimental ΔG^*_{aq} for pKa_3

S. No.	Amino acid	ΔG^*_{aq} (298 K)			Correction	
		Exp*	PCM	SM8T	PCM	SM8T
1.	Glu	6.05	13.31	15.68	7.26	9.63
2.	Asp	5.30	11.08	12.28	5.78	6.98

*Exp ΔG^*_{aq} values are from pKa values given in Table 1. ** All Values are in kcal/mol

Table S14: Correction factors applied to PCM and SM8T ΔG^*_{aq} for pKa results compared with experimental ΔG^*_{aq} for pKa (carboxylic acids)

S. No.	Carboxylic acid	ΔG^*_{aq} (298 K)			Correction	
		Exp*	PCM	SM8T	PCM	SM8T
1.	Form	5.10[a]	7.64	0.11	-2.54	5.00
2.	Ace	6.47[b]	10.80	6.01	-4.34	0.45
3.	Prop	6.63[c]	10.92	6.45	-4.29	0.18
4.	Oxa	1.77[d]	-1.56	-7.83	3.33	9.60
5.	Benz	5.73[e]	9.25	5.73	-3.53	-0.01

*Experimental data from: a: Harned et al.[96] b: Larson et al.[115] c: Harned et al.[94] d: Parton et al.[128] e: Briegleb et al.[70]

Table S15: Comparison of correction factor (CF) applied to ΔG^*_{aq} for amino acids and carboxylic acids with amines. (kcal/mol).

Amino Acid	CF for pK_1		CF for pK_2		CF for pK_3		RNH2	CF for pK_a		RCOOH	CF for pK_a	
	PCM	SM8T	PCM	SM8T	PCM	SM8T		PCM	SM8T		PCM	SM8T
Gly	16.09	19.08	-4.52	-5.23			PZ	2.60	1.70	Form	-2.54	5.00
β-ala	16.37	11.49	-7.50	-1.41			morpholine	0.40	1.16	Ace	-4.34	0.45
Tau	-0.58	-3.42	-10.62	-9.72			piperidine	-5.45	-2.59	Prop	-4.29	0.18
Sar	16.96	16.65	-2.27	-6.43			AEP	4.38	3.59	Oxa	3.33	9.60
Meth	9.22	11.22	-4.45	-4.33			DMEDA	-0.21	2.49	Benz	-3.53	-0.01
Pro	14.04	13.72	0.77	-3.87			2-methylPZ	2.43	1.85			
Phe-ala	13.84	14.55	-1.14	-0.04			1-methylPZ	0.33	-0.55			
6-AHA	20.56	20.59	-16.95	-16.24			1-ethylPZ	3.53	3.40			
Glu	10.50	10.38	2.97	-7.99	7.26	9.63	MDEA	1.28	-1.05			
Asp	11.44	10.74	-2.01	-17.32	5.78	6.98	MEA	-2.71	5.03			

Table S16: Experimental data for pK_1 for Glycine

Temp (K)	King	King	Owen	Branch	Li	Glasstone	Schwarzenbach	Ellenbogan
273				2.27				
278	2.4176	2.3971	2.405					
283	2.398	2.38						
288	2.3795	2.364						
293	2.364	2.3503	2.366	2.29		2.33	2.752	
298	2.3508	2.3394	2.35		2.86			2.47
303	2.3404	2.3312	2.338					
308	2.3318	2.3266						
313	2.3252	2.3242	2.318					
318	2.3212	2.32	2.313					
323	2.3194							

Table S17: Experimental data for pK_1 for β-alanine

Temp (K)	May	Boyd	Sharma	Irving	Albert	Schmidt
273	3.66	3.65				
278	3.63					
288	3.58	3.58	3.68			
293				3.52	3.57	
298	3.55	3.55	3.66			3.54
308	3.52	3.53				
313	3.52		3.65			
318		3.52				

Table S18: Experimental data for pK_1 for Taurine

Temp (K)	Andrews	Albert
293		1.5
298	1.5	

Table S19: Experimental data for pK_1 for Sarcosine

Temp (K)	Izatt	Datta	Cocker	Basolo
293	2.12			
298		2.21	2.35	2.24
303	2.09			

Table S20: Experimental data for pK_1 for Methionine

Temp (K)	Pelletier	Hawkins	Emerson	Albert
283	2.13			
293		2.17		2.17
298	2.125		2.22	
303	2.125			
313	2.12			

Table S21: Experimental data for pK_1 for Proline

Temp (K)	Smith	Kirk
274.15	2.011	
285.65	1.964	
298.15	1.952	1.86
310.65	1.95	
323.15	1.958	

Table S22: Experimental data for pK_1 for Phenylalanine

Temp (K)	Izatt	temp	Anderson	temp	Nagai
273.15	2.28	283	2.14	283.1	2.32
283.15	2.21	298	2.2	298.1	2.28
293.15	2.2	313	2.21	313.1	2.32
303.15	2.23			333.1	2.33
313.15	2.2				

Table S23: Experimental data for pK_1 for 6-Aminohexanoic acid

Temp (K)	Smith	Edsall
274.15	4.42	
285.65	4.387	
298.15	4.373	4.37
310.65	4.384	
323.15	4.41	

Table S24: Experimental data for pK_1 for Glutamic Acid

Temp (K)	Nagai	Schmidt	Albert	Wilson	Kirk	Neuberger
273.15		2.23				
283.1	2.13					
293			2.16			
298				2.19		
298.1	2.19					
298.15		2.1			2.13	2.155
313.1	2.19					
333.1	2.19					

Table S25: Experimental data for pK_1 for Aspartic Acid

Temp (K)	Smith	Schmidt	Batchelder
273.15		1.95	
274.15	2.122		
285.65	2.054		
298.15	1.99		2.01
303.15		1.68	
310.65	1.945		
323.15	1.907		

Table S26: Experimental data for pK_2 for Glycine

Temp (K)	Hamborg	Datta	King	Owen	Clarke	Izatt	Gillespie
278.15	10.33	-4.49					
283.15	10.18		10.19	10.20			
288.15	10.04	-4.36	10.05	10.05			
293.15	9.90		9.91	9.91			
298.15	9.77	-4.24	9.78	9.77			
303.15	9.64		9.65	9.64			
308.15	9.52	-4.13	9.53	9.52			
313.15	9.41		9.41	9.40			
318.15	9.29	-4.03	9.30	9.29			
323.15	9.19		9.19			9.19	9.19
348.15	8.71				8.99	8.69	8.70
378.15	8.23				8.54		
398.15	7.97				8.23		7.95

Table S27: Experimental data for pK_2 for β-alanine

Temp (K)	Hamborg	May	Gillespie	Boyd	Sharma
273.15	11.08	11.01		11.05	
278.15	10.92	10.83			
288.15	10.61	10.52		10.58	10.44
298.15	10.33	10.23		10.30	10.16
308.15	10.06	9.96		10.03	
313.15	9.93	9.83			9.8
318.15	9.81			9.78	
323.15	9.70		9.59		
348.15	9.16		9.05		
398.15	8.29		8.17		

Table S28: Experimental data for pK_2 for Taurine

Temp (K)	Hamborg	King	Datta
273			9.92
283.15	9.44	9.45	
288.15	9.31	9.31	
293.15	9.18	9.18	
298			9.18
298.15	9.06	9.06	
303.15	8.94	8.94	
308.15	8.82	8.82	
313.15	8.71	8.71	
318.15	8.60	8.60	
323.15	8.50	8.50	

Table S29: Experimental data for pK_2 for Sarcosine

Temp (K)	Hamborg	King	Datta	Izatt
278.15	10.71	10.71	10.71	
288.15	10.45	10.45	10.45	
293				10.19
298.15	10.21	10.20	10.20	
303				10.08
308.15	9.98	9.97	9.97	
318.15	9.77	9.76	9.76	

Table S30: Experimental data for pK_2 for Methionine

Temp (K)	Hamborg	Pelletier	Lenz	Friedman	Perkins	Manning	Hawkins	Emerson	Albert
283.15	9.709	9.73							
290					9.31				
293							9.2		9.37
298.15	9.30	9.28	9.04			9.1		9.27	
303.15	9.17	9.15		9.08					
313.15	8.94	8.92							

Table S31: Experimental data for pK_2 for Proline

Temp (K)	Hamborg	Smith	Azab
274.15	11.39	11.29	
285.65	11.07	10.97	
298.15	10.76	10.64	10.62
310.65	10.46	10.34	
323.15	10.18	10.06	

Table S32: Experimental data for pK_2 for Phenylalanine

Temp (K)	Hamborg	Izatt	Anderson	Nagai
273.15	9.97	9.95		
283			9.75	
283.1				9.69
283.15	9.68	9.66		
293.15	9.42	9.38		
298			9.31	
298.1				9.34
303.15	9.17	9.15		
313			8.96	
313.1				9.06
313.15	8.94	8.89		
333.1				8.48

Table S33: Experimental data for pK_2 for 6-Aminohexanoic acid

Temp (K)	Hamborg	Smith	Edsall	Gillespie	Brandariz
274.15	11.81	11.666			
285.65	11.38	11.244			
298.15	10.95	10.804			10.91
298.16			10.81		
310.65	10.55	10.406			
323.15	10.18	10.036		10.02	
348.15	9.51			9.37	
398.15	8.41			8.33	

Table S34: Experimental data for pK_2 for Glutamic Acid

Temp (K)	Nagai	Wilson	Schmidt	Albert	Kirk	Hamborg	Neuberger
273.15			10.32				
283.1	10.09						
293				9.98			
293.15						10.08	
298		9.94					
298.1	10.1						
298.15			9.47		9.76	9.97	9.96
313.1	9.7						
333.1	9.5						

Table S35: Experimental data for pK_2 for Aspartic Acid

Temp (K)	Hamborg	Smith	Schmidt	Batchelder
273.15			10.41	
274.15	10.80	10.60		
285.65	10.48	10.30		
298.15	10.16	10.00		9.84
303.15			9.57	
310.65	9.87	9.74		
323.15	9.61	9.51		

Table S36: Experimental data for pK_3 for Glutamic Acid

Temp (K)	Nagai	Schmidt	Wilson	Albert	Kirk	Neuberger
273.15		4.2				
283.1	4.32					
293				4.36		
298			4.32			
298.1	4.45					
298.15		4.07			4.31	4.32
313.1	4.45					
333.1	4.45					

Table S37: Experimental data for pK_3 for Aspartic Acid

Temp (K)	Smith	Schmidt	Batchelder
273.15		3.83	
274.15	4.006		
285.65	3.944		
298.15	3.9		
298.5			3.895
303.15		3.63	
310.65	3.878		
323.15	3.87		

Table S38: Experimental data for pK_a for Formic Acid

Temp (K)	Harned	Larson	Harned[1]	Darken	Saxton	Guggenheim
273	3.79		3.75	3.73	3.74	3.74
278	3.77					
283	3.76					
288	3.76					
291		3.75		3.73		
293	3.75					
298	3.75		3.75		3.74	3.74
303	3.75					
308	3.76					
313	3.77					
318	3.77					
323	3.78					
328	3.79					

Table S39: Experimental data for pK_a for Acetic Acid

Temp (K)	Harned	Harned[1]	Larson	Kilpi	Ives	Dippy	Kilpatrick	Darken	MacInnes	Saxton	Ellis	Fisher	Lind	Mesmer
273	4.79	4.78												4.78
278	4.77	4.77												
283	4.76	4.76												
288	4.76	4.76												
291			4.76											
293	4.76	4.76		4.76										
298	4.76	4.76			4.75	4.75	4.74	4.75	4.75	4.75	4.76	4.76		4.76
303	4.76	4.76												
308	4.76	4.76												
313		4.77												
318		4.78												
323		4.79									4.78			4.79
328		4.80												
333		4.81												
348														4.85
373											4.95	4.95	4.95	4.94
398														5.05
423											5.2	5.21		5.18
429													5.24	
448														5.33
473											5.51	5.54		5.52
491													5.74	
498														5.73
523												5.99		5.98
548														6.28
573												6.53		6.66
579													6.74	
623												7.46		

Table S40: Experimental data for pK_a for Propanoic Acid

Temp (K)	Harned	Larson	Belcher	Harned[1]	Kortum	Mesmer
273	4.89			4.89		
278	4.88					
283	4.88			4.88		
288	4.87					
291		4.88				
293	4.87			4.87	4.89	
298	4.87		4.87			
303	4.88			4.88		
308	4.88					
313	4.89			4.89		
318	4.90					
323	4.91			4.91		
328	4.92					
333	4.94			4.94		
373						5.07
423						5.30
473						5.64
498						5.92

Table S41: Experimental data for pK_a for Oxalic Acid

Temp (K)	Parton	Speakman	Parton[1]	Gane	Darken	Kettler
273						1.25
293		1.25				
298	1.34		1.30	1.23	1.27	1.28
303	1.26					
308	1.27					
323						1.36
348						1.46
373						1.58
398						1.71

Table S42: Experimental data for pK_a for Benzoic Acid

Temp (K)	Jones	Briegleb	Larson	Grunwald	Ives	Dippy	Minnick	Abichandani	Jeffery	Kilpatrick	Mesmer
288	4.21	4.21									
291			4.22								
293	4.21	4.21									
298	4.20	4.21		4.20	4.19	4.20	4.21	4.21	4.20	4.20	4.2
303	4.20	4.22									
308	4.21	4.22									
313		4.23									
318		4.24									
373											4.4
423											4.62
473											4.95
523											5.41

Table S43: Effect of Turning on and off temperature dependency of gaseous phase basicity (ΔG^*_{gas}) for the calculation of pKa for propanoic acid.

Temp	Without adding Temperature dependence of (ΔG^*_{gas})		(ΔG^*_{gas})	With adding Temperature dependence of (ΔG^*_{gas})	
	ΔG^*_{aq}	pKa		ΔG^*_{aq}	pKa
273	5.83	4.68	337.412	5.84	4.69
293	6.46	4.83	337.404	6.46	4.83
298	6.62	4.87	337.402	6.62	4.87
313	7.10	4.98	337.397	7.10	4.97
333	7.77	5.11	337.393	7.76	5.11
353	8.45	5.25	337.390	8.44	5.24
373	9.15	5.38	337.389	9.14	5.37
393	9.87	5.51	337.389	9.85	5.50

Table S44: Gaseous phase free energy for Amino Acids at 298 K using HF/6-31G* level (A, B, C, D forms as explained in the manuscript, all values in Hartrees)

Amino Acid	A	B	C	D
Gly	-283.12	-282.74	-282.24	
β-ala	-322.14	-321.71	-321.24	
Tau	-756.54	-756.19	-755.70	
Sar	-322.13	-321.75	-321.24	
Meth	-797.66	-797.28	-796.77	
Pro	-399.01	-398.62	-398.11	
6-AHA	-439.18	-438.77	-438.26	
Phe-ala	-551.61	-551.23	-550.72	
Glu	-548.77	-548.38	-547.86	-547.23
Asp	-509.75	-509.37	-508.86	-508.21

Table S45: Free energy of Solvation for Amino Acids at 298 K using Density Functional Theory (DFT) at PCM-B3LYP/6-311++G (d, p)// HF/6-31+G (d, p) and SM8T-B3LYP/6-311++G (d, p)// HF/6-31+G (d, p) level of theory. (A, B, C, D forms as explained in the manuscript, all values in kcal/mol)

Amino Acid	A		B		C		D	
	PCM	SM8T	PCM	SM8T	PCM	SM8T	PCM	SM8T
Gly	-81.72	-86.33	-31.56	-33.18	-71.3	-73.63		
β-ala	-73.04	-76.15	-54.35	-62.31	-73.04	-74.93		
Tau	-78.32	-86.18	-31.13	-41.82	-68.54	-78.33		
Sar	-76.38	-75.15	-29.88	-28.96	-70.27	-73.51		
Meth	-66.15	-69.65	-24.82	-26.32	-63.8	-65.17		
Pro	-71.05	-68.72	-29.51	-27.50	-69.63	-72.25		
Phe-ala	-69.96	-72.87	-19.83	-21.86	-64.67	-65.76		
6-AHA	-59.4	-61.46	-28.44	-30.63	-75.46	-76.77		
Glu	-74.85	-73.99	-35.7	-34.95	-73.65	-70.53	-190.63	-198.47
Asp	-81.39	-79.12	-38.18	-36.61	-76.99	-74.21	-203.27	-215.80

Table S46: Gaseous phase free energy and Free energy of Solvation for Carboxylic Acids at 298 K using DFT/B3LYP/6-311++G(d,p) method (A, B forms explained in the manuscript).

Carboxylic Acid	Gaseous Phase free energy (Hartress)		Free energy of Solvation (kcal/mol)			
	A	B	A		B	
			PCM	SM8T	PCM	SM8T
Form	-189.82	-189.28	-7.82	-6.48	-71.97	-78.16
Ace	-229.13	-228.58	-7.45	-7.42	-73.26	-78.02
Prop	-268.43	-267.88	-7.50	-6.59	-71.90	-75.45
Oxa	-378.43	-377.93	-12.64	-12.31	-62.79	-68.72
Benz	-420.87	-420.33	-6.75	-7.59	-66.78	-71.14

Table S47: Breaking down SM8T solvation energy output for carboxylic acids to its various contributions by fitting the results to following equation

$$\Delta \mathbf{G}^{*}_{\mathbf{S(T)}} = \Delta \mathbf{G}^{*}_{\mathbf{S(T_0)}} - \Delta \mathbf{S}^{*}_{\mathbf{S(T_0)}}[\mathbf{T} - \mathbf{T_0}] + \Delta \mathbf{C}^{*}_{\mathbf{P,S(T_0)}} \left[(\mathbf{T} - \mathbf{T_0}) - \mathbf{T} \ln \left(\frac{\mathbf{T}}{\mathbf{T_0}} \right) \right]$$

Carboxylic Acid	$\Delta G^{*}_{S(T_0)}$		$\Delta H^{*}_{S(T_0)}$		$\Delta S^{*}_{S(T_0)}$		$\Delta C^{*}_{P,S(T_0)}$	
	RCOO-	RCOOH	RCOO-	RCOOH	RCOO-	RCOOH	RCOO-	RCOOH
For	-78.1603	-6.4824	-75.3591	-3.0852	0.0094	0.0114	-0.0096	0.0045
Ace	-78.0162	-7.4172	-73.6654	-2.4704	0.0146	0.0166	0.0092	0.0236
Prop	-75.4525	-6.5861	-69.7607	-0.2387	0.0191	0.0213	0.0231	0.0371
Oxa	-68.7221	-12.3091	-64.9971	-7.1537	0.0125	0.0173	-0.0044	0.0181
Benz	-71.1368	-7.59	-64.8192	-0.5572	0.0212	0.0236	0.0403	0.0542

Table S48: Temperature dependent Gas Phase Free energy of Glycine (Species A, B, C of Figure 1), at HF/6-31G*, G3MP2B3 and DFT at B3LYP/6-311++G (d, p) levels of theory. (all values are in Hartrees).

Temp(K)	HF/6-31G*			G3MP2B3			DFT(B3LYP/6-311++G (d, p))		
	A	B	C	A	B	C	A	B	C
273	-283.116	-282.738	-282.233	-284.423	-284.087	-283.544	-284.811	-284.474	-283.935
293	-283.118	-282.740	-282.235	-284.425	-284.089	-283.547	-284.813	-284.476	-283.938
298	-283.119	-282.741	-282.236	-284.429	-284.093	-283.550	-284.814	-284.477	-283.938
313	-283.121	-282.742	-282.237	-284.427	-284.091	-283.549	-284.816	-284.478	-283.940
333	-283.123	-282.745	-282.240	-284.430	-284.094	-283.551	-284.818	-284.481	-283.942
353	-283.126	-282.747	-282.242	-284.432	-284.096	-283.554	-284.821	-284.483	-283.945
373	-283.128	-282.749	-282.244	-284.434	-284.099	-283.556	-284.823	-284.485	-283.947
393	-283.131	-282.752	-282.246	-284.437	-284.101	-283.559	-284.826	-284.488	-283.950

Table S49: Gas Phase Free energy change of Glycine (Species A, B, C of Figure 1) in a Temperature window of 120 K (273K-393K), at HF/6-31G*, G3MP2B3 and DFT at B3LYP/6-311++G (d, p) levels of theory.

Glycine	HF/6-31G*	G3MP2B3	DFT(B3LYP/6-311++G (d, p))
A	-4.36	-4.18	-4.40
B	-4.22	-4.27	-4.09
C	-4.05	-4.25	-4.30

*all values are in kcal/mol

Table S50: Gas Phase Free energy change of protonation of Glycine, ($\Delta G^{0}_{g,deprotonation}$) for pKa_1 and pKa_2 in a Temperature window of 120 K (273K-393K), at HF/6-31G*, G3MP2B3 and DFT at B3LYP/6-311++G (d, p) levels of theory.

Temp (K)	HF/6-31G*		G3MP2B3		DFT(B3LYP/6-311++G (d, p)	
	$\Delta G^{0}_{g,deprotonation}$		$\Delta G^{0}_{g,deprotonation}$		$\Delta G^{0}_{g,deprotonation}$	
	pKa_2	pKa_1	pKa_2	pKa_1	pKa_2	pKa_1
273	310.51	231.15	333.98	204.56	331.66	205.16
293	310.88	231.45	333.99	204.53	331.59	205.26
Difference	0.370	0.296	0.004	-0.029	-0.073	0.100

*all values are in kcal/mol