ESI: The interaction of aluminum with catecholamine-based neurotransmitters: can the formation of these species be considered a potential risk factor for neurodegenerative diseases?

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- **Table S6:** Binding enthalpies and free energies of 1:1,1:2,1:3 Al-ligand complexes using the SMD solvation model.
- **Figure S3:** Binding free energies of 1:1,1:2,1:3 Al-ligand complexes calculated with two different solvation models (IEFPCM and SMD) compared with experimental stability constants ($log\beta$).

1 Single point calculations with different DFT functionalsa and the MP2 method

Table S1: . Binding enthalpies (ΔH_{aq}^{comp}) and binding free energies (ΔG_{aq}^{comp}) with available experimental stability constant ($log\beta$)[1, 2] obtained with single point energy calculations at the MP2/6-311++G(3df,2p) - IEFPCM level of theory.

		ΔH_{aq}^{comp}	ΔG_{aq}^{comp}	$log\beta$
Catechol-based ligands		Protonated Amine		
L-DOPA	1:1	-88.1	-92.6	16.0
	1:2	-160.6	-167.2	29.2
	1:3	-187.4	-193.6	38.4
Dopamine	1:1	-85.5	-88.4	15.6
	1:2	-148.9	-155.1	28.6
	1:3	-185.1	-193.3	37.6
Noradrenaline	1:1	-83.3	-87.4	15.6
	1:2	-144.3	-152.0	28.6
	1:3	-180.8	-191.7	37.9
Adrenaline	1:1	-83.3	-87.5	15.6
	1:2	-144.3	-152.0	28.6
	1:3	-181.7	-190.3	37.9
Catechol	1:1	-88.4	-91.4	16.3
	1:2	-152.4	-158.5	31.7
	1:3	-186.8	-195.4	41.1
4-nitro Catechol	1:1	-74.9	-79.1	13.3
	1:2	-130.2	-137.0	24.8
	1:3	-163.4	-173.3	33.7

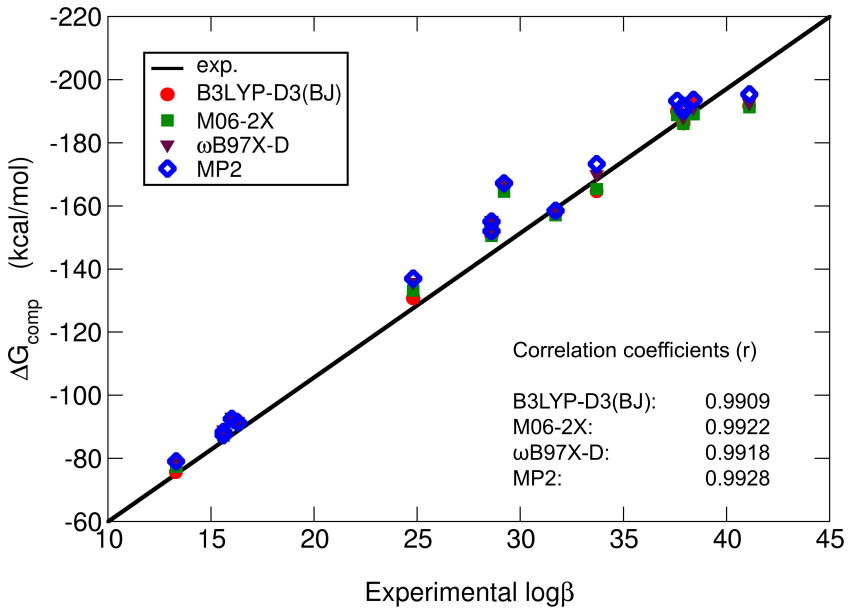
Table S2: . Binding enthalpies (ΔH_{aq}^{comp}) and binding free energies (ΔG_{aq}^{comp}) with available experimental stability constant ($log\beta$)[1, 2] obtained with single point energy calculations at the M06-2X/6-311++G(3df,2p) - IEFPCM level of theory.

		ΔH_{aq}^{comp}	ΔG_{aq}^{comp}	$log\beta$
Catechol-based ligands		Protonated Amine		
L-DOPA	1:1	-87.7	-92.2	16.0
	1:2	-157.8	-164.5	29.2
	1:3	-182.7	-189.0	38.4
Dopamine	1:1	-85.1	-88.0	15.6
	1:2	-147.2	-153.4	28.6
	1:3	-180.5	-188.7	37.6
Noradrenaline	1:1	-83.1	-87.2	15.6
	1:2	-142.8	-150.5	28.6
	1:3	-176.5	-187.3	37.9
Adrenaline	1:1	-83.2	-87.3	15.6
	1:2	-142.8	-150.5	28.6
	1:3	-177.4	-186.0	37.9
Catechol	1:1	-88.1	-91.2	16.3
	1:2	-151.0	-157.0	31.7
	1:3	-182.7	-191.2	41.1
4-nitro Catechol	1:1	-73.2	-77.4	13.3
	1:2	-126.3	-133.1	24.8
	1:3	-155.4	-165.3	33.7

Table S3: . Binding enthalpies (ΔH_{aq}^{comp}) and binding free energies (ΔG_{aq}^{comp}) with available experimental stability constant ($log\beta$)[1, 2] obtained with single point energy calculations at the ωB97X-D/6-311++G(3df,2p) - IEFPCM level of theory.

		ΔH_{aq}^{comp}	ΔG_{aq}^{comp}	$log\beta$
Catechol-based ligands		Protonated Amine		
L-DOPA	1:1	-88.7	-93.2	16.0
	1:2	-160.1	-166.7	29.2
	1:3	-185.1	-191.3	38.4
Dopamine	1:1	-86.2	-89.1	15.6
	1:2	-149.3	-155.5	28.6
	1:3	-182.9	-191.2	37.6
Noradrenaline	1:1	-84.1	-88.2	15.6
	1:2	-144.8	-152.5	28.6
	1:3	-178.6	-189.5	37.9
Adrenaline	1:1	-84.1	-88.2	15.6
	1:2	-144.7	-152.3	28.6
	1:3	-179.5	-188.1	37.9
Catechol	1:1	-88.7	-91.8	16.3
	1:2	-152.3	-158.4	31.7
	1:3	-184.1	-192.7	41.1
4-nitro Catechol	1:1	-74.7	-78.8	13.3
	1:2	-129.1	-135.9	24.8
	1:3	-160.1	-170.0	33.7

Figure S1: Binding energies (ΔG_{aq}^{comp}) calculated with different functionals (B3LYP-D3(BJ[3, 4, 5, 6], M06-2X[7], ωB97XD[8]) and with the MP2 method[9, 10] compared with experimental stability constants ($log\beta$)[1, 2]. All single point calculations are performed using the 6-311++G/3df,2p) basis set on geometries optimized at the B3LYP-D3(BJ)/6-31++G(d,p) level of theory. All calculations include solvation effects through the IEFPCM model[11].



2 Bader's Quantum Theory of Aroms in Molecules (QTAIM)

Delocalization indices are a measure of the average number of electron pairs shared between two atoms, therefore they have been related to the measure of the covalent character of a given bond[12]. Results are reported in Table S4, while in Fig.S2 we represent the sum of the two $D.I._{Al-O}$ of each bidentate complex versus their binding enthalpies (ΔH_{aq}^{comp}).

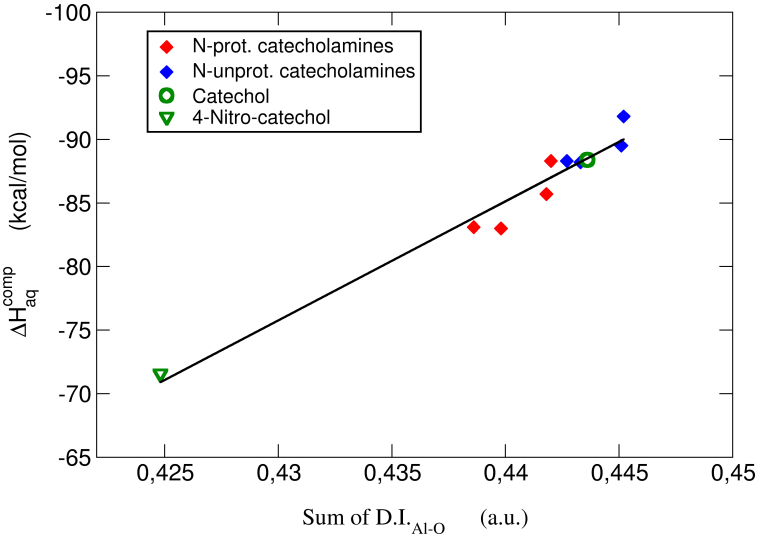
Delocalization indices of protonated catecholamines are slightly smaller than those of their unprotonated counterparts and of catechol, although differences are quite small. As previously hypothesized, this confirms the electron withdrawing effect mediated by the positively charged amino group (Fig. S2) that decreases the electron density from the two Al-O bonds. This effect, in turn, lowers the covalent character of these interactions, leading to lower binding enthalpies (Fig. S2). In both N-protonated and N-unprotonated cases, noradrenaline and adrenaline show smaller $D.I._{Al-O}$ and smaller binding affinities than L-DOPA, dopamine and catechol; this is due to the presence of an EW hydroxyl group in noradrenaline and adrenaline. Interestingly, N-unprotonated neurotransmitters L-DOPA and dopamine bear higher $D.I._{Al-O}$ than catechol. While, as discussed before, L-DOPA bears a higher total negative charge (-3) which is the main responsible of the stronger binding affinity to aluminum, in the case of dopamine the inductive ED effect of the alkyl chain increases the covalency of its Al-O interactions compared to catechol (table S4). Despite the unprotonated dopamine also contains an EW group (NH_2), the effect of the alkyl chain prevails leading to an overall electron donating behavior. The addition of a second EW group such as OH, in addition to NH_2, in the alkyl chain of noradrenaline and adrenaline shifts the overall behavior to an electron withdrawing one, making these two compounds the poorest aluminum binders in both protonated and unprotonated forms (table S4).

Finally, it is important to mention that 4-nitro catechol shows the lowest $D.I._{Al-O}$ values as well as the lowest binding enthalpy (table S4 and Fig. S2) in our dataset. As thoroughly discussed in our previous work[13], the EW nitro group added to an aromatic ring works through both inductive and resonance mechanisms of action, with resonance that prevails over induction. Therefore, the overall electron withdrawing nature of NO_2 is much more pronounced than than the inductive ones mediated by OH and/or NH_2 in catecholamines (Fig. S2).

Table S4: Characteristics of the Al-O Bond Critical Points (in a.u.) for the aluminum-chelator interactions: the electron density at the BCP (ρ_{BCP}), the Laplacian of electron density ($\nabla^2\rho_{BCP}$), and the total energy density at the BCP (H_{BCP}). All structures were optimized and refined at the B3LYP-D3(BJ)/6-311++G(3df,2p) level of theory as reported in the methods section. All calculations take into account implicit solvent effects according to the IEFPCM formalism.

	$Al-O_1$			$Al-O_2$			$D.I.(a.u.)$	
Ligand	ρ_{BCP}	$\nabla^2\rho_{BCP}$	H_{BCP}	ρ_{BCP}	$\nabla^2\rho_{BCP}$	H_{BCP}	$Al-O_1$	$Al-O_2$
Catecholamines with Protonated Amines								
L-DOPA	0.0845	0.5174	-0.0074	0.0856	0.5260	-0.0077	0.2221	0.2199
Dopamine	0.0854	0.5241	-0.0077	0.0843	0.5160	-0.0073	0.2218	0.2200
Noradrenaline	0.0841	0.5143	-0.0072	0.0849	0.5205	-0.0075	0.2198	0.2188
Adrenaline	0.0850	0.5210	-0.0075	0.842	0.5154	-0.0073	0.2204	0.2194
Catecholamines with unprotonated Amines								
L-DOPA	0.0849	0.5207	-0.0075	0.0860	0.5283	-0.0079	0.2236	0.2216
Dopamine	0.0860	0.5287	-0.0078	0.0848	0.5195	-0.0075	0.2239	0.2212
Noradrenaline	0.0856	0.5255	-0.0077	0.0847	0.5192	-0.0074	0.2220	0.2207
Adrenaline	0.0856	0.5254	-0.0077	0.0847	0.5189	-0.0074	0.2224	0.2209
Catecholate	0.0858	0.5271	-0.0078	0.0847	0.5193	-0.0074	0.2228	0.2208
4-nitro catechol	0.0846	0.5189	-0.0073	0.0802	0.4838	-0.0062	0.2183	0.2065

Figure S2: Sum of the delocalization indices of the two Al-O bonds in 1:1 Aluminum-Catechol/Catecholamine complexes versus their values of ΔH_{aq}^{comp}.



3 Energy Decomposition Analysis

Table S5: Energy Decomposition Analysis, values obtained at the full electron (no frozen core) B3LYP-D3(BJ)/ET-QZ3P-1DIFFUSE level of theory in gas phase, using the ADF2017 modeling suite of programs[14, 15, 16].

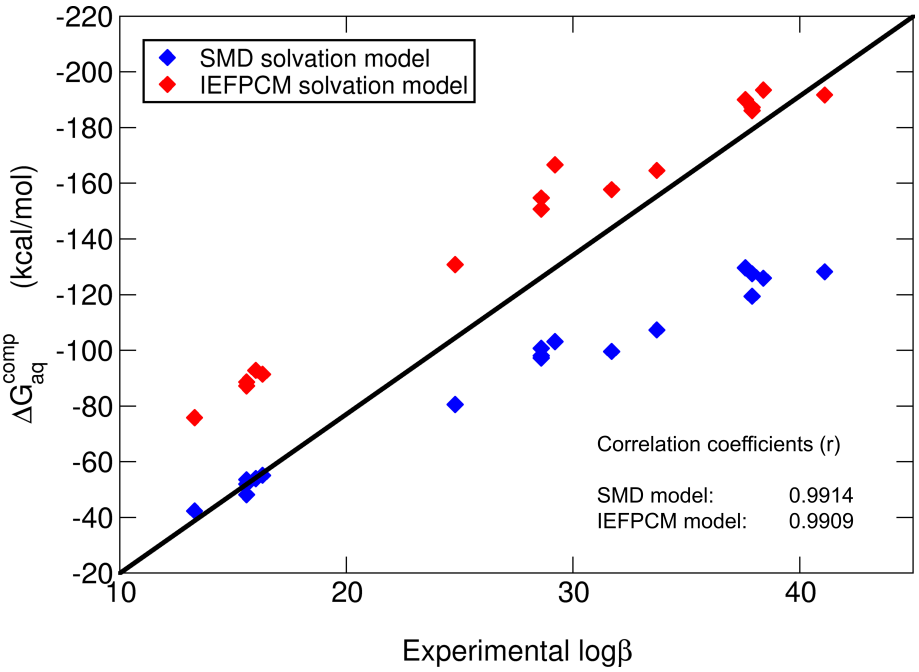
Structure	ΔE_{elstat}	(%)	ΔE_{oi}	(%)	ΔE_{Pauli}	ΔE_{disp}	ΔE_{int}
Catecholamines with protonated amines							
L-DOPA	-573.5	(62.3)	-346.5	(37.7)	146.6	-6.6	-779.8
Dopamine	-434.5	(57.3)	-323.7	(42.7)	142.0	-6.5	-622.7
Noradrenaline	-442.4	(58.5)	-313.3	(41.5)	141.8	-6.5	-620.4
Adrenaline	-451.6	(58.9)	-314.5	(41.1)	143.0	-6.5	-629.7
Catecholamines with unprotonated amines							
L-DOPA	-691.3	(64.5)	-380.3	(35.5)	150.2	-6.6	-927.9
Dopamine	-587.4	(63.1)	-343.4	(36.9)	148.8	-6.5	-788.6
Noradrenaline	-585.1	(63.0)	-343.6	(37.0)	147.9	-6.5	-787.2
Adrenaline	-578.7	(62.4)	-348.0	(37.6)	147.6	-6.5	-785.7
Catecholate	-610.4	(64.9)	-329.7	(35.1)	149.9	-6.5	-796.7
4-nitro catechol	-647.1	(72.4)	-247.1	(27.6)	147.2	-6.5	-753.5

4 Comparison of different solvation models

Table S6: . Binding enthalpies (ΔH_{aq}^{comp}) and binding free energies (ΔG_{aq}^{comp}) with available experimental stability constant ($log\beta$)[1, 2] obtained with single point energy calculations at the B3LYP-D3(BJ)/6-311++G(3df,2p) level of theory using the SMD solvation model[17].

		ΔH_{aq}^{comp}	ΔG_{aq}^{comp}	$log\beta$
Catechol-based ligands		Protonated Amine		
L-DOPA	1:1	-52.3	-53.9	16.0
	1:2	-98.6	-103.1	29.2
	1:3	-119.4	-125.9	38.4
Dopamine	1:1	-50.7	-53.5	15.6
	1:2	-93.4	-100.7	28.6
	1:3	-119.7	-129.6	37.6
Noradrenaline	1:1	-49.3	-51.9	15.6
	1:2	-90.7	-97.2	28.6
	1:3	-117.3	-127.5	37.9
Adrenaline	1:1	-45.4	-48.1	15.6
	1:2	-90.2	-98.0	28.6
	1:3	-109.3	-119.4	37.9
Catechol	1:1	-51.8	-55.1	16.3
	1:2	-93.9	-99.6	31.7
	1:3	-119.0	-128.2	41.1
4-nitro Catechol	1:1	-39.8	-42.3	13.3
	1:2	-73.90	-80.5	24.8
	1:3	-96.9	-107.3	33.7

Figure S3: Binding energies (ΔG_{aq}^{comp}) calculated at the B3LYP-D3(BJ)/6-311++G(3df,2p) level of theory using two different solvation models (IEFPCM[11] and SMD[17]) compared with experimental stability constants ($log\beta$)[1, 2].



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