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Contribution To The Molecular Lipophilicity Scale By Qspr Models Of Lipophilicity Prediction

Ouanlo Ouattara*, Mamadou Guy-Richard Kone, Thomas Sopi Affi,Kafoumba Bamba, Yafigui Traore, Nahossé Ziao

Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, UFR SFA, Université Nangui Abrogoua, 02 BP 801 Abidjan 02, République de Côte d'Ivoire.

**Corresponding author : Ouanlo Ouattara*

ABSTRACT

This work deals with the prediction of the lipophilicity of forty-four (44)aromatic substances whoseexperimental values of lipophilicity are non-existent to date. Using QSPR models of lipophilicpredictionbased on empirical and quantum descriptorsat the AM1 level, the lipophilicity of these 44 molecules has been predicted by quantum chemistrymethods, thuscontributing to the increase in scale of molecularlipophilicity. The reliability of the prediction of lipophilicity by model 1 at the level of the empiricaldescriptorsis 97.84%. The prediction by the model 2 at the level of the quantum descriptors of the AM1 levelis 95.60%.

Keywords : Prediction - MolecularLipophilicity - MolecularModeling - QSPR Models - Quantum Chemistry.

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I. INTRODUCTION

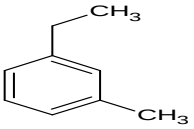
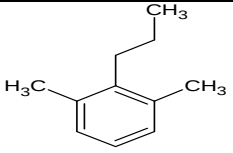
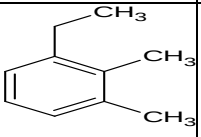
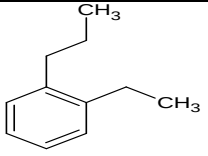
Molecularlipophilicityis the affinitythat a substance has for fatty substances likelipids. It expresses the bioavailability of a substance in living organisms. Essential parameter in the rationaldesignofdrugs,lipophilicityisintimatelylinke d to the partition coefficient P of the octanol-water system.However,tsexperimentaldeterminationisdiffi cult or even impossible in some cases.In addition to experimentalapproaches,thereareralsoseveraltheoreti calapproachestocalculatinglipophilicitywithmultipl e constraints, amongothers : averylimitedbase of experimentallipophilicitydataveryexpensiveequipm ent - dangerousness of certain tests - environmental pollution - ignorance stericeffects and electronic interactionsfailuretoaddresstheconformationalflexib ility of molecules.To solvetheseproblems, Ouanlo Ouattara and al. [1; 2], haveproposed in earlierworks the contribution of quantum chemistry in the prediction of lipophilicity by the use of empiricaland quantum descriptorsat AM1 level.The aim of thisworkis to predict the lipophilicity of 44 aromatic substances whoseexperimental values are non-existent to date. The QSPR models 1 and 2 respectivelybased on the empirical [1] and quantum descriptorsat AM1 level [2] wereused to predict the lipophilicityofthese44moleculeswithapredictivereli ability of 97.84% for model 1 and 95.60% for model 2.

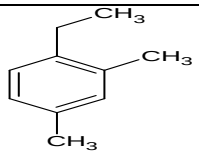
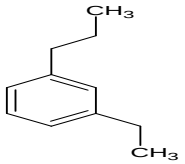
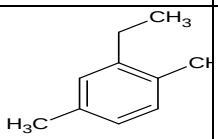
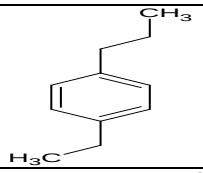
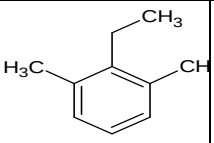
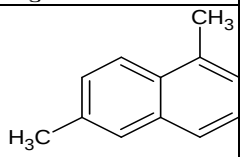
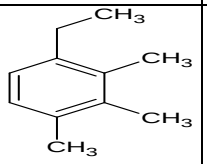
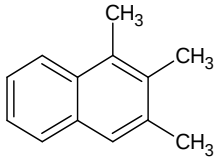
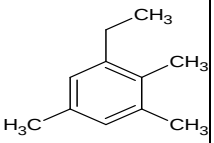
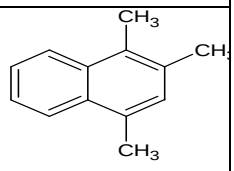
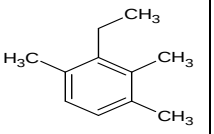
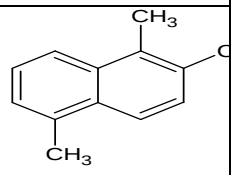
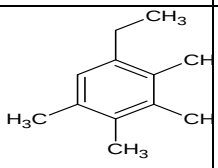
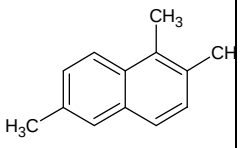
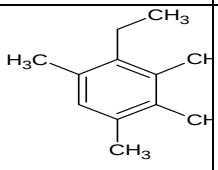
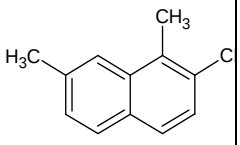
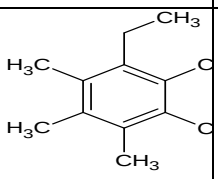
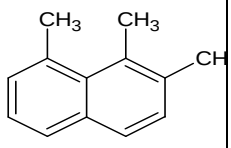
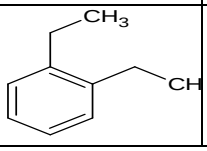
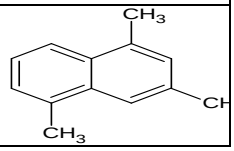
II. COMPUTATIONAL METHODS

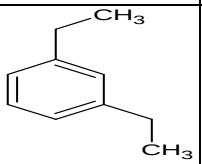
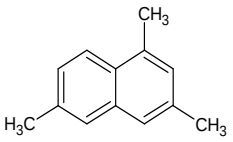
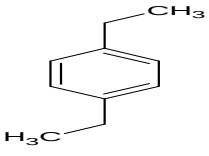
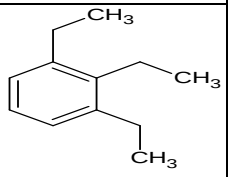
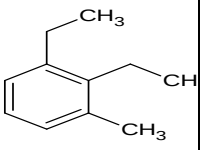
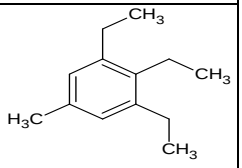
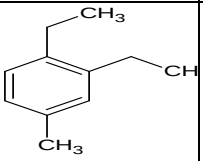
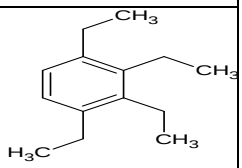
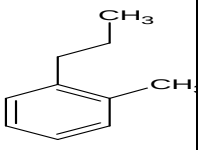
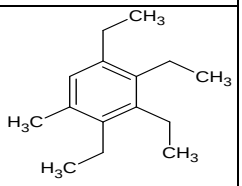
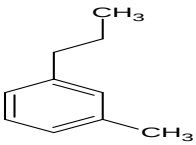
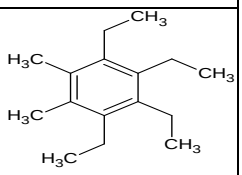
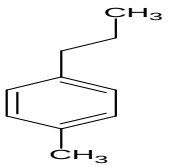
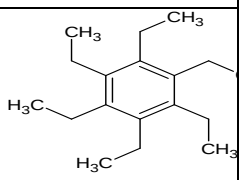
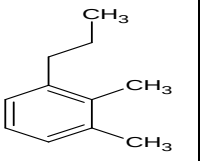
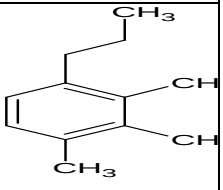
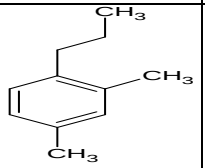
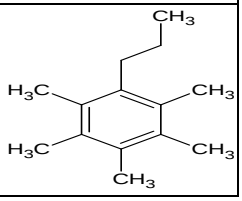
2.1 Presentation of the 44 molecules of unknownlipophilicity

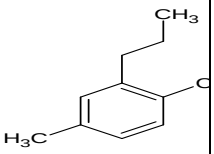
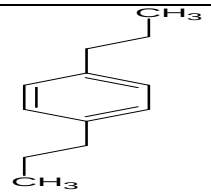
The codedmolecules Mi, i rangingfrom 1 to 44 of unknownexperimentallipophilia [3], are recorded in Table 1.

Table 1: Names and 2D structures of the 44 aromaticmolecules.

COD E	Substance chimique	Structure 2D	COD E	Substance chimique	Structure 2D
M1	1-ethyl-3-methylbenzene		**M23**	1,3-dimethyl-2-propylbenzene	
M2	1-ethyl-2,3-dimethylbenzene		**M24**	1-ethyl-2-propylbenzene	

M3	1-ethyl-2,4-dimethylbenzene		**M25**	1-ethyl-3-propylbenzene	
M4	2-ethyl-1,4-dimethylbenzene		**M26**	1-ethyl-4-propylbenzene	
M5	2-ethyl-1,3-dimethylbenzene		**M27**	1,6-dimethylnaphthalene	
M6	1-ethyl-2,3,4-trimethylbenzene		**M28**	1,2,3-trimethylnaphthalene	
M7	1-ethyl-2,3,5-trimethylbenzene		**M29**	1,2,4-trimethylnaphthalene	
M8	2-ethyl-1,3,4-trimethylbenzene		**M30**	1,2,5-trimethylnaphthalene	
M9	1-ethyl-2,3,4,5-tetramethylbenzene		**M31**	1,2,6-trimethylnaphthalene	
M10	2-éthyl-1,3,4,5-tetramethylbenzene		**M32**	1,2,7-trimethylnaphthalene	
M11	1-ethyl-2,3,4,5,6-pentamethylbenzene		**M33**	1,2,8-trimethylnaphthalene	
M12	1,2-diethylbenzene		**M34**	1,3,5-trimethylnaphthalene	

M13	1,3-diethylbenzene		**M35**	1,3,6-trimethylnaphthalene	
M14	1,4-diethylbenzene		**M36**	1,2,3-triethylnaphthalene	
M15	1,2-diethyl-3-methylbenzene		**M37**	1,2,3-triethyl-5-methylnaphthalene	
M16	1,2-diethyl-4-methylbenzene		**M38**	1,2,3,4-tetraethylbenzene	
M17	1-methyl-2-propylbenzene		**M39**	1,2,3,4-tetraethyl-5-methylbenzene	
M18	1-methyl-3-propylbenzene		**M40**	1,2,3,4-tetraethyl-5,6-dimethylbenzene	
M19	1-methyl-4-propylbenzene		**M41**	Hexaethylbenzene	
M20	1,2-dimethyl-3-propylbenzene		**M42**	1,2,3-trimethyl-4-propylbenzene	
M21	2,4-dimethyl-1-propylbenzene		**M43**	1,2,3,4,5-pentamethyl-6-propylbenzene	

M22	1,4-dimethyl-2-propylbenzene		**M44**	1,4-dipropylbenzene	

2.2 Computationaldetails

All the moleculeswerefullyoptimizedusing the GAUSSIAN 03 software [4] for the semi-empiricalmethod AM1 of model 2, which made it possible to calculate the quantum descriptors of the AM1 level. The empiricaldescriptors of model 1 werecalculatedusing the ACD / CHEMSKETCH software [5].

2.3 QSPR models of molecularlipophilicityprediction

ThemolecularlipophilicitypredictionQSPR modelsused to predict the lipophilicity of the moleculesinTable1arederivedfromourpreviouswork [1; 2].Thesemodels 1 and 2 are performing in the prediction of lipophilicitybecausetheysatisfy all Tropsha criteria[6]. Theyalso check normality tests (Shapiro-Wilk test) [7] and autocorrelation tests (Durbin-Watson test) [8].The predictivecapacity of model 1 is 97.84% and that of model 2 is 95.60%. Thesemodels are as follows:

Model 1 : Empiricaldescriptors

$$\mathbf{logP = -0.4547 + 0.0217 \cdot V_M + 0.7689 \cdot R_M - 1.8745 \cdot P_M}$$

$n = 14$; $R = 0.9925$; $R^2 = 0.9851$; $s = 0.0867$; $F = 220.9188$; $FIT = 2.2877$

Model 2: Quantum descriptors of the AM1 level

$$\mathbf{logP = 1.9891 - 417.8917 \cdot \varepsilon_B + 3.2938 \cdot \chi + 1.8490 \cdot Q}$$

$n = 14$; $R = 0.9863$; $R^2 = 0.9729$; $s = 0.1171$; $F = 119.4556$; $FIT = 1.2422$

2.4 Values of moleculardescriptors of models 1 and 2

Theexpressionsof the moleculardescriptorsinvolved in the expressions of models 1 and 2 aregiven in Tables 2 and 3. Table 4 gives the numerical values of thesedescriptors.

Table 2: Expression of empiricaldescriptors in model 1.

Empiricaldescriptors	Notation	Expression
Molecular volume [9]	V_M	V_M
Molarrefractivity[10]	R_M	$\frac{(n^2-1)}{(n^2+2)} \cdot \frac{M}{d}$
Molarpolarizability[11 ; 12]	P_M	$\frac{(\varepsilon_r-1)}{(\varepsilon_r+2)} \cdot \frac{M}{d}$

Table 3: Expression of quantum descriptors in model 2

Quantum descriptors	Notation	Expression
Basicitybyhydrogenbonding[13]	ε_B	$\varepsilon_B = 0.01 \cdot [\varepsilon_{LUMO}(H_2O) - \varepsilon_{HOMO}]$
Chemicalelectronegativity[14]	χ	$\chi = \frac{\varepsilon_{HOMO} - \varepsilon_{LUMO}}{2}$
Sumofabsolutevalues absolues of net electrical charges of Mulliken	Q	

Table 4: Values moleculardescriptors in models 1 and 2.

CODE	Model 1descriptors			Model 2descriptors		
	$V_M\ (cm^3)$	$R_M\ (cm^3)$	$P_M\ (10^{-24} cm^3)$	$\varepsilon_B(a.u)$	$\chi(a.u)$	$Q(e)$
M1	138.50	40.62	16.10	0.0050	-0.1792	2.3286
M2	154.80	45.45	18.01	0.0050	-0.1786	2.5586

M3	154.80	45.45	18.01	0.0049	-0.1747	2.5557
M4	154.80	45.45	18.01	0.0049	-0.1744	2.5547
M5	154.80	45.45	18.01	0.0050	-0.1789	2.5580
M6	171.00	50.27	19.93	0.0049	-0.1746	2.7870
M7	171.00	50.27	19.93	0.0049	-0.1738	2.7860
M8	171.00	50.27	19.93	0.0049	-0.1739	2.7879
M9	187.30	55.10	21.84	0.0049	-0.1721	3.0148
M10	187.30	55.10	21.84	0.0049	-0.1720	3.0172
M11	203.60	59.92	23.75	0.0048	-0.1714	3.2560
M12	155.00	45.35	17.97	0.0050	-0.1796	2.6273
M13	155.00	45.35	17.97	0.0050	-0.1798	2.6250
M14	155.00	45.35	17.97	0.0050	-0.1771	2.6222
M15	171.30	50.17	19.89	0.0050	-0.1791	2.8600
M16	171.30	50.17	19.89	0.0049	-0.1751	2.8566
M17	155.00	45.25	17.94	0.0050	-0.1786	2.6467
M18	155.00	45.25	17.94	0.0050	-0.1792	2.6488
M19	155.00	45.25	17.94	0.0050	-0.1761	2.6453
M20	171.30	50.08	19.85	0.0050	-0.1785	2.8799
M21	171.30	50.08	19.85	0.0049	-0.1744	2.8766
M22	171.30	50.08	19.85	0.0049	-0.1742	2.8755
M23	171.30	50.08	19.85	0.0050	-0.1787	2.8795
M24	171.50	49.98	19.81	0.0050	-0.1791	3.2691
M25	171.50	49.98	19.81	0.0050	-0.1796	2.9453
M26	171.50	49.98	19.81	0.0050	-0.1768	2.9424
M27	156.00	53.74	21.30	0.0048	-0.1523	2.5857
M28	172.30	58.57	23.21	0.0047	-0.1511	2.8204
M29	172.30	58.57	23.21	0.0047	-0.1496	2.8181
M30	172.30	58.57	23.21	0.0047	-0.1500	2.8226
M31	172.30	58.57	23.21	0.0047	-0.1510	2.8170
M32	172.30	58.57	23.21	0.0047	-0.1514	2.8183
M33	172.30	58.57	23.21	0.0047	-0.1487	2.8199
M34	172.30	58.57	23.21	0.0047	-0.1502	2.8240
M35	172.30	58.57	23.21	0.0047	-0.1518	2.8207
M36	187.80	54.90	21.76	0.0050	-0.1788	3.1735
M37	204.10	59.72	23.67	0.0049	-0.1743	3.4011
M38	220.70	64.44	25.54	0.0049	-0.1747	3.7035
M39	236.90	69.27	27.46	0.0049	-0.1730	3.9204
M40	253.20	74.09	29.37	0.0049	-0.1725	4.1611
M41	286.30	83.54	33.12	0.0049	-0.1736	4.7645
M42	187.50	54.90	21.76	0.0049	-0.1744	3.1085
M43	220.10	64.55	25.59	0.0048	-0.1714	3.5793
M44	188.00	54.61	21.65	0.0050	-0.1766	3.2626

III. RESULTS AND DISCUSSION

The results of the prediction are shown in Table 5. According to Table 5, the predicted values obtained by the models 1 and 2 are all positive, thusshowingthatthesearomaticmoleculesare lipophilic.Themodel1basedonempiricaldescriptorsgives values of logP substantiallyidentical to those of the model 2 established on the basis of the quantum descriptors of the AM1 level.

Table 5: Prediction of the lipophilicity of 44 aromatic compounds whose non-existent experimental data.

COD	Chemical substance	Model 1 $logP_{pred}$	Model 2 $logP_{pred}$	CODE	Chemical substance	Model 1 $logP_{pred}$	Model 2 $logP_{pred}$
M1	1-ethyl-3-methylbenzene	3.60	3.61	**M23**	1,3-dimethyl-2-propylbenzene	4.56	4.64

M2	1-ethyl-2,3-dimethylbenzene	4.09	4.05	**M24**	1-ethyl-2-propylbenzene	4.56	5.35
M3	1-ethyl-2,4-dimethylbenzene	4.09	4.08	**M25**	1-ethyl-3-propylbenzene	4.56	4.75
M4	2-ethyl-1,4-dimethylbenzene	4.09	4.08	**M26**	1-ethyl-4-propylbenzene	4.56	4.77
M5	2-ethyl-1,3-dimethylbenzene	4.09	4.04	**M27**	1,6-dimethylnaphthalene	4.32	4.28
M6	1-ethyl-2,3,4-trimethylbenzene	4.55	4.51	**M28**	1,2,3-trimethylnaphthalene	4.81	4.73
M7	1-ethyl-2,3,5-trimethylbenzene	4.55	4.52	**M29**	1,2,4-trimethylnaphthalene	4.81	4.74
M8	2-ethyl-1,3,4-trimethylbenzene	4.55	4.52	**M30**	1,2,5-trimethylnaphthalene	4.81	4.74
M9	1-ethyl-2,3,4,5-tetramethylbenzene	5.04	4.96	**M31**	1,2,6-trimethylnaphthalene	4.81	4.73
M10	2-ethyl-1,3,4,5-tetramethylbenzene	5.04	4.97	**M32**	1,2,7-trimethylnaphthalene	4.81	4.73
M11	1-ethyl-2,3,4,5,6-pentamethylbenzene	5.52	5.42	**M33**	1,2,8-trimethylnaphthalene	4.81	4.75
M12	1,2-diethylbenzene	4.09	4.16	**M34**	1,3,5-trimethylnaphthalene	4.81	4.75
M13	1,3-diethylbenzene	4.09	4.15	**M35**	1,3,6-trimethylnaphthalene	4.81	4.73
M14	1,4-diethylbenzene	4.09	4.17	**M36**	1,2,3-triethylnaphthalene	5.04	5.19
M15	1,2-diethyl-3-methylbenzene	4.55	4.60	**M37**	1,2,3-triethyl-5-methylnaphthalene	5.52	5.65
M16	1,2-diethyl-4-methylbenzene	4.55	4.63	**M38**	1,2,3,4-tetraethylbenzene	6.01	6.21
M17	1-methyl-2-propylbenzene	4.07	4.20	**M39**	1,2,3,4-tetraethyl-5-methylbenzene	6.47	6.63
M18	1-methyl-3-propylbenzene	4.07	4.20	**M40**	1,2,3,4-tetraethyl-5,6-dimethylbenzene	6.95	7.09
M19	1-methyl-4-propylbenzene	4.07	4.23	**M41**	Hexaethylbenzene	7.91	8.19
M20	1,2-dimethyl-3-propylbenzene	4.56	4.64	**M42**	1,2,3-trimethyl-4-propylbenzene	5.04	5.11
M21	2,4-dimethyl-1-propylbenzene	4.56	4.67	**M43**	1,2,3,4,5-pentamethyl-6-propylbenzene	5.99	6.02
M22	1,4-dimethyl-2-propylbenzene	4.56	4.67	**M44**	1,4-dipropylbenzene	5.03	5.36

IV. CONCLUSION

The contribution of quantum chemistry in the prediction of molecularlipophilicitysolves the thorny question of multiple constraintsrelated to the experimental and theoreticaldetermination of the lipophilicity of organic compounds.The establishment of QSPR models for predictinglipophilia by quantum chemicalmethods in ourpreviousworkallowed us to predict the molecularlipophilicity of 44 chemical substances

whoseexperimental values are unknown to date.The model 1 based on the empiricaldescriptors has a predictivecapacity of 97.84% and the model 2 based on the AM1 quantum descriptors has a predictivecapacity of 95.60%.The predicted values in thiswork are thereforereliableabove 95%, contributingsignificantly to an increase in the database on molecularlipophilicity.

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