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Determination of the pKa value of some 1,2,4-triazol derivatives in forty seven different solvents using semi-empirical quantum methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1, and MNDO) by MOPAC computer program

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Abstract. In this study, we calculated the enthalpy (ΔH, kcal/mol), entropy (ΔS, cal/K·mol) and free energy (ΔG, kcal/mol) thermodynamic values of each molecule for forty-seven different solvent media according to semi-empirical quantum methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1, and MNDO) using the MOPAC computer program. The theoretical pKa values were calculated by placing these values in the thermodynamic cycle. It was determined that the triazole derivative molecules examined in this study showed a very high acidity in trifluoroacetic acid and a very low acidity in cyclohexane. The fifth molecule of the triazole derivative molecules examined in this study showed a very high acidity (pKa :1.2457) in trifluoroacetic acid according to the RM1 semi-empirical quantum method. On the other hand, it was determined that the fourth molecule showed a very low acidity (pKa : 69.5668) in cyclohexane according to the RM1 semi-empirical quantum method.

***Keywords*:** pKa; 1,2,4-triazole; semi-empirical quantum method; MOPAC computer program.

1. Introduction

Triazoles and their derivatives belong to one of the most important heterocyclic family [1]. 1,2,4-triazole derivatives have received much attention in medicinal chemistry due to their broadspectrum biological activities such as antiviral [2], antibacterial [3], antifungal [4, 5] (examples of antifungal drugs are fluconazole [6, 7], itraconazole [8], ravuconazole [9], voriconazole [10-12] and posaconazole [13]), anti-tubercular [14-16], immunosuppressant [17], antihypertensive [18], anti-inflammatory [19, 20], anticonvulsant [21, 22], analgesic [23], hypoglycemic [24], antidepressant [25, 26] and anticancer [27-29] activities. 1,2,4-Triazole derivatives are an important class of antifungal agents that widely use in the treatment of fungal infections [30]. 1,2,4 – triazole derivatives are reported as insecticides [31], antiasthmatics [32], antidepressants [33], insecticidal [34] and plant growth regulators [35]. In addition, compounds having triazole moieties, such as vorozole, letrozole, and anastrozole are found to be very effective aromatase inhibitors, which could prevent breast cancer [36-38]. 1,2,4-triazole moiety is reported to interact strongly with heme iron, and aromatic substituents on the triazole are very effective in interacting with the active site of aromatase [39, 40].

pKa is one of the fundamental chemical properties of the organic molecules, defining their ability not only to release or attract acidic protons, but also to interact with the environment [41].

The pKa value is a important parameter of a substance because it gives information about acidity, hydrogen-bonding capacity, and solubility, which are useful for understanding the nature of compounds [42]. Knowing the pKa value(s) of a biologically active compound is essential in drug research because pKa values determine the solubility, absorption, distribution, metabolism, and elimination of molecules. Furthermore, the pKa value is also a useful parameter to optimize separation procedures [43-47].

We have studied semi-empirical quantum methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1, and MNDO) for the prediction of pKa for some 1,2,4-triazol derivatives. This gives rise to a important model that can be applied reliably across acidic and basic functionalities. The model performs as well as more computationally intensive method sets, which were devised to specifically benchmark pKa prediction methods and cover important areas of drug-like molecules [48].

MOPAC (Molecular Orbital Package) 2016 computer program is a computational chemistry software with strong semi-empirical quantum chemistry practices for the prediction of chemical properties, calculations of chemical molecules, and modeling of chemical reactions [49]. MOPAC 2016 computer program is faster and highly reliable software for chemical property predictions and physical property predictions such as Gibbs free energies, activation energies, reaction paths, dipole moments, non-linear

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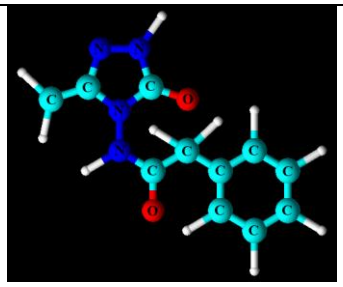
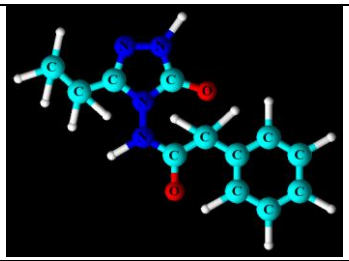
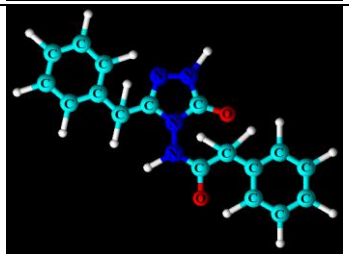
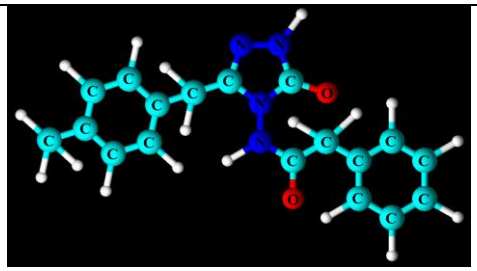
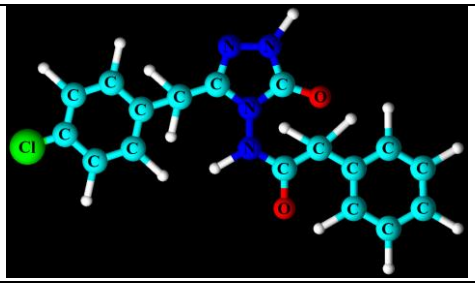
optical properties, enthalpy, heat capacity, entropy, and infrared spectra [50].

2. Experimental

2.1. Studied molecules

In this article, pKa value of five 1,2,4-triazol derivatives (**(1)** N-(3-methyl-5-oxo-1,5-dihydro- 4H-1,2,4- triazol-4-yl)-2-phenyl acetamide, **(2)** N-(3-ethyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-phenylacetamide, **(3)** N-(3-benzyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-phenyl acetamide, **(4)** N-{3-[(4-methylphenyl)methyl]-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl}-2-phenylacetamide, **(5)** N-{3-[(4-chlorophenyl)methyl]-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl}-2-phenyl acetamide) has been theoretically determined in forty seven different solvents using semi-empirical quantum methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1, and MNDO) by MOPAC computer program. The nomenclature, molecular formulas and SMILE forms of the studied molecules are given in Table 1.

Table 1. Nomenclature, molecular formulas and SMILE forms of studied molecules

Molecule	Name	Structure SMILES form	Structural formula
1	N-(3-methyl-5-oxo-1,5-di hydro-4H-1,2,4-triazol-4-yl)-2-phenyl acetamide	O=C(NN1C(=O)NN=C1C)Cc1ccccc1	
2	N-(3-ethyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)-2-phenyl acetamide	CCC1=NNC(=O)N1NC(=O)Cc1ccccc1	
3	N-(3-benzyl-5-oxo-1,5-di hydro-4H-1,2,4-triazol-4-yl)-2-phenyl acetamid	O=C1NN=C(Cc2ccccc2)N1NC(=O)Cc1ccccc	
4	N-{3-[(4-methyl phenyl) methyl]-5-oxo-1,5-dihydro -4H-1,2,4-triazol-4-yl}-2-phenyl acetamide	Cc1ccc(CC2=NNC(=O)N2NC(=O)Cc2ccccc2)cc1	
5	N-{3-[(4-chloro phenyl) methyl]-5-oxo-1,5-dihydro -4H-1,2,4-triazol-4-yl}-2-phenyl acetamide	Clc1ccc(CC2=NNC(=O)N2NC(=O)Cc2ccccc2)cc1	

2.2. Studied solvents

There are forty-seven different solvers in the library of the MOPAC 2016 computer program that we used in this study. We included all the solvents in the library of the program to calculate the pKa values of the molecules. All the solvents in the library of the MOPAC 2016 computer program and used in this study are given in Table 2.

Table 2. Solvents and molecular formulas used in pKa calculations

Number	Solvent	Number	Solvent
1	Water (H_2O)	25	Dichloroethane ($ClCH_2CH_2Cl$)
2	Acetic acid (CH_3COOH)	26	Ethylene glycol ($HOCH_2CH_2OH$)
3	Acetone (CH_3COCH_3)	27	Formamide ($HCONH_2$)
4	Acetonitrile (CH_3CN)	28	Formic acid ($HCOOH$)
5	Ammonia (NH_3)	29	Glycerol ($C_3H_8O_3$)
6	Aniline ($C_6H_5NH_2$)	30	Hexamethyl phosphoramide ($C_6H_{18}N_3OP$)
7	Benzene (C_6H_6)	31	Hexane (C_6H_{14})
8	Benzyl alcohol ($C_6H_5CH_2OH$)	32	Hydrazine (N_2H_4)
9	Bromoform ($CHBr_3$)	33	Methanol (CH_3OH)
10	Butanol (C_4H_9OH)	34	Methyl ethyl ketone ($CH_3CH_2COCH_3$)
11	Iso-butanol ($(CH_3)_2CHCH_2OH$)	35	Dichloromethane (CH_2Cl_2)
12	Tert-butanol ($(CH_3)_3COH$)	36	Methyl formamide ($HCONHCH_3$)
13	Carbon disulphide (CS_2)	37	Methyl pyrrolidinone (C_5H_9NO)
14	Carbon tetrachloride (CCl_4)	38	Nitrobenzene ($C_6H_5NO_2$)
15	Chloroform ($CHCl_3$)	39	Nitromethane (CH_3NO_2)
16	Cyclohexane (C_6H_{12})	40	Phosphoryl chloride ($POCl_3$)
17	Cyclohexanone ($C_6H_{10}O$)	41	Iso-propanol ($(CH_3)_2CHOH$)
18	Dichlorobenzene ($C_6H_4Cl_2$)	42	Pyridine (C_5H_5N)
19	Diethyl ether ($(CH_3CH_2)_2O$)	43	Sulfolane ($C_4H_8SO_2$)
20	Dioxane ($C_4H_8O_2$)	44	Tetrahydrofuran (C_4H_8O)
21	Dimethyl formamide ($(CH_3)_2NCHO$)	45	Toluene ($C_6H_5CH_3$)
22	Dimethyl sulfoxide ($(CH_3)_2SO$)	46	Triethylamine ($(CH_3CH_2)_3N$)
23	Ethanol (CH_3CH_2OH)	47	Trifluoroacetic acid (CF_3COOH)
24	Ethyl acetate ($CH_3COOCH_2CH_3$)		

2.3. Semi-empirical quantum methods

Semi-experimental quantum methods are based on quantum mechanical principles such as *ab-initio* molecular methods as well as experimental results. Semi-experimental quantum methods cannot calculate two-electron integrals of electron-electron interactions. For these integral expressions, they use parameters that are formed from the information obtained experimentally, from molecules with electronic structure similar to the molecule under investigation. In other words, semi-experimental quantum methods include the Schrödinger wave equation with parameters derived from experimental data and calculates the solution by converting it to an easier form. Semi-empirical quantum methods are very advantageous in that they can perform very fast calculations that are compatible with experimental data in calculations to be made on biological, macromolecules where ab-initio calculation methods are insufficient [50].

2.4. Thermodynamic cycle method

In this study, we used the thermodynamic cycle method [51, 52] which is given in Figure 1, and which is widely used in the literature for theoretical pKa calculations.

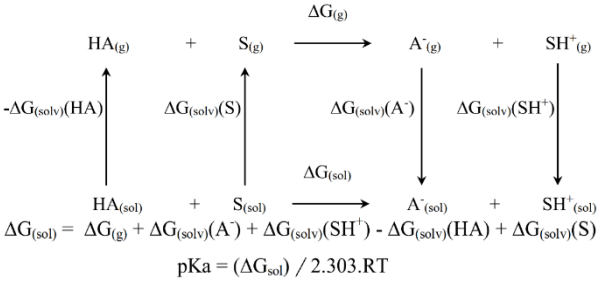


Figure 1. Thermodynamic cycle

We performed the theoretical pKa calculations with the help of seven different semi-experimental quantum methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1, and MNDO) in 47 different solvent systems using the MOPAC 2016 computer program for each parameter in this thermodynamic cycle.

3. Results and discussion

To find the free energy changes of SH^+ (protonated solvent), S (solvent), HA (weak acid) and A^- (deprotonated weak acid) forms according to the thermodynamic cycle, firstly, the enthalpy change (ΔH, cal/mol), and entropy change (ΔS, cal/ K·mol) values were calculated. Then, using these free energy changes (ΔG, cal/mol), pKa values were calculated separately for each solvent at 298 K with the help of semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO). It is defined as enthalpy H, H = U+ pV where p is the pressure of the system and V is its volume. Since U is the internal energy, p and V are all state functions, enthalpy is also a state function. As with any state function, the enthalpy change (ΔH) between any pair of initial and final states is independent of the path between them. While the definition of enthalpy may seem arbitrary, it has important implications for thermochemistry. Enthalpy means heat exchanged under constant pressure. The internal energy of a substance increases as the temperature rises. The increase is dependent on the conditions under which the heating takes place and the sample is assumed to be confined to a constant volume. The internal energy of a system increases as the temperature rises. The second law of thermodynamics is expressed as entropy. Entropy is a measure of the disorder of a system. As disorder increases, entropy increases; as disorder decreases, entropy decreases. Since in most cases temperature, pressure and volume change together, choosing two of these three variables

independently, the algebraic sum of the entropy changes resulting from the change of these variables gives the entropy change in the system. The equation $\Delta G = \Delta H - T \cdot \Delta S$ was used to calculate the free energy change. If the free energy change is greater than zero, the reaction is involuntary, if the free energy change is less than zero, the reaction is optional. The pKa values of the molecules calculated according to the thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) are given in Table 3-7. The graphical representation of the data and values in these tables is given in Figure 2-6.

Table 3. pKa values of the Molecule 1, calculated with thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) in forty-seven different solvent media

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Water	15.8671	14.5823	15.0834	17.2447	14.6207	16.8149	16.4671
Acetic acid	5.1346	5.6623	6.4273	5.1127	6.2347	5.8741	4.7886
Acetone	19.4263	20.0018	21.1368	19.8069	19.9266	20.4529	21.4962
Acetonitrile	25.4835	26.5833	25.9328	26.1149	26.4283	26.6672	25.3940
Ammonia	38.9631	39.6227	39.9449	40.1829	39.6425	40.1243	39.4672
Aniline	8.4375	7.7540	7.6045	8.5692	9.1125	7.8449	9.1377
Benzene	44.2473	45.2997	45.3386	43.2762	46.4374	46.8349	45.9662
Benzyl alcohol	16.2439	15.9457	16.3566	14.6882	16.5758	15.6334	17.1008
Bromoform	13.8963	14.2262	14.1957	15.1883	16.4174	15.4658	14.9983
Butanol	17.4156	18.1527	17.0695	18.4822	18.6629	18.4457	17.9445
Iso-butanol	17.6549	17.9467	17.6384	19.1145	18.5692	17.8547	18.9546
Tert-butanol	19.2367	19.6448	20.5591	18.7449	20.1463	19.4374	20.2214
Carbon disulphide	48.2374	50.0629	49.5378	51.7468	50.7433	48.8295	50.3747
Carbon tetrachloride	57.3864	59.4833	60.3843	58.3551	60.4839	63.2781	63.8142
Chloroform	15.8126	16.1278	16.9477	15.7742	16.5434	17.0043	16.9483
Cyclohexane	60.4127	62.2548	63.2740	65.2049	64.3845	66.1741	65.7346
Cyclohexanone	12.2463	13.1496	13.2335	14.0145	13.7463	14.1146	13.0014
Dichlorobenzene	11.8635	12.8469	13.1106	13.4281	12.9437	13.5471	13.1578
Diethyl ether	11.3428	12.4379	12.3054	13.5513	12.9645	13.3863	13.1857
Dioxane	4.9447	5.0047	5.1132	5.6832	4.8347	4.9639	5.6893
Dimethyl formamide	19.2746	20.1164	19.9157	20.6375	18.7386	19.5826	20.1341
Dimethyl sulfoxide	35.9638	36.0064	36.7867	35.5584	37.4074	36.5427	36.7339
Ethanol	16.9429	17.3564	17.4919	17.9327	17.9916	16.9341	17.1250
Ethyl Acetate	26.4385	25.9637	26.7843	26.8349	25.7356	27.1564	26.7463
Dichloroethane	49.4813	50.7149	51.3545	48.9617	49.8179	50.7633	49.8565
Ethylene glycol	14.9835	15.9342	16.0054	15.8681	17.0148	16.0875	15.8219
Formamide	22.8147	23.5816	24.3823	24.9326	26.1849	25.8412	26.1978
Formic acid	3.9348	5.1846	4.9053	4.2867	5.1828	4.6972	4.7738
Glycerol	15.2386	14.9691	15.8573	16.0745	15.7647	14.8765	15.9749
Hexamethyl phosphoramide	26.8143	27.1384	27.4847	26.6973	26.4479	25.9874	27.4681
Hexane	48.6883	50.6119	50.7741	49.8374	50.3315	49.8854	50.7449
Hydrazine	9.8364	10.3971	9.5796	11.2583	10.9745	9.7416	9.9518
Methanol	14.8574	15.8841	15.5649	14.5132	15.4918	16.7845	16.8243
Methyl ethyl ketone	22.4387	21.8531	20.9683	20.8749	22.3854	21.8449	20.8458
Dichloromethane	47.5835	48.8145	48.9068	48.1869	49.9106	47.3659	46.8749
Dimethyl formamide	16.8347	17.2553	17.7268	18.0854	17.6284	18.1435	16.5442
Methyl pyrrolidinone	23.8752	24.6859	24.8993	24.8316	25.1286	23.2763	23.6978
Nitrobenzene	5.6687	6.0835	5.2895	6.2862	5.2379	6.3942	4.9763
Nitromethane	17.5428	16.2513	16.8811	15.6072	17.2068	15.3927	14.7069
Phosphoryl chloride	28.4639	30.2851	29.4878	27.7956	30.1578	29.5512	28.4317
Iso-propanol	17.9568	18.4372	16.7983	19.5671	18.4857	18.5530	17.7991
Pyridine	11.6183	12.0973	12.3068	11.9581	13.2587	11.8542	12.4008
Sulfolane	31.1878	32.2745	30.4983	32.4816	30.1933	31.9912	30.6849
Tetrahydrofuran	9.6372	8.1964	10.1368	8.6739	7.6349	9.7743	10.4936
Toluene	42.3907	43.1187	41.5068	43.7638	40.3672	42.4467	43.6183
Triethylamine	11.3925	11.9675	12.6833	10.9768	10.6553	11.4952	12.2942
Trifluoroacetic acid	2.4981	2.0853	1.5934	1.3285	2.6722	1.5407	2.0568

Table 4. pKa values of the Molecule 2, calculated with thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) in forty-seven different solvent media

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Water	15.8843	14.6582	15.1286	17.3562	15.1148	16.5724	16.8247
Acetic acid	5.2630	5.7182	6.8429	5.3025	6.1573	5.9304	4.8915
Acetone	19.5921	20.1281	21.2642	19.8214	19.9923	20.4882	21.7468

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	**PM6**	**PM6-DH2**	**RM1**	**PM3**	**AM1**	**MNDO**
Acetonitrile	25.5994	26.5992	26.2510	26.3522	27.1960	26.9284	25.4745
Ammonia	38.9947	39.8424	40.1387	40.4562	40.0334	40.5463	39.8391
Aniline	8.6419	7.8469	7.6963	8.8606	9.2863	7.9643	9.2618
Benzene	44.2867	45.6354	45.3657	44.1864	46.5413	47.1368	46.1219
Benzyl alcohol	16.4524	15.9843	16.4837	14.9435	16.7241	15.7748	17.2342
Bromoform	13.9917	14.2509	14.4983	15.2742	16.3558	15.5917	14.9997
Butanol	17.2538	18.1612	17.1573	18.5536	19.1725	19.6173	18.1382
Iso-butanol	18.3813	17.9942	17.9523	19.2463	18.7541	17.9639	18.9827
Tert-butanol	19.4581	19.9460	20.6443	19.2664	20.4785	19.6581	20.4539
Carbon disulphide	49.6427	50.1573	49.3761	51.9473	50.7705	49.6277	50.6329
Carbon tetrachloride	59.2731	64.2981	59.8428	62.7436	63.7417	65.3406	66.4372
Chloroform	16.7483	17.2446	18.2449	16.3964	18.2961	19.1105	17.5638
Cyclohexane	64.5338	66.3723	66.3825	68.7485	67.2992	68.8552	67.2483
Cyclohexanone	13.7849	14.4783	15.0418	15.2892	15.2841	15.2351	14.7642
Dichlorobenzene	12.7642	13.7657	14.1521	14.2464	13.6841	15.1346	14.3841
Diethyl ether	12.6329	13.8006	14.7541	14.5326	13.0537	14.8743	14.4139
Dioxane	5.3812	5.9632	6.2893	6.5336	5.5413	5.8134	6.5247
Dimethyl formamide	20.3874	21.5649	20.3851	21.4228	19.4738	20.4852	21.5138
Dimethyl sulfoxide	37.0463	37.8128	38.4371	36.7962	38.3961	37.1469	38.0618
Ethanol	17.2348	18.4043	18.0382	18.1364	18.8779	17.3917	18.4107
Ethyl acetate	27.2740	26.2148	27.4086	28.0012	26.9846	28.4816	27.7018
Dichloroethane	50.2561	51.3851	52.1886	50.2748	50.5172	51.6188	50.7548
Ethylene glycol	15.3841	16.0382	16.5405	16.2364	17.7343	17.1384	16.5224
Formamide	23.7149	24.8035	25.4208	26.0031	27.4227	26.6015	27.3615
Formic acid	4.4862	6.2538	5.4317	5.0924	6.1379	5.9325	5.5963
Glycerol	16.5413	15.2908	16.6391	17.1543	16.4681	15.7109	16.2983
Hexamethyl phosphoramide	27.6458	28.2197	28.1674	27.4116	27.5861	26.6842	28.6360
Hexane	49.7862	50.9785	51.1849	50.2933	51.8043	50.8274	51.5865
Hydrazine	10.2576	11.2743	10.7647	11.9748	11.5472	10.8241	10.5483
Methanol	15.6329	16.3554	16.1832	15.4959	15.9267	17.2956	16.9558
Methyl ethyl ketone	23.6149	22.5926	21.5165	22.0054	23.1269	22.3563	21.7532
Dichloromethane	48.4363	49.5433	49.3645	49.5763	50.2832	48.3862	47.5064
Dimethyl formamide	16.9551	18.3648	18.2597	18.9743	17.9658	19.0870	17.2864
Methyl pyrrolidinone	24.7830	25.3576	25.7835	25.5637	26.3440	24.5083	24.8162
Nitrobenzene	6.0852	6.9217	6.2548	7.0258	6.2587	7.1220	5.3842
Nitromethane	18.6235	17.0855	17.4309	16.2148	18.0148	16.2549	15.2846
Phosphoryl chloride	29.5782	30.9742	30.6250	28.8242	31.2839	30.6109	29.6805
Iso-propanol	18.3643	19.6308	17.2844	19.7893	19.3645	19.2962	18.6809
Pyridine	12.5947	13.1559	13.4542	12.3792	13.9583	12.6738	13.1763
Sulfolane	32.6933	33.1869	31.6117	33.0873	31.7082	32.6085	31.3775
Tetrahydrofuran	10.4783	9.4755	11.5745	9.5635	8.5274	10.2988	11.3149
Toluene	43.1571	43.9562	42.3149	44.5140	41.2733	43.2806	44.3649
Triethylamine	12.5430	12.5991	13.4609	11.7196	11.8632	12.2860	13.5491
Trifluoroacetic acid	2.8978	2.6971	2.2361	2.4971	3.1548	2.3813	3.0130

Table 5. pKa values of the Molecule 3, calculated with thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) in forty-seven different solvent media

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	**PM6**	**PM6-DH2**	**RM1**	**PM3**	**AM1**	**MNDO**
Water	16.2437	15.4029	16.2117	17.9621	15.6472	17.1463	17.2305
Acetic acid	6.2841	6.2705	7.1256	5.9418	6.3840	6.3212	5.0742
Acetone	20.4572	20.9467	22.0434	20.4212	20.5814	20.9463	22.2049
Acetonitrile	26.1268	27.2046	26.9672	26.8341	27.6427	27.2017	26.5138
Ammonia	39.6352	40.0969	41.4456	41.5970	39.8861	41.1296	40.6593
Aniline	9.2743	8.2544	8.2549	9.1327	10.2106	8.6502	10.1552
Benzene	45.3452	46.2012	46.2493	44.5681	47.3892	47.6371	46.4370
Benzyl alcohol	17.1029	16.5428	16.9554	15.7313	17.3018	16.5415	18.4036
Bromoform	14.3245	15.0013	15.4416	15.9663	16.9319	16.2341	15.5441
Butanol	18.1443	18.7463	18.4268	19.2747	19.3548	19.6068	18.6951
Iso-butanol	18.6427	18.2954	18.4927	20.1472	19.2593	18.5163	20.5349
Tert-butanol	20.5428	20.4813	20.9884	19.3822	20.9674	20.1459	20.6173
Carbon disulphide	49.8533	50.6551	50.2995	50.6842	49.4852	50.1539	50.6744
Carbon tetrachloride	62.4877	65.8217	61.7244	63.4287	63.8249	66.2814	66.6194
Chloroform	16.8729	17.8141	18.5625	16.9025	17.8115	18.8464	18.1545
Cyclohexane	65.7412	67.5042	67.1946	68.8813	67.5438	69.2933	67.5637

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Cyclohexanone	13.9405	15.6274	15.2573	15.6471	16.0756	14.9745	14.8126
Dichlorobenzene	12.8455	14.4455	14.1856	14.1748	13.7683	14.7852	14.6658
Diethyl ether	12.6349	14.2758	14.1983	14.1162	13.6894	14.5971	14.5647
Dioxane	5.4659	6.1074	6.3864	6.7213	5.7862	5.9672	6.8356
Dimethyl formamide	20.5617	21.3872	20.4972	21.6550	19.7104	20.7109	21.8665
Dimethyl sulfoxide	37.1254	37.9932	38.5639	36.9286	38.8345	37.4381	38.2513
Ethanol	17.3529	18.5429	18.1275	18.2568	18.6349	17.4381	18.3422
Ethyl acetate	27.8523	26.1925	27.5117	27.8834	26.8583	28.6237	27.6139
Dichloroethane	50.1887	51.4669	52.5463	50.3612	50.3693	51.5019	50.6413
Ethylene glycol	15.3765	16.0048	16.4830	16.3951	17.6918	17.0693	16.3943
Formamide	23.5602	24.7321	25.4091	26.1745	27.2618	26.5235	27.1957
Formic acid	4.3105	6.1455	5.3802	5.1129	6.0823	5.8631	5.4604
Glycerol	16.4509	15.1841	16.5205	17.0692	16.3325	15.6344	16.1562
Hexamethyl phosphoramide	27.6539	28.3513	28.2205	27.2756	27.4928	26.7386	28.7143
Hexane	49.7749	51.3573	51.2526	50.3865	51.7668	50.7461	51.5933
Hydrazine	10.3284	11.3651	10.7854	11.8467	11.4989	10.7965	10.5626
Methanol	15.7281	16.4537	16.2503	15.3892	16.0032	17.3813	17.2861
Methyl ethyl ketone	23.7138	22.7385	21.7208	22.1967	23.2503	22.4851	21.8649
Dichloromethane	48.5437	49.6029	49.5108	49.6815	50.3518	48.6836	47.5378
Dimethyl formamide	17.2372	18.4392	18.3602	18.8818	18.1343	19.1383	17.3523
Methyl pyrrolidinone	24.8211	25.4038	25.8146	25.6215	26.4378	24.6296	24.8303
Nitrobenzene	6.1349	6.9838	6.3716	7.1540	6.3145	7.2538	5.4957
Nitromethane	18.7102	17.2564	17.5227	16.3459	18.2554	16.3668	15.3571
Phosphoryl chloride	29.7416	30.9874	30.9517	28.9315	32.2906	30.7384	29.9523
Iso-propanol	18.5517	19.7115	17.3651	20.1562	19.5370	19.3845	18.7327
Pyridine	12.6539	13.2781	13.4635	12.3607	13.9762	12.7049	13.2745
Sulfolane	33.7412	33.2541	31.6354	33.1961	31.7553	32.7143	31.4283
Tetrahydrofuran	10.5916	9.6849	11.8831	9.9226	8.6632	10.3547	11.4681
Toluene	43.2658	44.1305	42.4064	44.5627	41.3614	43.3471	44.5172
Triethylamine	12.7148	13.2057	13.5247	11.8378	11.8711	12.3439	13.6037
Trifluoroacetic acid	2.9835	2.7849	2.4072	2.5336	3.1964	2.3924	3.1487

Table 6. pKa values of the Molecule 4, calculated with thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) in forty-seven different solvent media

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Water	15.9829	16.2811	16.3465	16.8842	16.0081	16.8924	17.3612
Acetic Acid	6.3550	6.3522	7.2103	6.2447	7.1563	6.4186	5.1668
Acetone	20.6642	20.8154	21.8627	20.6380	20.7247	21.1509	21.9931
Acetonitrile	26.2660	27.1143	26.9448	26.5538	26.4592	26.8552	26.5048
Ammonia	39.5820	40.2215	41.3927	41.8436	40.5293	41.4074	40.8668
Aniline	9.3515	8.3318	8.5218	9.4233	10.2211	8.8464	10.2734
Benzene	45.8043	46.1894	46.5106	43.5205	47.4315	47.6545	46.5926
Benzyl alcohol	17.2381	16.5519	17.2488	15.8144	17.4129	16.6019	18.5174
Bromoform	14.4119	15.1741	15.4743	15.9947	16.9672	16.4036	15.5688
Butanol	18.2657	18.8929	18.4094	19.2956	18.8141	18.9962	18.5603
Iso-butanol	18.8811	18.4577	18.5304	20.2543	19.5687	18.7848	20.5772
Tert-butanol	20.5540	20.4927	20.9917	19.6217	21.2219	20.3642	21.1469
Carbon disulphide	50.6329	50.6876	50.3627	51.5977	51.6229	50.2546	51.2783
Carbon tetrachloride	63.5429	66.1829	62.2797	63.1829	60.5335	65.4705	64.2836
Chloroform	17.0031	18.4109	19.0427	17.2769	17.6324	18.9147	18.1639
Cyclohexane	66.4829	68.3492	68.2307	69.5668	68.2149	68.4925	68.2664
Cyclohexanone	14.2711	15.4981	14.9767	16.2579	16.1251	15.5619	14.4318
Dichlorobenzene	12.9641	13.9673	13.7319	13.8753	14.0139	14.8633	15.1264
Diethyl ether	12.3548	13.5769	13.4432	13.6951	14.2137	14.4517	15.2386
Dioxane	6.0328	6.2348	5.9657	5.7449	5.7329	6.0381	7.0318
Dimethyl formamide	20.0549	20.9837	20.1153	20.7819	18.8552	19.8732	20.8973
Dimethyl sulfoxide	36.4911	36.2945	37.2316	35.5923	37.9326	36.8529	37.4116
Ethanol	16.8660	17.2874	17.6354	17.8615	17.9751	16.8968	17.0656
Ethyl acetate	26.3849	25.9509	26.6984	27.5107	27.6371	27.3192	26.6881
Dichloroethane	49.4936	50.8744	51.2920	48.9557	49.7112	50.7483	49.8405
Ethylene glycol	14.9027	15.8863	15.9936	15.8527	16.9652	16.0762	15.7025
Formamide	22.5692	23.5620	24.2996	24.8810	26.1483	25.8268	26.1885
Formic acid	3.8971	5.1562	4.8842	4.2583	5.1346	4.6357	4.7649
Glycerol	15.0848	14.9518	15.8327	16.1708	15.6202	14.8553	15.8846

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Hexamethyl phosphoramide	26.7145	27.2672	27.3962	26.6839	26.4355	25.9613	27.3962
Hexane	48.6706	50.5864	50.7652	49.7962	50.3179	49.8918	50.7192
Hydrazine	9.8179	10.3885	9.5936	11.2439	10.9681	9.7827	10.0837
Methanol	14.7697	15.7951	15.5754	15.3643	16.1252	16.7938	16.8286
Methyl ethyl ketone	22.4128	21.7659	20.8841	20.7981	22.2957	21.7957	20.7336
Dichloromethane	47.5772	48.7831	48.8834	48.0617	49.7642	47.3741	46.8352
Dimethyl formamide	16.8068	17.2371	17.7115	18.1249	17.6159	18.0652	16.5297
Methyl pyrrolidinone	23.7934	24.6778	24.7928	24.8092	25.1159	23.2541	23.5460
Nitrobenzene	5.7118	6.1250	5.2797	6.1915	5.1654	6.3841	4.8521
Nitromethane	17.5229	16.2492	16.7962	15.6125	17.1872	15.3716	14.7257
Phosphoryl chloride	28.4570	30.1965	29.3629	27.7827	30.1467	29.5228	28.4386
Iso-propanol	17.8664	18.4269	16.7566	19.4983	18.4981	18.5129	17.6506
Pyridine	11.5865	12.1363	12.2981	11.9878	13.2448	11.8657	12.4116
Sulfolane	31.1771	32.2667	30.4882	32.4660	30.1896	31.9870	31.5971
Tetrahydrofuran	10.6259	8.2071	10.1756	8.7341	7.6451	9.5240	11.5037
Toluene	42.4050	43.1076	41.4903	43.7534	41.3583	42.4388	43.6093
Triethylamine	11.2964	11.8463	12.5831	10.9627	10.6492	11.4862	12.2856
Trifluoroacetic acid	2.2847	2.1054	1.5209	1.3183	2.6135	1.4262	2.0665

Table 7. pKa values of the Molecule 5, calculated with thermodynamic cycle with semi-experimental quantum chemical methods (PM7, PM6, PM6-DH2, RM1, PM3, AM1 and MNDO) in forty-seven different solvent media

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	PM6	PM6-DH2	RM1	PM3	AM1	MNDO
Water	14.8104	13.4655	15.0021	16.4208	14.2066	15.3341	15.8213
Acetic acid	4.8927	5.1174	5.6636	5.0843	5.7722	5.7818	4.9216
Acetone	19.3340	19.7253	20.9461	19.2488	19.5054	20.1838	21.0173
Acetonitrile	25.3672	26.3771	25.8166	25.4663	25.8991	26.1346	25.3833
Ammonia	38.8343	39.5683	39.8227	40.0529	39.4352	39.8262	39.4714
Aniline	8.4452	7.7465	7.5770	8.5771	9.5243	7.7412	9.1496
Benzene	44.2392	45.3048	45.3213	43.2216	46.4197	45.9260	45.9351
Benzyl alcohol	16.2340	15.9225	16.3693	14.7127	16.5660	15.6027	17.1265
Bromoform	13.7881	14.2384	14.1840	15.1531	15.8742	15.3909	14.8417
Butanol	17.3841	17.8445	17.0027	18.4135	18.5972	18.7436	17.8827
Iso-butanol	17.6472	17.9531	17.6115	19.0876	18.4339	17.8516	19.3841
Tert-butanol	19.1982	19.6339	19.9645	18.8104	20.0862	19.3927	20.1125
Carbon disulphide	48.1548	49.8535	49.5114	50.8207	49.3941	48.8142	49.7662
Carbon tetrachloride	57.3652	59.7722	60.2386	58.8327	59.2968	63.5418	63.7928
Chloroform	15.8554	16.1537	16.9663	15.8103	16.5773	17.2368	17.1208
Cyclohexane	61.7718	63.2038	64.1553	66.1437	65.1073	66.4894	66.1843
Cyclohexanone	12.6038	13.2962	13.6109	14.1638	14.0237	14.7382	13.2537
Dichlorobenzene	11.9508	12.9918	13.4677	13.5417	13.1174	13.7457	13.7205
Diethyl ether	11.7864	12.3733	13.5872	13.4260	13.2371	13.5329	13.3027
Dioxane	4.9981	5.1756	5.4908	5.7358	4.9714	5.0779	5.8735
Dimethyl formamide	19.6382	20.2285	19.9996	20.7731	18.8349	19.7916	20.3546
Dimethyl sulfoxide	35.8127	36.1873	36.7741	35.5466	37.3930	36.4983	36.6824
Ethanol	16.8543	17.0148	17.3847	17.8963	17.8543	16.8714	16.9649
Ethyl acetate	26.2961	25.8972	26.6651	26.9442	27.7149	27.0038	26.5327
Dichloroethane	49.5672	50.6378	51.2387	48.8962	49.7327	50.7237	49.8326
Ethylene glycol	14.8623	15.8519	15.9847	15.7249	16.813	16.0039	15.5478
Formamide	22.5508	23.4723	24.2714	24.8762	26.0072	25.8189	26.0568
Formic acid	3.8205	5.0637	4.8157	4.1961	5.1635	4.6584	4.7582
Glycerol	15.1967	14.9563	15.8468	16.0083	15.6938	14.8619	15.8771
Hexamethyl phosphoramide	26.6819	27.0868	27.2994	26.5172	26.4106	25.8758	27.2385
Hexane	48.5938	50.5732	50.7598	49.7937	50.2952	49.8044	50.6718
Hydrazine	9.8025	10.2257	9.5327	11.2275	10.8357	9.7058	9.9351
Methanol	14.6323	15.7889	15.4386	14.5067	15.4959	16.7014	16.7237
Methyl ethyl ketone	22.2954	21.4973	20.7436	20.6345	22.2835	21.7466	20.6109
Dichloromethane	47.5104	48.6744	48.8256	48.0528	49.7035	47.3612	46.8143
Dimethyl formamide	16.7458	17.2065	17.6834	17.8635	17.5836	18.0031	16.4805
Methyl pyrrolidinone	23.7657	24.6541	24.6513	24.7325	25.0039	23.1867	23.4397
Nitrobenzene	5.5203	5.9673	5.1365	6.0872	5.1276	6.2959	4.7658
Nitromethane	17.4183	16.1886	16.6815	15.5518	17.1563	15.2553	14.6139
Phosphoryl chloride	28.4154	29.5892	29.2683	27.6318	30.1082	29.4796	28.3039
Iso-propanol	17.7103	18.4016	16.7087	19.4652	18.4533	18.4673	17.5329
Pyridine	11.4388	12.0047	12.1675	11.5846	13.1109	11.8043	12.3671

Solvent	Semi-Experimental Quantum Chemical Methods						
	PM7	**PM6**	**PM6-DH2**	**RM1**	**PM3**	**AM1**	**MNDO**
Sulfolane	30.4968	32.1305	30.4035	32.5462	30.1007	31.6156	31.5032
Tetrahydrofuran	10.5847	8.1667	10.1233	8.6258	7.5303	9.5198	11.4826
Toluene	42.3618	42.8965	41.3676	43.6295	41.2716	42.2104	43.4781
Triethylamine	11.1683	11.7706	12.4029	10.6449	10.6037	11.3509	12.0391
Trifluoroacetic acid	1.9654	1.7846	1.4650	1.2457	2.5021	1.3793	1.9341

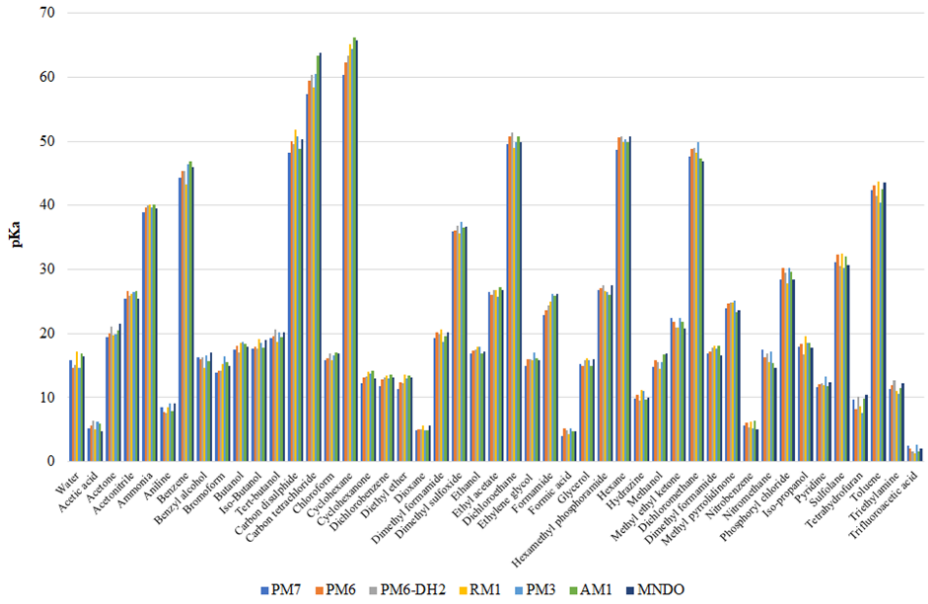


Figure 2. Graphical display of pKa values of the Molecule 1

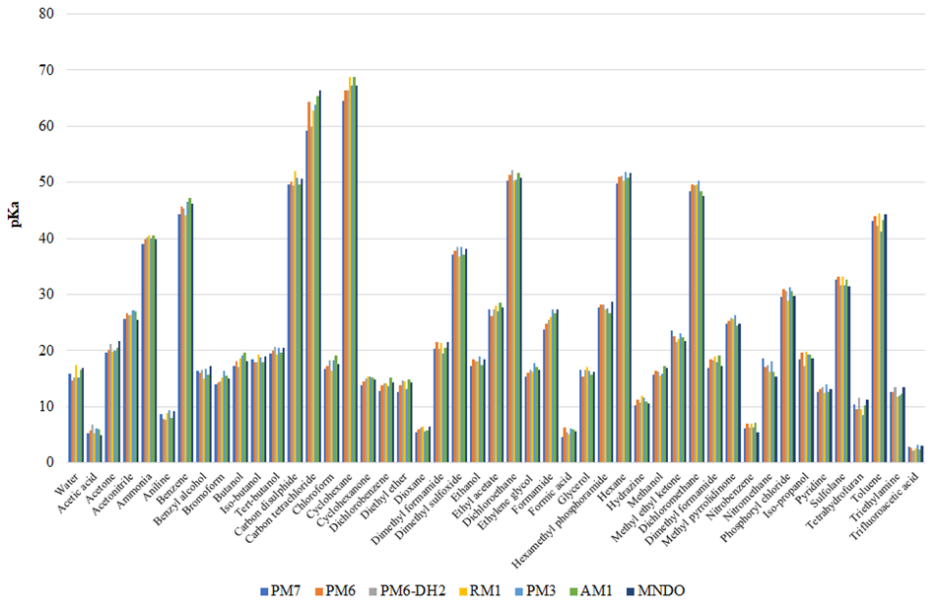


Figure 3. Graphical display of pKa values of the Molecule 2

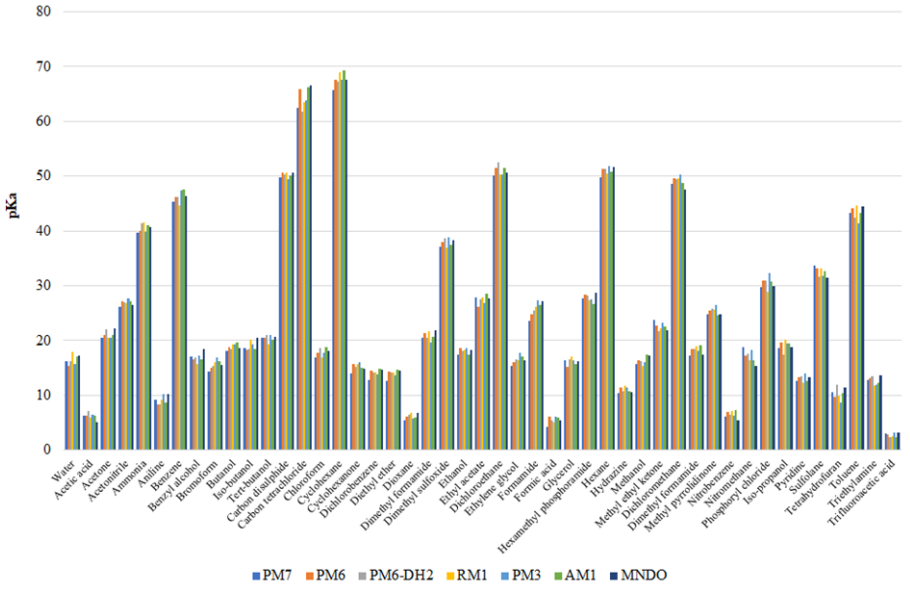


Figure 4. Graphical display of pKa values of the Molecule 3

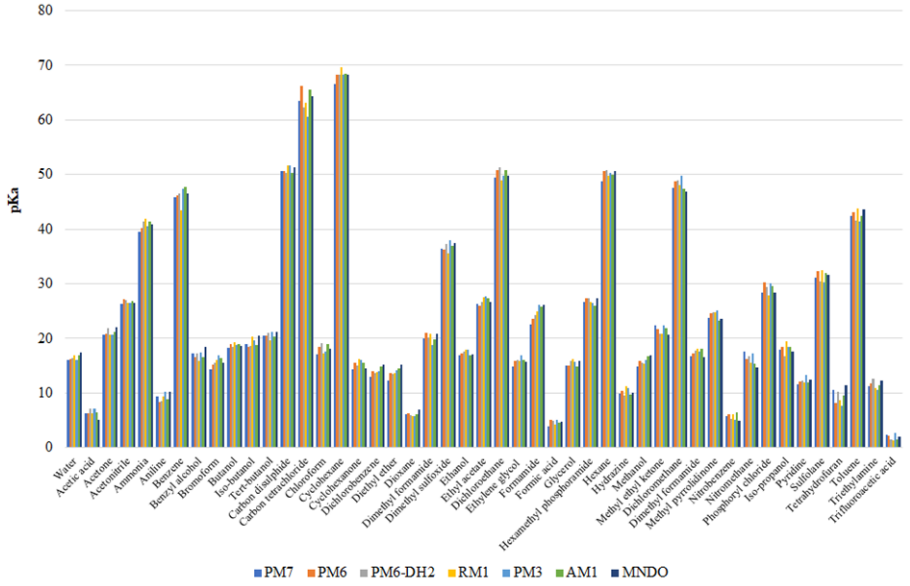


Figure 5. Graphical display of pKa values of the Molecule 4

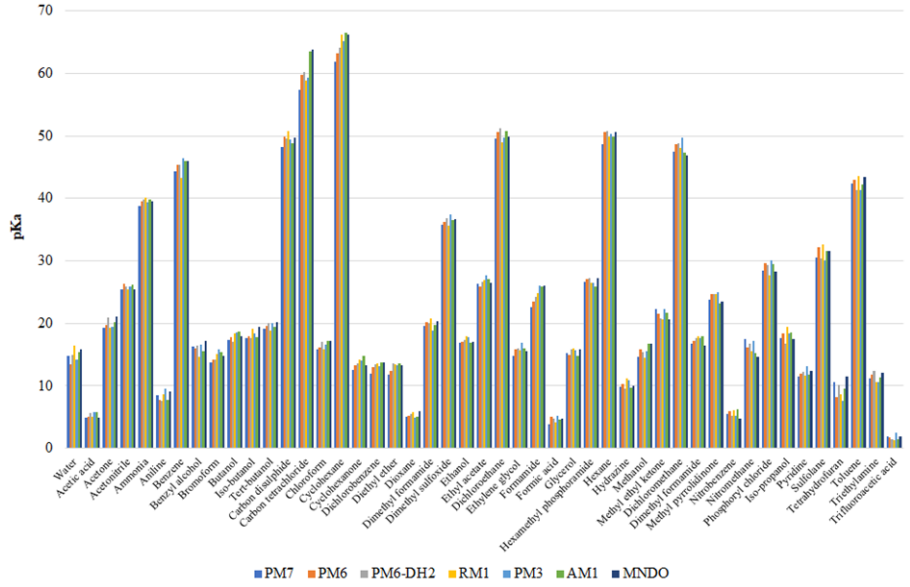


Figure 6. Graphical display of pKa values of the Molecule 5

We obtained a total 1645 pKa values for the five molecules in the calculations we made with seven different models in forty-seven different solvent medium. These values are given in the tables above. We interpreted these values in three different ways (solvent medium, model and molecule) to better understand the results. We first interpreted it according to the solvent medium. Here, we identified the strongest acidic property and weakest acidic property molecules and models in the solvent medium studied. These determined values are given in Table 8. According to the data in this table, the strongest acidic property was calculated as pKa 1.2457 in trifluoroacetic acid solvent medium according to the molecule 5 and RM1 model. The weakest acidic feature was calculated as pKa 69.5668 according to the molecule 4 and RM1 model in cyclohexane medium.

Table 8. Strongest acidic property and weakest acidic property molecules and models in the solvent medium

Solvent	**Strongest acidic property**			**Weakest acidic property**		
	Molecule	**Model**	**pKa**	**Molecule**	**Model**	**pKa**
Water	5	PM6	13.4655	3	RM1	17.9621
Acetic acid	1	MNDO	4.7886	4	PM6-DH2	7.2103
Acetone	5	RM1	19.2488	3	MNDO	22.2049
Acetonitrile	5	PM7	25.3672	3	PM3	27.6427
Ammonia	5	PM7	38.8343	4	RM1	41.8436
Aniline	5	PM6-DH2	7.5770	4	MNDO	10.2734
Benzene	5	RM1	43.2216	4	AM1	47.6545
Benzyl alcohol	1	RM1	14.6882	4	MNDO	18.5174
Bromoform	5	PM6-DH2	14.1840	4	PM3	16.9672
Butanol	5	PM6-DH2	17.0027	2	AM1	19.6173
Iso-butanol	5	PM6-DH2	17.6115	4	MNDO	20.5772
Tert-butanol	1	RM1	18.7449	4	PM3	21.2219
Carbon disulphide	5	PM7	48.1548	2	RM1	51.9473
Carbon tetrachloride	5	PM7	57.3652	3	MNDO	66.6194
Chloroform	1	RM1	15.7742	2	AM1	19.1105
Cyclohexane	1	PM7	60.4127	4	RM1	69.5668
Cyclohexanone	1	PM7	12.2463	4	RM1	16.2579
Dichlorobenzene	1	PM7	11.8635	2	AM1	15.1346
Diethyl ether	1	PM7	11.3428	4	MNDO	15.2386
Dioxane	1	PM3	4.8347	4	MNDO	7.0318
Dimethyl formamide	1	PM3	18.7386	3	MNDO	21.8665
Dimethyl sulfoxide	5	RM1	35.5466	3	PM3	38.8345
Ethanol	1	PM7	16.8543	2	PM3	18.8779
Ethyl acetate	1	PM3	25.7356	3	AM1	28.6237
Dichloroethane	5	RM1	48.8962	3	PM6-DH2	52.5463
Ethylene glycol	5	PM7	14.8623	2	PM3	17.7343
Formamide	5	PM7	22.5508	2	PM3	27.4227
Formic acid	5	PM7	3.8205	2	PM6	6.2538
Glycerol	4	AM1	14.8553	2	RM1	17.1543
Hexamethyl phosphoramide	5	AM1	25.8758	3	MNDO	28.7143
Hexane	5	PM7	48.5938	2	PM3	51.8043
Hydrazine	5	PM6-DH2	9.5327	2	RM1	11.9748
Methanol	5	RM1	14.5067	3	AM1	17.3813
Methyl ethyl ketone	5	MNDO	20.6109	3	PM7	23.7138
Dichloromethane	5	MNDO	46.8143	3	PM3	50.3518
Dimethyl formamide	5	MNDO	16.4805	3	AM1	19.1383
Methyl pyrrolidinone	5	AM1	23.1867	3	PM3	26.4378
Nitrobenzene	5	MNDO	4.7658	3	AM1	7.2538
Nitromethane	5	MNDO	14.6139	3	PM7	18.7102
Phosphoryl chloride	5	RM1	27.6318	3	PM3	32.2906
Iso-propanol	5	PM6-DH2	16.7087	3	RM1	20.1562
Pyridine	5	PM7	11.4388	3	PM3	13.9762
Sulfolane	5	PM3	30.1007	3	PM7	33.7412
Tetrahydrofuran	5	PM3	7.5303	3	PM6-DH2	11.8831
Toluene	1	PM3	40.3672	3	RM1	44.5627
Triethylamine	5	PM3	10.6037	3	MNDO	13.6037
Trifluoroacetic acid	5	RM1	1.2457	3	PM3	3.1964

As a second method, we evaluated the results through models. Here, the same results of the evaluation of solvent medium were obtained. The strongest acidic property and the weakest acidic property were obtained in the RM1 models. Finally, when the results are evaluated on the basis of molecules, the strongest acidic feature is obtained in molecule 5 and the weakest acidic feature is obtained in molecule 4. Here we used the MOPAC computer program. Comparisons can be made between the results using different computer programs.

We used the thermodynamic cycle method to calculate pKa. Apart from this, different methods can be used.

4. Conclusions

By doing this, the work can be enriched even more. By adding different functional groups to the molecules, the number of molecules studied can be increased to even higher numbers. By doing all this, the study can reach a much wider scope.

Conflicts of interest. The author declares no conflict of interest.

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