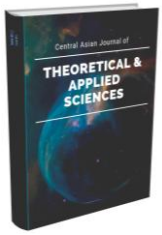

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Article

Theoretical Prediction of (pKa) and Thermodynamic Parameters Using Dft and PM3 Methods: Application to NSAIDs

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Abstract: In this study, the thermodynamic functions of six pharmaceutical chemical compounds were calculated, and their theoretical ionization constants were determined, including enthalpy change (ΔH), Gibbs free energy change (ΔG), and entropy change (ΔS). These calculations were performed using different theoretical methods, namely the DFT/6-31G method, which is classified as an ab initio computational approach, and the PM3 method, which belongs to the semi-empirical computational methods. A statistical correlation was conducted between the calculated thermodynamic functions (ΔH, ΔG, ΔS) and the experimentally determined ionization constants. The results showed that the DFT/6-31G method yielded the best correlation coefficient between enthalpy values and experimental ionization constants, with a value of $R^2 = 0.9396$. Similarly, for the PM3 method, the highest correlation coefficient obtained was $R^2 = 0.9392$, also between enthalpy values and experimental ionization constants. An increase in the thermodynamic functions leads to an increase in pKa values, indicating a decrease in acidity, whereas a decrease in the thermodynamic functions results in lower pKa values, corresponding to increased acidity. Hence, the relationship between thermodynamic functions and acidity is inverse.This method is an effective tool for drug and understanding its properties, offering high precision ($R^2 > 0.93$).

Keywords: DFT, PM3, pKa, ΔH, ΔG, ΔS, Application, Quantum Calculations.

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1. Introduction

1. Ionization Constant

The ionization constant is a quantitative measure of the strength of an acid or a base. It is defined as the ratio of the concentration of products to the concentration of reactants; that is, the concentration of the ionized (dissociated) acid or base relative to the concentration of the non-ionized (undissociated) species.

$$AH + H2O \leftrightarrow A^- + H3O^+ \quad (1)$$

The ionization of an acid AH in water is represented by the following equilibrium reaction:(Schwoebel 2021)

The above equation represents a reversible process, in which the acid AH donates a proton to water, forming the negatively charged anion A^-, which in turn has a tendency to accept a proton and thus behaves as a base. Consequently, the acid and base function as a conjugate pair. (Aguilera, 2017)

The ionization constant, also referred to in the literature as the dissociation constant, is widely used to assess the acidic or basic strength of chemical compounds. (Ibrahim 2020)

Since ionization constant values are typically very small, the negative logarithm of the ionization constant, pKa, is commonly used to express acid strength, according to the following relation: (Hu, Z. (2019)

2. Computational Chemistry

Computational chemistry is considered one of the modern branches of chemistry and has wide-ranging applications in most fields of chemistry and biochemistry. Its primary objective is to compare the properties of chemical compounds with those obtained experimentally. Through computational chemistry, many important molecular properties can be determined (Hameed 2021), such as total energy, atomic charges, vibrational frequencies, NMR parameters, reaction mechanisms, and the three-dimensional structures of transition states, as well as IR spectroscopy, Raman spectroscopy, dipole moment, and thermochemical properties (Abadya 2024).

Computational chemistry provides a significantly lower material and economic cost compared with laboratory experiments. It also enables the calculation of several variables that are sometimes difficult or impossible to determine experimentally due to the lack of appropriate instruments or chemical reagents. The rapid advancement in computer technology and software development has encouraged many researchers to increasingly adopt computational chemistry. (Al-Hyali, E. S., et al. (2022). The main aim of computational chemistry is to develop mathematical equations capable of solving chemical problems efficiently and within a short time (Mezael, F.W. 2024).

The importance of computational chemistry software lies in the following applications:

1. Determining transition state structures and reaction pathways.
2. Calculating potential energy surfaces.
3. Determining the minimum energy of molecules.
4. Identifying the electronic structure.
5. Performing calculations on complex molecules, such as proteins.
6. Calculating bond vibrational frequencies
7. Determination of thermodynamic values (ΔS, ΔH, ΔG).
8. Used to determine the rate constant in chemical reactions.
9. Used to identify the three-dimensional (spatial) configuration of a compound.
10. Determination of electron distribution and charge calculations.(Al-Douh ,M .H elt,. 2019)

Computational chemistry is classified into two main categories according to the following scheme:

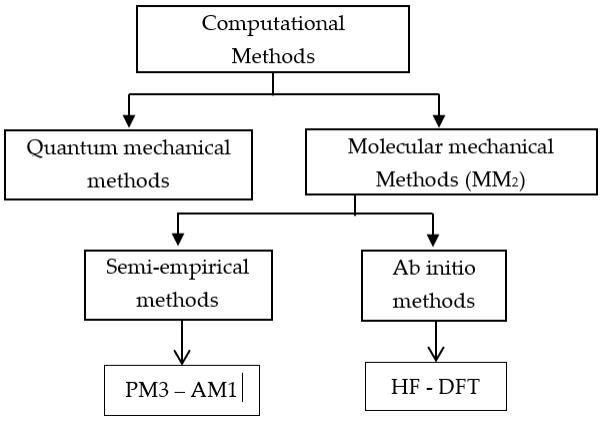

Figure 1. Computational Chemistry Methods.

3. Molecular Mechanics (Molecular Mechanics)

Molecular mechanics is based on Newton's laws and their application to atoms, while neglecting the presence of electronic effects (Al-Hyali, E. A. et al. 2022)

4. **Quantum Mechanics**

Quantum mechanics is based on the Schrödinger equation and its application to molecules while considering their electronic effects.

PM3 Method (Parameterized Method), (Hage, D. S. 2013)

The PM3 method employs the same equations used in the Austin method and is considered more accurate than the AM1 method in calculating hydrogen bond angles. However, the results obtained using the Austin method are more accurate when measuring compounds at high temperatures (Irfan, A. I,el .at 2020).

The difference between the two methods lies in the fact that each method has the capability to calculate certain elements of the periodic table. For example, the AM1 method has the ability to calculate group II elements, whereas the PM3 method is preferred for calculating heavy elements, in addition to providing a lower error rate.

The values calculated by this method depend on experimental laboratory techniques, and its calculations require short computational time compared to ab initio methods, which sometimes require long computation times. Semi-empirical methods provide the best solution (Ismael, S. M,et al 2016) when dealing with a large number of small molecules or a very large molecule.

5. Density Functional Theory (DFT)

This theory was first developed and applied by Hohenberg and Kohn (Imming, P. 2008) in 1964. Subsequently, this method became one of the fundamental analytical methods and has been widely used in theoretical studies, especially after the advancement in computer and electronic software (Kumar, P et al 2023).

This method is considered one of the most widely used approaches due to its applicability to many systems with high accuracy and speed. It is employed to determine the most important electronic properties of a molecule in the ground state, which are obtained using electron density.

One of the main advantages of this method is its ability to determine electronic correlations more accurately than those obtained using the Hartree–Fock method. This demonstrates that Density Functional Theory possesses high reliability, allowing it to be used with great confidence, and it is widely accepted in theoretical studies and research (Lewars, P.E.G. (2011)

6. **Medicine Compounds**

Drug design is an innovative process aimed at discovering new drugs based on knowledge of the biological target. A drug is a chemical substance used for medical purposes, as it interacts with the complex chemical systems of humans and animals, with a focus on the organic and biochemical interactions between the drug substance and the target molecule. The purpose of a drug substance is to kill cells or microorganisms.

Compounds used as drugs are often organic compounds and are classified into small organic molecules and proteins. A drug is an organic molecule that functions by inhibiting or activating a biological molecule within the body, thereby producing a beneficial effect. For a compound to be suitable and active as a drug, it must possess several properties that enable it to reach its intended target while avoiding interaction with other sites that may be affected. In other words, it should not cause side effects resulting from the metabolic products of the parent compound.(Lima, N. B et al 2019)

Drug design relies on the three-dimensional structure of the biological target to which the drug compound binds. In general, a drug must be effective and safe at the same time. Drugs are typically produced through chemical reactions and are designed for a

specific purpose or target; therefore, they should not affect other molecules or sites in the body. That is, the drug must be capable of reaching a primary target or specific cells in the body without causing toxic or dangerous side effects.

If a drug interacts with an undesired target or site, this interaction may lead to the formation of side effects, as the drug may bind to binding sites similar to those of the primary target, resulting in unwanted symptoms and adverse effects. Knowledge of drug kinetics represents an important aspect of the limited usefulness of a compound in terms of absorption, distribution, metabolic excretion, and metabolism, particularly via the liver after oral administration, and its elimination through urine or feces.(Mu, D. and Li, Q. S. (2023)

The primary goal of medicinal chemistry, in addition to its scientific importance, is to identify new compounds that can be used as effective lead compounds for the development of active drugs.

7. Methods Used in Drug Design

There are numerous methods used in drug design, and despite the differences in the principles on which these methods operate, they all rely on a fundamental concept: drug activity arises from the binding between the drug and the target protein. A drug cannot exert its effect on the body unless it is first absorbed and then binds effectively to the target protein.

Based on their working principles, drug design software can be classified into two main categories. The first category focuses on designing drugs based on the shape of the target protein, while the second category relies on the chemical structure of the drug molecule that binds to the target protein. A number of software programs are used to calculate various physical and chemical properties, as well as different pharmacological properties, such as water solubility, toxicity, rate of intestinal absorption, distribution in the bloodstream, metabolic processes in the liver, and drug excretion via urine or feces (Notari, R. E. (1973).

These software programs calculate the binding energy between the protein and the drug and correlate it with the drug's biological activity. Such programs differ in their nomenclature as well as in their ease or difficulty of use. Some are available as trial versions, while others require an annual subscription to obtain a version that is renewed yearly (Salgado, L. V. and Vargas-Hernández, C. (2014)

Examples of these software programs include:

Molecular Docking, ArgusLab, Accelrys Discovery Studio, Marvin, ChemDraw, MathMol, DeepView, PayMol, Catalyst, Cerius, and TSAR

Many software programs differ in terms of the functions they perform and the results obtained from them. As illustrative steps for the use of these programs, the process begins with selecting the protein to be studied. Subsequently, the significance of this protein is verified as a primary cause of the disease, such that the development of inhibitors against this protein would lead to the treatment of the resulting disease (SEM, I. (2023) -Titov, D. V. and Liu, J. O. (2012).

8. **Literature review**

Theoretical calculations and manipulation of the ionization constant of chemical compounds, particularly Schiff's rules, are an important method that has occupied many researchers for many years, where experimental addition coefficients and various structural and electronic variables have been used to predict values. Highly accurate pKa. In 1964(Grant, B. and Paul, M., 1964) Paul and Grant published their work on developing empirical additive coefficients for predicting the pKa values of atoms. These coefficients were later developed and improved by other researchers such as Steroids et al. (Steroids, A. et al., 1969) and Johnson et al. (Johnson, B. et al., 1970). By relying on variables such as bond length, electron density, HOMO/LUMO levels, total energy, and others, based on

quantum chemistry methods, to arrive at More reliable theoretical results. This methodology was later extended to include Schiff rules, as (Homeda at el2025) studied the calculation of the ionization constant for a set of Schiff rules, while (Toohi and Al-Hyali,. (2023) dealt with it. Developing theoretical methods for calculating the ionization constants of different compounds of these bases, while analyzing the effect of structural and electronic factors and comparing theoretical values with practical values to explain the ionization behavior of those systems.

2. Experimental part

Practical Part

Theoretical Calculations

The rapid development in computer technology and software has encouraged many researchers to use theoretical methods to determine pKa values. Among these programs are ChemOffice and the Gaussian program (GaussView 5.0.8, Gaussian 09W). These programs are fundamentally based on the application of quantum mechanics and molecular mechanics.

Quantum mechanical methods include ab initio methods represented by Density Functional Theory (DFT) and semi-empirical methods such as PM3. The information obtained using the Gaussian 09W program is extensive and includes the following:

1. Atomic orbital energies (HOMO, LUMO).
2. Atomic charges.
3. Transition state geometries.
4. Bond dissociation energy.
5. Heat of formation.
6. Electrostatic potential or energy.
7. Bond angles between atoms.
8. Bond lengths between atoms.
9. Total energy.
10. Thermodynamic functions (ΔH, ΔG, ΔS).
11. Dipole moment.

The distinctive feature of the Gaussian 09W program is that it contains a vast amount of information. The reason for selecting multiple theories is to conduct a comprehensive survey of most theoretical methods in the field of computational chemistry and to choose the best of these methods and theories in order to obtain the most accurate theoretical pKa values.

In this study, many variables were calculated using ab initio and semi-empirical methods, among which are the thermodynamic functions (ΔH, ΔG, ΔS).

The calculations were performed using the following methods:

- Semi-empirical Methods (PM3).
- DFT = B3LYP, Basis set (6-31G).

The calculations were carried out using a computer with the following specifications:

- System Model: DELL Latitude E6530.
- Processor: Intel(R) Core(TM) i7 CPU @ 3.00 GHz, 3.00 GHz.
- Memory: 4.00 GB RAM.
- System type: 64-bit Operating System.
- Basis Sets.
- 6-31G.
- 3-21G.

Gaussian 09W Program

Theoretical calculation steps for compounds using the Gaussian 09W program:

1. Drawing the molecular structures of the compounds using the (Chem Draw) program.
2. Transferring the compound drawn in the ChemDraw program to Chem3D.
3. Saving the compound in Chem3D as an Input File.
4. Opening the GaussView 6.0 program, then opening the file saved as an Input File.
5. Clicking the Calculate button, then selecting Gaussian Calculation Setup.
6. From the Job Type button, selecting Optimization, then choosing Minimum to obtain the lowest energy, making the compound more stable with the best spatial geometry.
7. Next, from the Method button, selecting the theoretical method and specifying the basis set.
8. Then selecting Submit, and the calculation will be executed in the Gaussian 09W program.
9. After completion and obtaining the results, they will be saved using Notepad.

Statistics

Regarding statistics, the correlation coefficient values were extracted using Excel between the calculated thermodynamic functions (ΔH, ΔG, ΔS) and the experimental ionization constants, where univariate statistical values (R^2) were obtained.

3. Results and Discussion

The following table shows the values of the thermodynamic functions using the DFT/6-31G method.

Tablet 1.

DFT-6-31G COMP.	ΔH	ΔG	ΔS
Terbutaline	0.44753	0.37589	178.75
Timolol	0.43214	0.34569	158.63
Ticarcillin	0.14565	0.17825	138.71
Sotalol	0.3864	0.29521	169.85
Quinmerac	0.18564	0.17235	119.28
Trimethoprim	0.36598	0.29213	148.91

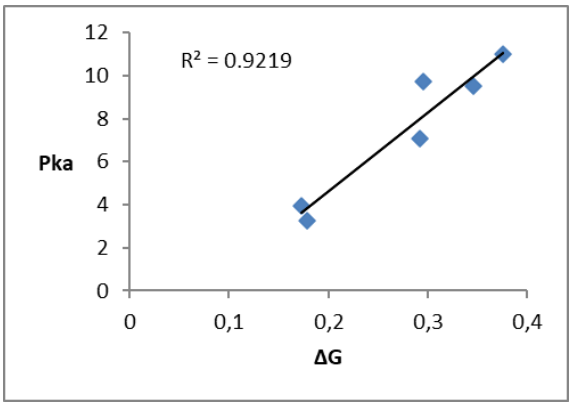

Figure 1. Relationship between experimental ionization constants and ΔG values using the DFT/6-31G method.

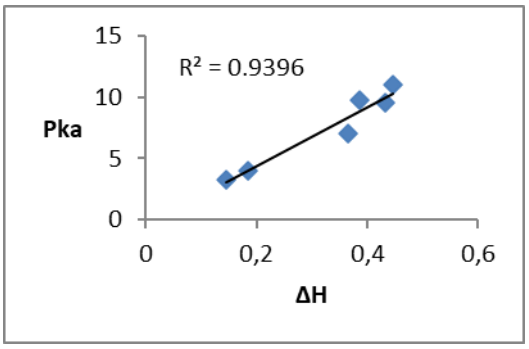

Figure 2. Relationship between experimental ionization constants and ΔH values using the DFT/6-31G method.

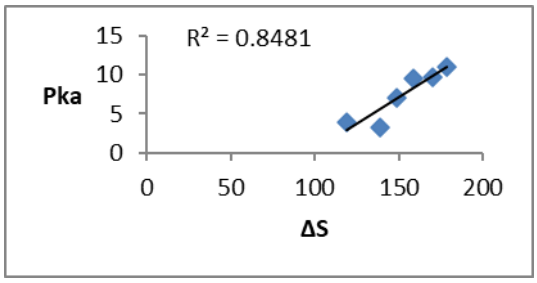

Figure 3. Relationship between experimental ionization constants and ΔS values using the DFT/6-31G method.

Table 3. Values of the thermodynamic functions using the PM3 method.

PM3 COMP.	ΔH	ΔG	ΔS
Terbutaline	0.4835	0.456231	166.45
Timolol	0.4215	0.312045	163.13
Ticarcillin	0.2468	0.143281	138.95
Sotalol	0.4517	0.378213	156.21
Quinmerac	0.1823	0.192563	114.59
Trimethoprim	0.3527	0.285762	156.38

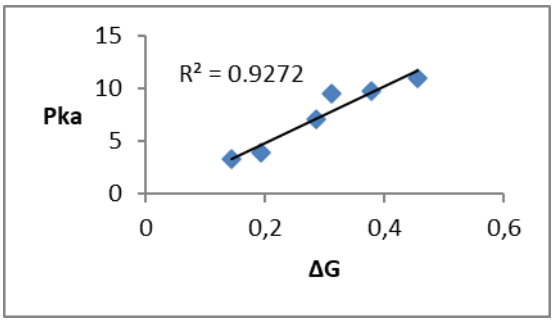

Figure 6. Relationship between experimental ionization constants and ΔG values using the PM3 method.

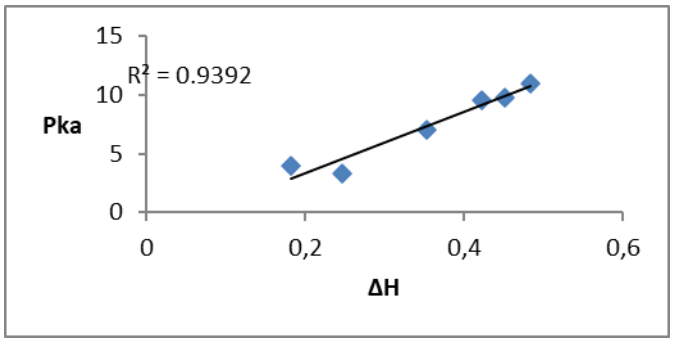

Figure 4. Relationship between experimental ionization constants and ΔH values using the PM3 method.

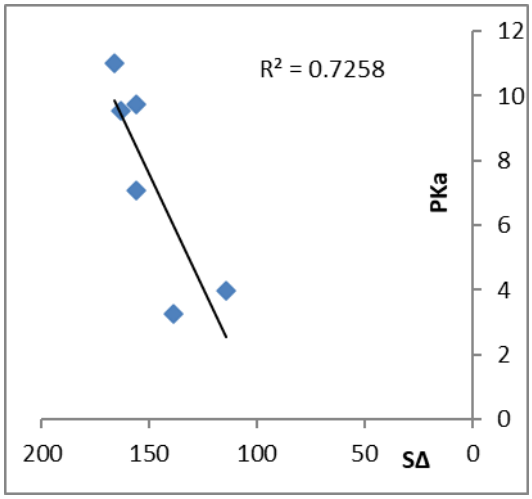

Figure 5. Relationship between experimental ionization constants and ΔS values using the PM3 method.

Table 5. Experimental and theoretical ionization constants and their differences using the DFT/6-31G method.

COMP	pka (Practical)	pKa (Theoretical)	Δpka
1	11.02	10.33844	0.681562
2	9.53	9.966385	-0.43638
3	3.28	3.040489	0.239511
4	9.72	8.86062	0.85938
5	3.96	4.007247	-0.04725
6	7.07	8.366967	-1.29697

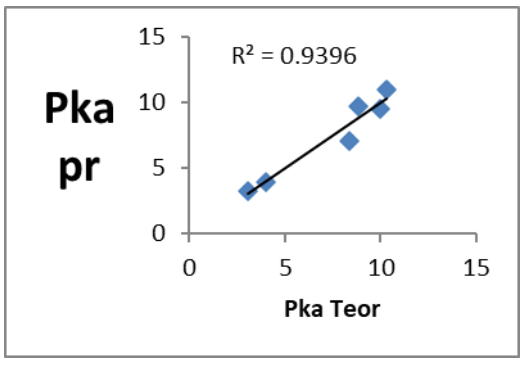

Figure 8. Graphical relationship between experimental and theoretical ionization constants using the DFT/6-31G method.

Table 4. Experimental and theoretical ionization constants and their differences using the PM3 method.

COMP	pka(Practical)	pKa (Theoretical	Δpka
1	11.02	10.74208	0.277923
2	9.53	9.126233	0.403767
3	3.28	4.573202	-1.2932
4	9.72	9.913305	-0.19331
5	3.96	2.892203	1.067797
6	7.07	7.333167	-0.26317

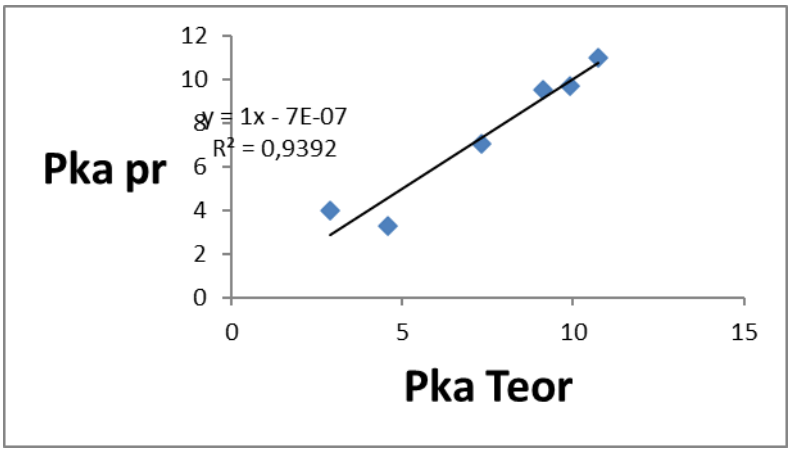

Figure 7. Graphical relationship between experimental and theoretical ionization constants using the PM3 method.

In general, the results of the theoretical study of thermodynamic functions showed the following:

Key observations:

1. Nature of the theoretical study:
   Calculations were performed in the gas phase, neglecting the effect of the solvent.
2. Relationship between thermodynamic functions and pKa:
   Increasing ΔH and ΔG values → Increasing pKa values → Decreasing acidity
   Decreasing ΔH and ΔG values → Decreasing pKa values → Increasing acidity
   The relationship between thermodynamic functions and acidity is inverse.
3. Statistical analysis:

Method	Variable	Correlationship coefficient(R^2)
DFT\6-31G	ΔH	0.9369
	ΔG	0.9219
	ΔS	0.8481
PM3	ΔH	0.9392
	ΔG	0.9272
	ΔS	0.7258

4. Predictive equations for ionization constants:
   DFT/6-31G: $pKa = 24.175 \times \Delta H - 0.4806$ ($R^2 = 0.9396$)
   PM3: $pKa = 26.062 \times \Delta H - 1.8589$ ($R^2 = 0.9392$)
   (1 Cal = 4.184 J ، 1 Hartree = 4.3597×10^{-18} J)

The results showed excellent agreement between the enthalpy (ΔH) and ionic constants (pKa) in both methods, with harmonic concordance $R^2 = 0.9396$ for the DFT/6-31G method and $R^2 = 0.9392$ for PM3. Therefore, the study found a direct linear relationship between increasing thermodynamic functions and, consequently, pKa values, which

necessarily reflects a high degree of accuracy, and an inverse relationship between thermodynamic energies and power.

4. Conclusion

In this study, the thermodynamic functions (ΔH, ΔG, ΔS) were calculated for six basic pharmaceutical compounds, with theoretical ionization constant values determined using two methods: DFT/6-31G (basic) and PM3 (quasi-empirical), based on a statistical analysis comparing these functions with experimental pKa values. DFT/6-31G achieved the highest correlation coefficient (R^2 = 0.9396) between ΔH and practical pKa values, compared to (R^2 = 0.9392) for PM3 in the same relationship. The results reveal DFT's superior accuracy, with a clear inverse relationship: increasing the thermodynamic functions increases pKa (decreases acidity), which is consistent with previous findings (R = 0.984 for DFT versus R = 0.948 for AM1). The importance of the study: These methods provide a powerful tool for drug design and understanding their acidic properties with high accuracy (R^2 > 0.93), especially with (Ticarcillin) having the lowest ΔH value and (Quinmerac) having the lowest ΔG, which enhances their applications in pharmaceutical chemistry.

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