International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

EXPERIMENTAL LIPOPHILICITY PROFILES OF DRUG-LIKE MOLECULES: COMPARATIVE ANALYSIS OF PH-DEPENDENT PARTITION AND DISTRIBUTION COEFFICIENTS

Zaharaddeen Muhammad Adam

NASENI. Email: zahramad001@gmail.com

CorrespondingAuthor: *ZaharaddeenMuhammadAdam, zahramad001@gmail.com*

Received: 16/05/2026 Revised: 22/07/2026 Acceptance: 16/08/2026 Published: 29/08/2026

ABSTRACT

Lipophilicity is one of the main physicochemical properties that determine the absorption, distribution, permeability and pharmaceutical behaviour of drug-like molecules. In the present study the experimental lipophilicity profiles were assessed by comparing the partition and distribution coefficients at various pHs with a focus on the molecular ionization behaviour. LogPN, LogPI, LogD, pKa, pH, acid–base classification, measurement method information was also used in a secondary QSAR. A total of 297 experimental observations for 114 different compounds were analysed. Descriptive statistics, correlation analysis, Mann–Whitney U testing and graphical pH-dependent profiling were used. The mean logD was 0.55 ± 1.93, while experimental pH ranged from 0.50 to 13.40. The overall results indicated a weak to moderate negative correlation between the pH and the logD ($\rho = -0.286$, $p < 0.001$). However, on stratified analysis, there were opposite associations for acidic compounds (moderate negative association, $\rho = -0.586$, $p < 0.001$) and basic compounds (positive association, $\rho = 0.282$, $p = 0.001$). A good correlation was found between LogD and logPN or logPI, which indicated that there were close relationships between the experimental lipophilicity measures. The pKa and experimental pH of acidic and basic compounds were very different, but the logD distributions were similar. The results indicate that the pH-dependent lipophilicity profiling is more informative than a single partition coefficient, especially for the characterization of ionizable drug-like molecules. It is recommended that standardized measurements be made over wider pH ranges.

Keywords: Lipophilicity; logP; logD; pH-dependent distribution; Drug-like molecules

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

1. Introduction

Lipophilicity is an inherent physical chemical characteristic that affects the behavior of drug-like molecules during the entire drug development process. It also shows the preference of a compound for lipid or aqueous environment and is thus significant in the context of membrane permeability, absorption, distribution, protein binding, metabolism and elimination. Physicochemical properties are especially relevant early in the drug discovery process as well as solubility and permeation, as too high or too low lipophilicity can have an impact on drug-like behaviour and therapeutic outcome. Nowadays, an important aspect of examining modern small molecule drugs is ensuring that molecular properties are balanced, and the physicochemical design space plays a key role in the successful drug development process (Holm, 2023). The trends in oral small molecule products also illustrate that development of such products still prioritizes a balance of lipophilicity with other molecular properties, and not the use of physicochemical criteria alone (Stegemann et al., 2023). The same has been highlighted in defining a physicochemical design space for certain specialized classes of drugs (Karami et al., 2022), and integrated ADME assessments have demonstrated the need to consider drug-likeness along with the potential kinetic and toxicity liability of a drug (Akumu, 2026).

The most popular lipophilicity parameters are the partition coefficient, logP, and the distribution coefficient, logD. LogP is the equilibrium partition coefficient of the neutral molecule while logD is the overall partition coefficient where an unknown compound is distributed as both ionized and non-ionized molecules at the specified pH. LogP can thus give an intrinsic measure of molecular lipophilicity and logD is very useful for ionizable molecules at physiologically or experimentally relevant pH. The deviations between the experimental and predicted values have led to the further development and evaluation of logP and logD correction models (Aliagas et al., 2022). Lipophilicity is also increasingly studied together with other properties, such as aqueous solubility, using modern computational methods as well as experimental methods for reliable reference values (Wu et al., 2022). On a larger scale, it is known that structure–property relationships are now considered as important elements of pharmaceutical molecular design (Kabdraisova et al., 2026).

For molecules with ionizable functional groups, the interpretation of lipophilicity can be very important, as the apparent hydrophobicity may vary significantly with environment pH. The pH and pKa affect the extent of protonation and deprotonation and hence the actual distribution between the aqueous and non-aqueous phases. However, a critical evaluation of pH-dependent lipophilicity profiles has indicated that the type of lipophilicity parameter used should be dependent on the molecular ionization and the aim of the analysis (Bertsch et al., 2023). Thus, the determination of pKa is significant as it represents the range of pH at which significant changes in ionization can be anticipated (Wagen, 2025). This close relationship between pH, ionization and physicochemical behavior is reflected in experimental studies of pH-dependent solubility, where the changes in protonation state significantly alter the apparent behaviour of the compound (Bodiwala et al., 2024).

The lipophilicity is also strongly dependent on the experimental technique employed. Complementary information can be obtained by classical shake-flask measurements, by potentiometric procedures and by chromatographic techniques, but methodological differences may lead to variations in the reported values. Chromatographic methods are particularly helpful for initial assessment of physicochemical properties, as the retention behavior can relate to lipophilicity and permeability properties (Castagnini, 2026). Simultaneously, absorption studies have shown that physicochemical values must be carefully interpreted when attempting to extrapolate to biological/pharmaceutical effects (Llompart et al., 2025). The increasing validation of solubility models for drug-like molecules also highlights the need to precisely specify the physicochemical conditions in which predictive relationships hold true (Bertsch-Aguilar et al., 2026).

Thus, comparing experimentally measured logP and logD values at various pH values can help to gain a better insight into the influence of ionization on the apparent lipophilicity. This analysis can help to separate intrinsic partitioning behaviour from pH dependent distribution, differentiate between acidic and basic compounds and explain the correlation of pH, pKa and the experimental lipophilicity. This study thus tests experimentally reported lipophilicity profile of drug-like molecules with special

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

focus on the partition and distribution pH dependent behaviour.

Objectives

- To characterize the experimental partition and distribution coefficients of drug-like molecules across the available physicochemical measurements.
- To evaluate the relationships among pH, pKa, partition coefficients and experimentally measured distribution coefficients.
- To compare lipophilicity profiles according to molecular ionization class and experimental measurement approach.

2. Materials and Methods

2.1 Study Design and Data Source

This study was secondary quantitative research with experimental publicly available physicochemical data of small drug like molecules (Bertsch et al., 2024). A database of experimental n-octanol/water partition and distribution coefficients, which includes measurements of molecular lipophilicity under various physicochemical conditions, was used for the analysis. The compound identifiers, molecular structures (SMILES), acid–base classification, partition coefficients, distribution coefficients, pKa, experimental pH conditions, references, and information on analytical method used to obtain measurements were included in the database. A number of compounds were analysed more than once at different pH levels, so that to preserve the pH dependent variability, individual records were kept as independent observations.

2.2 Compound Selection and Data Preparation

Initially, all records where lipid/partition coefficient data were experimentally reported were reviewed. Compounds with available logP or logD type measurements were deemed as fit for analysis. Records were checked for data gaps, duplication, label mismatches, and the presence of pH and/or pKa data. Repeated measurements for the same compound were not considered duplicate when they were measured with different pH values or experimental procedures as it was necessary to examine the pH dependent changes in lipophilicity. The compound names and ionization classes were standardized prior to analysis, and the acidic and basic molecules were kept as the major comparison groups.

2.3 Study Variables

The main experimental parameter measured was the experimentally determined distribution coefficient (logD). Also, experimental partition related properties such as the neutral and ionized partition coefficients (when available) were investigated. The main explanatory variables were the experimental pH, pKa and molecular acid–base classification. Other description variables were compound name, SMILES representation, experimental method and source information. These variables were chosen because they enable the intrinsic partitioning behavior to be explored and because they can monitor the effect of apparent lipophilicity changes resulting from molecular ionization under different pH conditions.

2.4 Classification of Molecular Lipophilicity and Ionization

Compounds were classified based on the number of reported acid–base behavior as acidic and basic molecules. Experimental pH values were compared with the reported pKa of each compound to determine conditions that would result in changes of protonation or deprotonation. Partition and distribution coefficients were analysed separately since logP pertains mainly to the non-ionized molecular form, while logD is a combination of the distribution of both the non-ionized and ionized forms at a specific pH. If the pH was measured repeatedly for the same compound, these data were exploited to describe the lipophilicity profile of this compound as a function of pH.

2.5 Assessment of pH-Dependent Lipophilicity

The pH dependent behaviour of the compounds was assessed by analysing how the logD values

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

measured in the range tested varies as a function of pH. Special care was given to molecules that had measurements at different pHs since the apparent lipophilicity variation could be assessed from these measurements. The overall and acid–base class wise relationships between pH and logD were investigated. A relationship between pKa and logD was also evaluated to see if the differences in the ionization characteristics were also manifested in the experimental distribution behaviour. If there were enough repeated measurements, it was shown that the graph profiles of the logD vs. pH were plotted to show the direction and extent of the lipophilicity changes.

2.6 Comparison of Experimental Measurement Methods

The experimental procedures detailed in the source data were assessed and categorized into the principle analytical techniques reported in the source data: potentiometric, shake-flask, reversed-phase high-performance liquid chromatography, counter current chromatographic and other reported procedures. Lipophilicity values derived from these different approaches were descriptively summarized and analysed to see if there were discernable differences between analytical approaches. Such a comparison was not meant to indicate the superiority of any one experimental method, but it was meant rather to describe the variation in experimental methods.

2.7 Statistical Analysis

The continuous variables (pH, pKa, logP-related measures, logD) were presented as mean and SD if the data were approximately normally distributed, and as median with an interquartile range if the data were skewed. Min and Max values were also provided to indicate the range of measurements to be taken. Frequency and percentage were used to summarize categorical variables such as Ionization class, Experimental method. For approximately normally distributed continuous variables, Pearson correlation analysis was performed and for other variables, Spearman correlation was used. The relationship between pH, pKa, partition coefficients and logD were explored with the appropriate correlation test. Independent-samples t-test or the Mann–Whitney U test was used to assess differences in continuous lipophilicity parameters between acidic and basic compounds, based on the distribution of the data. Simple linear regression was also used to assess the relationship between pH and logD when assumptions of the model were satisfied. A p value of < 0.05 (two-tailed) was considered statistically significant.

2.8 Ethical Considerations

This study did not employ human subjects, personally identifiable information, biological specimens, or confidential clinical information that are not publicly available and already incorporated into experimental, physicochemical information. Thus, the ethical approval and the informed consent of the institution and the participants were not necessary. The analysis was only performed for scientific evaluation of the molecular lipophilicity characteristics experimentally reported.

3. Results

3.1 Characteristics of the Experimental Lipophilicity Records

A total of 297 experimental observations of 114 different compounds were analysed. In the unique compounds, there were 42 acids (36.84%) and 72 bases (63.16%). In terms of observations, 172 times (57.91%) were made for acidic compounds compared to 125 times (42.09%) for basic compounds. The set of measurements spanned 61 different pH values from 0.50 to 13.40, covering a wide range of acid, neutral and alkaline experimental conditions. A total of 31.58% of the compounds (n = 36) had measurements at more than one pH while 28.95% (n = 33) had measurements at three or more pH. The widest pH range was for salicylic acid (14 pH values), followed by tyrosine (10 pH values) and diclofenac and naproxen (9 pH values each). The main features of the records analysed are shown in Table 1.

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

Table 1. General Characteristics of the Experimental Lipophilicity Data

Characteristic	Value
Total experimental observations	297
Unique compounds	114
Acidic compounds, n (%)	42 (36.84%)
Basic compounds, n (%)	72 (63.16%)
Acidic observations, n (%)	172 (57.91%)
Basic observations, n (%)	125 (42.09%)
Distinct experimental pH values	61
pH range	0.50–13.40
Compounds measured at >1 pH, n (%)	36 (31.58%)
Compounds measured at ≥3 pH values, n (%)	33 (28.95%)
Maximum number of pH levels for one compound	14

3.2

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

Distribution of Experimental Lipophilicity and Ionization Parameters

A large variation was obtained in the experimental physicochemical measurements. The mean neutral partition coefficient (logPN) was 2.13 ± 2.00 with a range from −2.93 to 7.80, while the mean ionized partition coefficient (logPI) was −1.02 ± 1.43. The average value of the experimental pKa was 6.46 ± 2.74 and the average value of the experimental pH was 6.71 ± 2.83. The distribution coefficient was rather widely scattered, with a mean logD of 0.55 ± 1.93, a median of 0.51 and a range from −3.41 to 7.40 (Table 2). LogPN, logPI and logD distributions are compared graphically in Figure 1, which indicates that the distribution of neutral partition coefficients is more central and that the range of experimentally measured distribution coefficients is wider. The total variation in the three experimental lipophilicity measures is shown in Figure 1.

Table 2. Descriptive Statistics of Experimental Physicochemical Parameters

Parameter	Mean ± SD	Median (IQR)	Minimum	Maximum
logPN	2.13 ± 2.00	2.21 (0.90–3.61)	−2.93	7.80
logPI	−1.02 ± 1.43	−0.99 (−2.15–0.20)	−4.00	4.02
pKa	6.46 ± 2.74	5.50 (4.15–9.19)	1.27	11.90
pH	6.71 ± 2.83	7.40 (5.00–8.00)	0.50	13.40
logD	0.55 ± 1.93	0.51 (−0.75–1.69)	−3.41	7.40

SD: standard deviation; IQR: interquartile range.

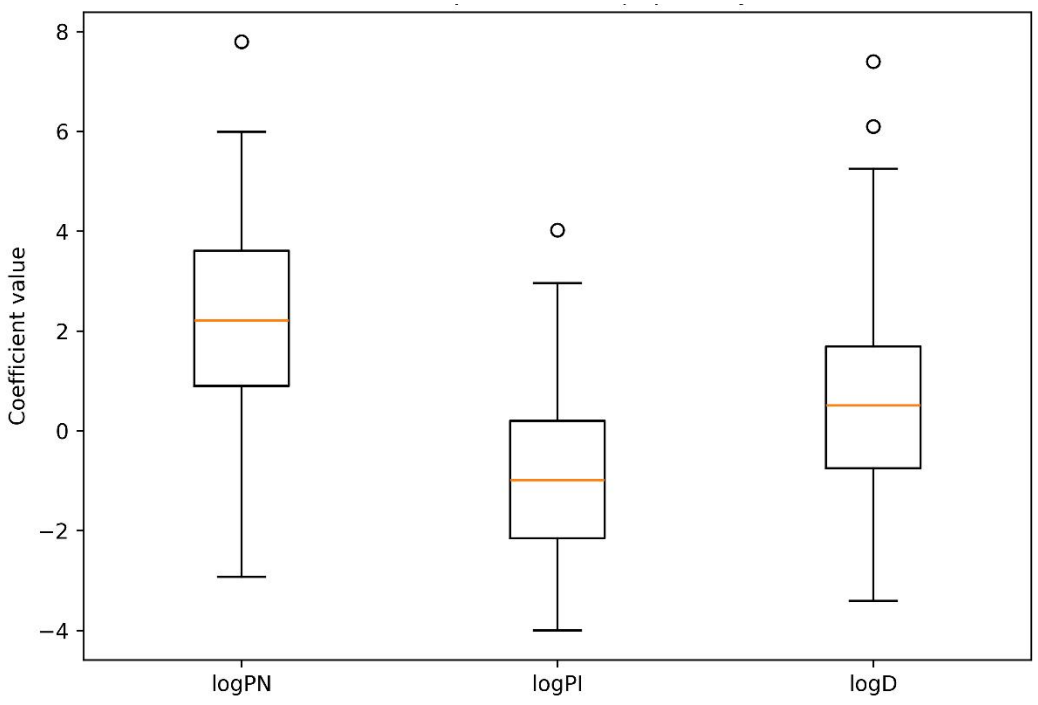


Figure 1. Distribution of Experimental Lipophilicity Measures

Box plots demonstrate the distributions of neutral partition coefficient (logPN), ionized partition

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

coefficient (logPI), and experimentally measured distribution coefficient (logD), highlighting substantial between-compound variability in lipophilic behavior.

3.3 pH-Dependent Variation in Distribution Coefficients

LogD changes with pH for several compounds for which multiple measurements were made. The representative profiles of salicylic acid, tyrosine, diclofenac and naproxen are shown in Figure 2. In general, both the logD of salicylic acid, diclofenac, and naproxen decreased with an increase of experimental pH. For instance, diclofenac had high logD values with strongly acidic conditions and then a dramatic drop when the pH reached neutral and alkaline conditions. A comparable downward trend was observed in the case of naproxen. Significant pH-dependent logD changes from positive to negative were also observed with salicylic acid. Tyrosine exhibited a relatively favorable profile over the major portion of the range tested; the log D values were lower at the most alkaline pH's. The results at the compound level demonstrated that one single lipophilicity parameter is not sufficient to describe molecules tested over wide pH ranges. The magnitude and direction of the pH related changes were different depending on the molecular ionization characteristics as shown in Figure 2.

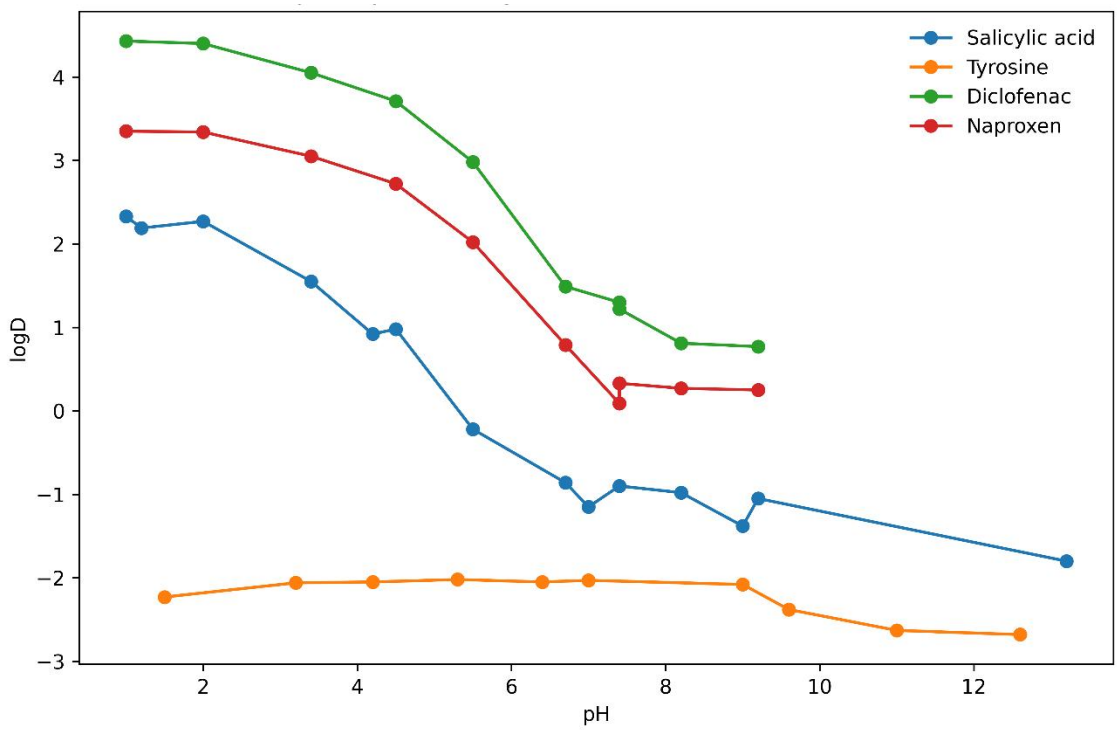


Figure 2. pH-Dependent logD Profiles of Selected Molecules

Experimental logD measurements across pH conditions demonstrate pronounced pH-dependent changes for salicylic acid, diclofenac, and naproxen, while tyrosine displays a comparatively smaller change over much of its observed pH range.

3.4 Relationships Among pH, pKa, Partition Coefficients, and logD

The main physicochemical variables were significantly correlated using Spearman correlation analysis (Table 3). All observations indicated a weak to moderate inverse correlation between pH and logD ($\rho = -0.286$, $p < 0.001$). But the relationships were significantly different for different ionization classes. The correlation between pH and logD was moderately negative ($\rho = -0.586$, $p < 0.001$) for the acidic compounds, but positive ($\rho = 0.282$, $p = 0.001$) for the basic compounds. Experimental logD was strongly positively correlated with logPN ($\rho = 0.707$, $p < 0.001$) and moderately-to-strongly

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

correlated with logPI ($\rho = 0.660$, $p < 0.001$). There was a strong correlation between LogPN and logPI ($\rho = 0.833$, $p < 0.001$). The correlation of pKa with logD, on the other hand, was weak and negative ($\rho = -0.151$, $p = 0.009$). The overall pH–logD relationship suggests the existence of counteracting trends for acidic and basic molecules. This difference in the pH–logD behavior of acids and bases is evident in Figure 3.

Table 3. Spearman Correlations Among Experimental Lipophilicity Parameters

Variable relationship	Spearman ρ	p-value
pH vs. logD, overall	−0.286	<0.001
pH vs. logD, acidic compounds	−0.586	<0.001
pH vs. logD, basic compounds	0.282	0.001
pKa vs. logD	−0.151	0.009
logPN vs. logD	0.707	<0.001
logPI vs. logD	0.660	<0.001
logPN vs. logPI	0.833	<0.001

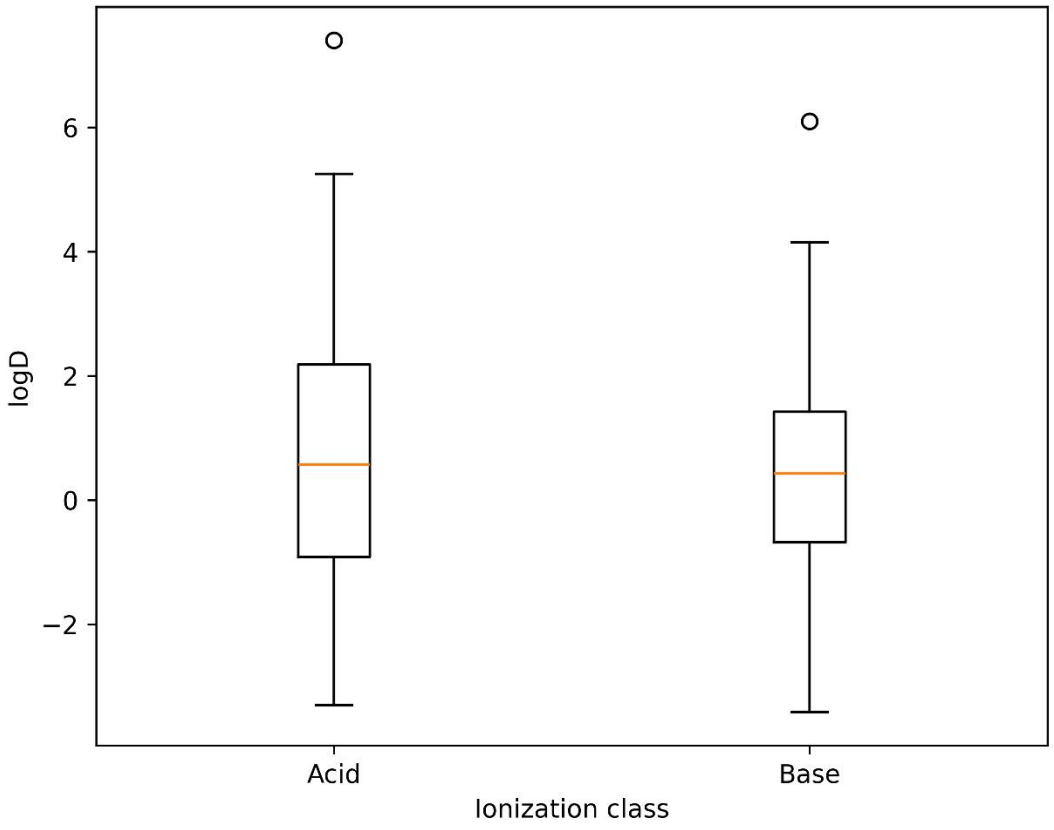


Figure 3. Relationship Between pH and Experimental logD According to Ionization Class

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

Acidic molecules show an overall decline in logD with increasing pH, whereas basic molecules demonstrate an opposite positive trend, emphasizing the importance of ionization class when interpreting pH-dependent lipophilicity.

3.5 Comparison of Acidic and Basic Molecules

The Mann–Whitney U test (Table 4) was used to compare differences between acidic and basic observations. Acidic compounds possessed higher median logPN than basic compounds (2.77 vs 1.61) and the difference was statistically significant (p=0.045). LogPI was not significantly different between the two classes, however, ($p = 0.474$). Not surprisingly, given their ionization properties, there was a significant difference between acid and base compounds for pKa (median 4.20 for acid and 9.04 for base, $p < 0.001$). Experimental pH also was found to vary among the groups ($p = 0.001$) as it is a result of the experimental pH at which the molecules were characterized. Although the logD values showed different pH-dependent tendencies, the median logD value was not significantly different between the acidic and basic observations (0.57 and 0.43, respectively, $p = 0.448$). Figure 4 shows that there is significant overlap of logD distributions.

Table 4. Comparison of Experimental Parameters Between Acidic and Basic Compounds

Parameter	Acid, Median (IQR)	Base, Median (IQR)	p-value
logPN	2.77 (0.88–3.97)	1.61 (1.13–3.18)	0.045
logPI	−1.05 (−2.02–0.31)	−0.94 (−2.60–−0.06)	0.474
pKa	4.20 (3.50–4.80)	9.04 (7.42–9.60)	<0.001
pH	6.95 (4.28–8.00)	7.40 (7.00–8.00)	0.001
logD	0.57 (−0.92–2.18)	0.43 (−0.68–1.42)	0.448

Comparisons were performed using the Mann–Whitney U test.

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

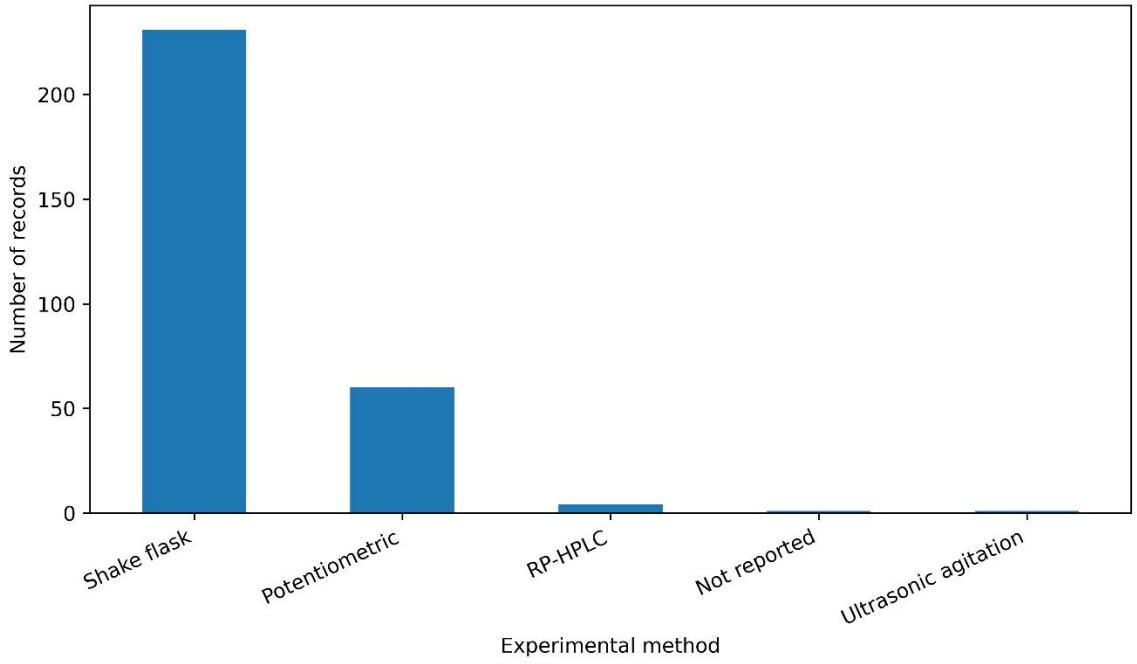


Figure 4. Distribution of Experimental logD According to Ionization Class

Acidic and basic observations showed substantial overlap in overall logD values, despite their distinctly different pKa distributions and opposing relationships between pH and logD.

3.6 Experimental Methods Used for logD Determination

Almost all observations were made by experimental method for logD. The most used method was the shake-flask method (231 measurements, 77.78%), followed by the potentiometric determination method (60 measurements, 20.20%). Four measurements out of 284 (1.35%) were used for RP-HPLC and one measurement (0.34%) was used for ultrasound agitation. One observation was not reported using a measurement method. The mean logD from the potentiometric measurements was 1.18 ± 1.79, and the mean logD from the shake-flask measurements was 0.34 ± 1.94 as shown in Table 5. RP-HPLC measurements gave a mean of 2.03 ± 0.85, but too few observations were made by this method to make meaningful direct statistics with the larger method groups.

Table 5. Distribution of logD Measurements According to Experimental Method

Experimental method	n (%)	Mean ± SD logD	Median (IQR)	Range
Shake flask	231 (77.78%)	0.34 ± 1.94	0.35 (−0.98–1.50)	−3.41 to 5.25
Potentiometric	60 (20.20%)	1.18 ± 1.79	0.73 (−0.10–2.30)	−2.17 to 7.40
RP-HPLC	4 (1.35%)	2.03 ± 0.85	1.78 (1.39–2.42)	1.38 to 3.18
Ultrasonic agitation	1 (0.34%)	1.72	1.72	1.72
Not reported	1 (0.34%)	1.44	1.44	1.44

The findings demonstrate substantial variability in experimental lipophilicity across the studied molecules and confirm that pH dependence differs fundamentally between acidic and basic compounds. Although the overall pH–logD correlation was negative, stratified analysis showed a considerably stronger inverse relationship among acids and a positive relationship among bases.

International Journal for Research in Biology & Pharmacy
(ISSN: 2208- 2093)
Vol. 12, Issue 03, August 2026
DOI:10.65327/bp.v12i3.2544

LogD also exhibited strong associations with both neutral and ionized partition coefficients, supporting the close relationship among the experimental measures while showing that pH-dependent distribution provides additional information beyond a single partition coefficient.

4. Discussion

In the present work, the lipophilicity observed was found to be quite different for the various drug-like molecules analyzed and the pH had a significant effect on the distribution behavior. The overall inverse association between pH and logD was modest, but there was a more informative pattern: acidic compounds exhibited a moderate decrease in logD with increasing pH, while the basic compounds exhibited a positive association. Chemically, this was to be expected since acidic molecules tend to be more ionized at higher pH and thus less soluble in the lipid phase, while the distribution behavior of basic compounds depends on the relationship between pH and their pKa. The high correlation coefficients between logD and logPN as well as logPI also suggest that distribution coefficients are still tightly coupled to intrinsic lipophilicity but can be used in addition to a partition measurement to add pH sensitivity.

The pH dependent behavior observed agrees with previous studies which stressed the need for ionization in explaining the experimental and predicted lipophilicity. The close dependence between logD7.4 and logP and microscopic pKa was demonstrated by Wang et al., who found that the inclusion of these other parameters in logD7.4 prediction improves the prediction. Likewise, Duan et al. showed the advantages of incorporating knowledge about physicochemical properties of molecules during logD prediction, further highlighting the importance of contextual molecular properties over the importance of single descriptors (Duan et al., 2023). Experimental studies also indicate that the lipophilicity may vary significantly with molecular structure and measuring conditions. The experimental distribution behaviour was also shown to be practically relevant with meaningful relationships between chromatographically derived lipophilicity and permeability (Vidović et al., 2022). Similar relationships between solubility, distribution and permeability were also observed for bicalutamide, where all the three properties jointly influenced the pharmaceutical behaviour (Volkova et al., 2022).

The present results also have implications on drug development and ADME interpretation. If the logD values change with pH, it may be more appropriate to use more than one value for a molecule that can be ionizable in an environment that has a varying pH. Integrated physicochemical assessment has been proven to help to understand the lipophilicity of large and complex drug-like molecules including PROTACs, which can display discrepancies between experimental and computational assessments and need to be interpreted in the context of the molecule (Venturi et al., 2024). A similar correlation between molecular properties and oral exposure has been shown in PROTAC optimisation where structural modifications affected the physicochemical behaviour and bioavailability (Garcia Jimenez et al., 2025). Extensive ADME studies also emphasize that lipophilicity is important together with absorption, metabolism, and distribution properties (Jurowski & Krośniak, 2025). Evaluations of ADME in vitro and PBPK further highlight the ability to interpret the data based on experimentally determined physicochemical parameters (Nunna et al., 2026).

Biological relevance of pH sensitivity of molecular behaviour is reinforced by studies demonstrating that pH may lead to changes in the molecular interactions and pharmacological responses. Computer-aided investigations of pH-dependent inhibition indicate the effect of protonation conditions on ligand--target interactions (Goyzueta-Mamani et al., 2024), and pH-responsive cytotoxicity studies reveal that structural modification can result in changes in activity at the different pH conditions (Tapia et al., 2024). Similar correlations have been observed for the drug-like properties of physicochemical properties in experimental biological systems (Kusaczuk et al., 2024). The present analysis should be interpreted with the knowledge of the methodological predominance of shake-flask measurements, which can give systematically different estimates than other analytical platforms. Comparative physicochemical modelling studies highlight the potential differences in the performance and applicability of analytical and predictive models (Formanek et al., 2026; da Silva et

al., 2025).

The wide pH range, repeated measurements and the direct experimental logP/logD information provide support to the study. Due to different measurements between the compounds, different experimental methods and limited repeated pH measurements for some compounds, however, direct comparisons are limited. The following work should focus on standardizing experimental protocols, sampling at balanced pH and external validation of the pH-dependent lipophilicity profiles over larger chemical classes to enhance the generalizability of pH-dependent lipophilicity profiles.

5. Conclusion

This study illustrates the importance of pH, molecular ionization state and pH/pKa correlation with experimental lipophilicity profiles for drug-like molecules. Partitioning parameters (neutral, ionized and distribution) showed a lot of variation between compounds analysed. The correlation between pH and logD was only slightly negative, but there were opposing trends for acid and basic compounds. When interpreting the distribution behaviour as a function of pH, the impact of the class of ionization of acidic and basic compounds was evident with a clear decline in logD with pH for the acidic compounds and a positive relation for the basic compounds. The high positive correlation values for logD with logPN and logPI indicated that distribution coefficients continue to be strongly associated with intrinsic molecular lipophilicity and under specific pH conditions, provide further information. Other compounds examined, including salicylic acid, diclofenac, naproxen, and tyrosine, showed that a single lipophilicity value is not sufficient to describe a molecule which can exist in more than one ionization state in different environments. Additionally, method differences used to determine the logD values suggest that context should be taken into account when comparing the reported values. Overall, the results indicate that pH-dependent lipophilicity profiling is a more informative method for characterising ionisable drug-like molecules. Further research is needed to standardise experimental techniques, expand the range of compounds examined and to take measurements over more defined pH ranges.

References

1. Akumu, E. O. (2026). Balancing Favourable Drug-Likeness Against Respiratory and Renal Liabilities: An Integrated In Silico ADME–Toxicity Profile of a Novel 3-{[2-(Formimidoylamino) ethyl] sulfanyl}-6-(1-methoxyethyl)-4-methyl-7-oxo-1-azabicyclo [3.2. 0] hept-2-ene-2-carbonyl fluoride. Editon Consortium Journal of Research in Medical and Health Sciences, 6(1), 28-40.
2. Aliagas, I., Gobbi, A., Lee, M. L., & Sellers, B. D. (2022). Comparison of logP and logD correction models trained with public and proprietary data sets. Journal of Computer-Aided Molecular Design, 36(3), 253-262.
3. Bertsch Aguilar, E., Suñer Sánchez, S., Pinheiro, S., & Zamora Ramírez, W. J. (2023). Critical Assessment of pH-Dependent Lipophilic Profiles of Small Molecules for Drug Design: Which One Should We Use and In Which Cases?.
4. Bertsch-Aguilar, E., Quirós, N., Schosinsky, F., Pinheiro, S., Medina-Franco, J. L., & Zamora, W. J. (2026). Data-driven critical evaluation of the General Solubility Equation: When is it a valid solubility predictor for Drug-like Molecules?.
5. Bodiwala, K. B., Dhameliya, T. M., Sureja, D. K., & Patel, M. P. (2024). Determination of pH-Solubility Profile and Development of Prediction Models for pH-Dependent Solubility of Atorvastatin Calcium. Current Pharmaceutical Analysis, 20(8), 808-824.
6. Castagnini, F. (2026). CHROMATOGRAPHIC METHODS FOR PHYSICO-CHEMICAL EVALUATION AND PERMEABILITY PREDICTION IN EARLY DRUG DISCOVERY.
7. da Silva, C. G., Niero, C. V., Duque, M. D., & Nordi, C. S. F. (2025). Comparative analysis of the applicability of prediction software to microcystin toxicity evaluation. Toxicon, 108620.
8. Duan, Y. J., Fu, L., Zhang, X. C., Long, T. Z., He, Y. H., Liu, Z. Q., ... & Cao, D. S. (2023). Improved GNNs for log D 7.4 prediction by transferring knowledge from low-fidelity data.

Journal of Chemical Information and Modeling, 63(8), 2345-2359.
9. Esteban Bertsch, Sebastian Suñer, Silvana Pinheiro, & William J. Zamora. (2024). Experimental n-octanol/water Partition/Distribution Coefficients Database for Small Molecules [Data set]. Zenodo. https://doi.org/10.5281/zenodo.13208946.
10. Formanek, A., Vincze, A., Bicsak, R., Balogh, G. T., Moreau, Y., & Arany, A. (2026). A Comparative Study of QSPR Methods on a Unique Multitask PAMPA Data Set. Journal of Chemical Information and Modeling, 66(9), 5508-5518.
11. Garcia Jimenez, D., Ermondi, G., Jandova, Z., Vallaro, M., Caron, G., & Arnhof, H. (2025). Linker methylation as a strategy to enhance PROTAC oral bioavailability: insights from molecular properties and conformational analysis. Journal of Medicinal Chemistry, 68(15), 16666-16677.
12. Goyzueta-Mamani, L. D., Barazorda-Ccahuana, H. L., Candia-Puma, M. A., Galdino, A. S., Machado-de-Avila, R. A., Giunchetti, R. C., ... & Chávez-Fumagalli, M. A. (2024). Targeting Leishmania infantum Mannosyl-oligosaccharide glucosidase with natural products: potential pH-dependent inhibition explored through computer-aided drug design. Frontiers in Pharmacology, 15, 1403203.
13. Holm, R. (2023). Physicochemical Properties of Drugs for Use in the Pharmaceutical Industry. In Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays (pp. 1-43). Cham: Springer International Publishing.
14. Jurowski, K., & Krośniak, A. (2025). ADME profile of AP-238-opioid designer drug (CAS: 140924-11-4): first application of multi-in silico approach methodology for comprehensive prediction of ADME profile (absorption, distribution, metabolism and excretion) important for clinical toxicology and forensic purposes. Chemico-Biological Interactions, 415, 111493.
15. Kabdraisova, A. Z., Umbetova, A. K., Kairalapova, G. Z., Litvinenko, Y. A., Sassykova, L. R., Yelibayeva, N. S., ... & Sadvakas, A. M. (2026). Machine-Learning-Driven Molecular Design and Structure–Property–Performance Relationships in Pharmaceutical Chemistry. Molecules, 31(12), 2162.
16. Karami, T. K., Hailu, S., Feng, S., Graham, R., & Gukasyan, H. J. (2022). Eyes on Lipinski's rule of five: A New “rule of thumb” for physicochemical design space of ophthalmic drugs. Journal of ocular pharmacology and therapeutics, 38(1), 43-55.
17. Kusaczuk, M., Tovar-Ambel, E., Martín-Cabrera, P., Lorente, M., Salvador-Tormo, N., Mikłosz, A., ... & Naumowicz, M. (2024). Cytotoxicity, proapoptotic activity and drug-like potential of quercetin and kaempferol in glioblastoma cells: preclinical insights. International Journal of Molecular Sciences, 25(19), 10740.
18. Llompart, P., Minoletti, C., Marcou, G., & Varnek, A. (2025). What Works, What Doesn’t, and Why? An Industrial Perspective on Absorption Modeling. Journal of Medicinal Chemistry, 68(14), 14609-14627.
19. Nunna, N., Ghoshal, T. S., Yadav, I., Arun, T., & Salgotra, V. (2026). Comparative In Vitro ADME Assessment and Physiologically Based Pharmacokinetic (PBPK) Modeling of Andrographolide and Its Tert-Butyldiphenylsilyl (TBDPS)-Protected Analogue.
20. Stegemann, S., Moreton, C., Svanbäck, S., Box, K., Motte, G., & Paudel, A. (2023). Trends in oral small-molecule drug discovery and product development based on product launches before and after the Rule of Five. Drug Discovery Today, 28(2), 103344.
21. Tapia, L., Pérez, Y., Carreira-Barral, I., Bujons, J., Bolte, M., Bedia, C., ... & Alfonso, I. (2024). Tuning pH-dependent cytotoxicity in cancer cells by peripheral fluorine substitution on pseudopeptidic cages. Cell Reports Physical Science, 5(9).
22. Venturi, A., Di Bona, S., Desantis, J., Eleuteri, M., Bartalucci, M., Baroni, M., ... & Cruciani, G. (2024). Between theory and practice: computational/experimental integrated approaches to understand the solubility and lipophilicity of PROTACs. Journal of Medicinal Chemistry, 67(18), 16355-16380.
23. Vidović, D., Milošević, N., Pavlović, N., Todorović, N., Panić, J. Č., Ćurčić, J., ... &

Lalić-Popović, M. (2022). In silico–in vitro estimation of lipophilicity and permeability association for succinimide derivatives using chromatographic anisotropic systems and parallel artificial membrane permeability assay. Biomedical Chromatography, 36(9), e5413.

24. Volkova, T. V., Simonova, O. R., & Perlovich, G. L. (2022). Physicochemical profile of antiandrogen drug bicalutamide: Solubility, distribution, permeability. Pharmaceutics, 14(3), 674.
25. Wagen, C. (2025). Physics-Informed Machine Learning Enables Rapid Macroscopic pKa Prediction.
26. Wang, Y., Xiong, J., Xiao, F., Zhang, W., Cheng, K., Rao, J., ... & Zheng, M. (2023). LogD7. 4 prediction enhanced by transferring knowledge from chromatographic retention time, microscopic pKa and logP. Journal of cheminformatics, 15(1), 76.
27. Wu, J., Wang, J., Wu, Z., Zhang, S., Deng, Y., Kang, Y., ... & Hou, T. (2022). ALipSol: an attention-driven mixture-of-experts model for lipophilicity and solubility prediction. Journal of Chemical Information and Modeling, 62(23), 5975-5987.