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# Comments on 1-octanol/water partition of several n-alkane related series

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## Summary

The basic experimental data of partition coefficient isothermally (25 $^0$C) determined in 1-octanol/water mixture are discussed in more detail in terms of structural significances and according to the topoenergetic principles in defining the behaviour of composite systems. The partition process of ten series of related n-alkane compounds containing no or one polar end group are considered as a function of alkane chain length. Some important conclusions result in view to optimize experiments for better defining the behaviour of each compound (ontogeny) and for obtaining databanks with higher phylogenies. HRMC is presented as an efficient technique in defining this important solution behaviour.

## Definitions

Amphiphilic behaviour of organic compounds can be suggestively and efficiently expressed by selective solution process in a standardized oil/water mixture. Bioavailability and pharmacodynamic potency of medicinal products can be efficiently predicted by this *in vitro* behaviour defined by topoenergetic UNIVERSAL procedure.

The equilibrium ratio of solute concentrations in the two phases of two partially miscible solvents in intimate contact has come to be known as the distribution or partition coefficient [1].

Most experiments have been done using 1-octanol/water mixture at 25 $^0$C and this is the reason for its consideration in this note. On the other hand, a detailed retrieval of literature on these experimental data has been made [2] representing the source of experimental data considered in this note.

The 1-octanol/water partition coefficient, P, can be quantitatively defined by the equilibrium concentration of solute X in organic phase, [X]org, and in aqueous phase, [X]aq

$$P = [X]org/[X]aq \qquad (1).$$

This definition substantially differs from the separate solution behaviour of solute in the two solvents. We may observe just from the beginning that experimental data of P will strongly depend on how intimate are the two solvents during experiments, so that a rigorous standard operating procedure (SOP) is necessary in view to correctly compare series of solutes. This important aspect is obvious at once by inspecting Tables of values obtained by different experimenters for the same compounds [2]. This quantity seems to be more sensitive on hydrodynamic conditions (basically defining dispersion of the two solvents) than on temperature.

Determination of the two equilibrium concentrations is another important stage of experiment, because it must first to freeze the two phases and secondly to separate them with no structural modifications. The classic extraction procedure by shake-flask method is still widely used by considering of it as simple, and with acceptable repeatability [3].

## Topoenergetic aspects

The definition of a system behaviour in topoenergetic terms implies the correlation between the system response to a (stepwise) perturbation of a driving potential in the framework of a measuring system and experienced according to a rigorous SOP [4]. Most of the majority cases studied up to now take into consideration temperature as driving potential and compare the obtained results with Arrhenius representation.

By simply inspecting Tables of P values [2] we may group series of chemically related compounds. For instance the following series:

1-end group-n-alkanes (2)

are 1-ended isomers (simply denoted for further without this prefix) in each series defined by the end group (-OH, phenyl, amine, nitro, nitrile, acid (-COOH), etc.). We may define the behaviour of entire each series as a function of n-alkane weight.

Figure 1 shows the P dependence on the overall weight, Mw, of each compounds for several selected series (the length of n-alkane chains are denoted by nC).2-n-ketones represent an exception of 2-end group-n-alkane isomers.

We may immediately observe that: (i) the behaviour of each series appears as limited by a threshold molecular weight at which P becomes as infinite value; (ii) P continuously increases with Mw without structural changes.

In these conditions, we may consider that the behaviour of each series of compounds can be determined by the **UNIVERSAL TOPOENERGETIC PARAMETERS (N, M, Mwo)** defined by relationship

$$\ln P = N^{*}\ln|Mw - Mwo| + M \qquad (3).$$

We will consider in the following as driving potential of this behaviour, the molecular weight of n-alkane group in each compound of the series in view to be the same measuring unit for all considered series. We must point out once again that UNIVERSAL parameters (N, M, Mwo) define the behaviour of each series as entirely. From structural point of view, Mwo represents a molecular species specific for each series for which [X]aq vanishes.

Figure 2 shows the phylogeny of all considered n-alkane related series (error bar for each point is smaller than diameter of graphic point also for all further graphics). All molecular separation processes by partition solution in 1-octanol/water mixture appear to have the same nature for all these series, and their amplitude (expressed by Ctr according to the general assignment [4]) evidences the specificity of end group. We may notice as for many other practical examples, that Ctr is not defined only by mass of kinetic entity, so NH2- and nitrile-groups are located to the extremes of this phylogeny, while pure n-alkanes stay in the middle. Kinetic entity involves also the solvent by hydrophile and lipophile power of specific molecular groups in the tested compound. This is the reason for which Cl appears “heavier” than Br.

Figure 3 shows the phylogeny of the coupling strength (CS) parameter as a function of amplitude of partition process for the ten considered related series. We may observe that CS increases with Ctr in the phylogeny of all related series for which the same relative distribution as in the previous phylogeny exists.

Figure 4 shows the dependence of Mwo on partition amplitude. We may consider *a priori* that Mwo is a measure of kinetic entity in each series, so it results that Ctr increases by ctr increasing.

Figure 5 verifies once again that Mwo ~ ctr and on the other hand the general assignments of UNIVERSAL parameters established on other practical cases [1].

## Concluding remarks

Following practical conclusions can be drawn from above comments:

(1) Presently available values of partition coefficient in oil/water mixtures may define in topoenergetic terms the amphiphilic behaviour of organic compounds in the series of related compounds as a function of molecular weight as governing potential;

(2) Topoenergetic view on this behaviour allows to identify the nature and the amplitude of an unknown compound and/or optimize it by exact structure modification;

(3) The amplitude of partition process (= molecular separation by selective solubility) increases by increasing the kinetic entity defined by specific molecular groups and their hydrophile and lipophile affinity;

(4) CS (= coupling strength between the transforming and inert components) increases also with the amplitude of partition process and kinetic entity;

(5) Rigorous SOP is necessary in view to define the correct ontogeny of each compound and to obtain efficient databanks with higher phylogenies. The thorough study of kinetics [4,5] of partition process is necessary in view to establish the exact response function and driving potentials able to ensure efficient databanks. We suggest again High Resolution Mixing Calorimetry (HRMC) as an efficient technique (rapid, simple, sensitive, with high repeatability and reproducibility, widely applicable and chip) for solubility studies [4,5].

HRMC technique was efficiently applied for defining in vitro the bioavailability and pharmacodynamic potency of medicinal products [6,7].

## References

1 A.Leo, C.Hansch, D.Elkins, Chem.Rev., **71**, 525 (1971).
2 J. Sangster, J.Phys.Chem.Ref.Data, **18** (3), 1111 (1989).
3 T.Fujita, J.Iwasa, C.Hansch, J.Am.Chem.Soc., **86**, 5175 (1964)
4 Gh.Dragan, GDF Databanks Bulletin, **1**(1),1997 (Solubility behaviour introducing topoenergetic working principles); see similar references in this bulletin.
5 Gh.Dragan, J.Thermal Anal., **31**, 677, 941 (1986); **32**, 293 (1987); see similar references in this bulletin.
6 Gh.Dragan, Definition of biological activity of pharmaceuticals by solubility tests by means of HRMC, The 3rd Symposium on Romanian Drugs, 21-22 November 1985, Bucharest, Romania.
7 Gh.Dragan, Solubility DATABANKS based on topoenergetic principles, The 10th International CODATA Conference, 14-17 July, 1986, Westin Hotel, Ottawa, Canada

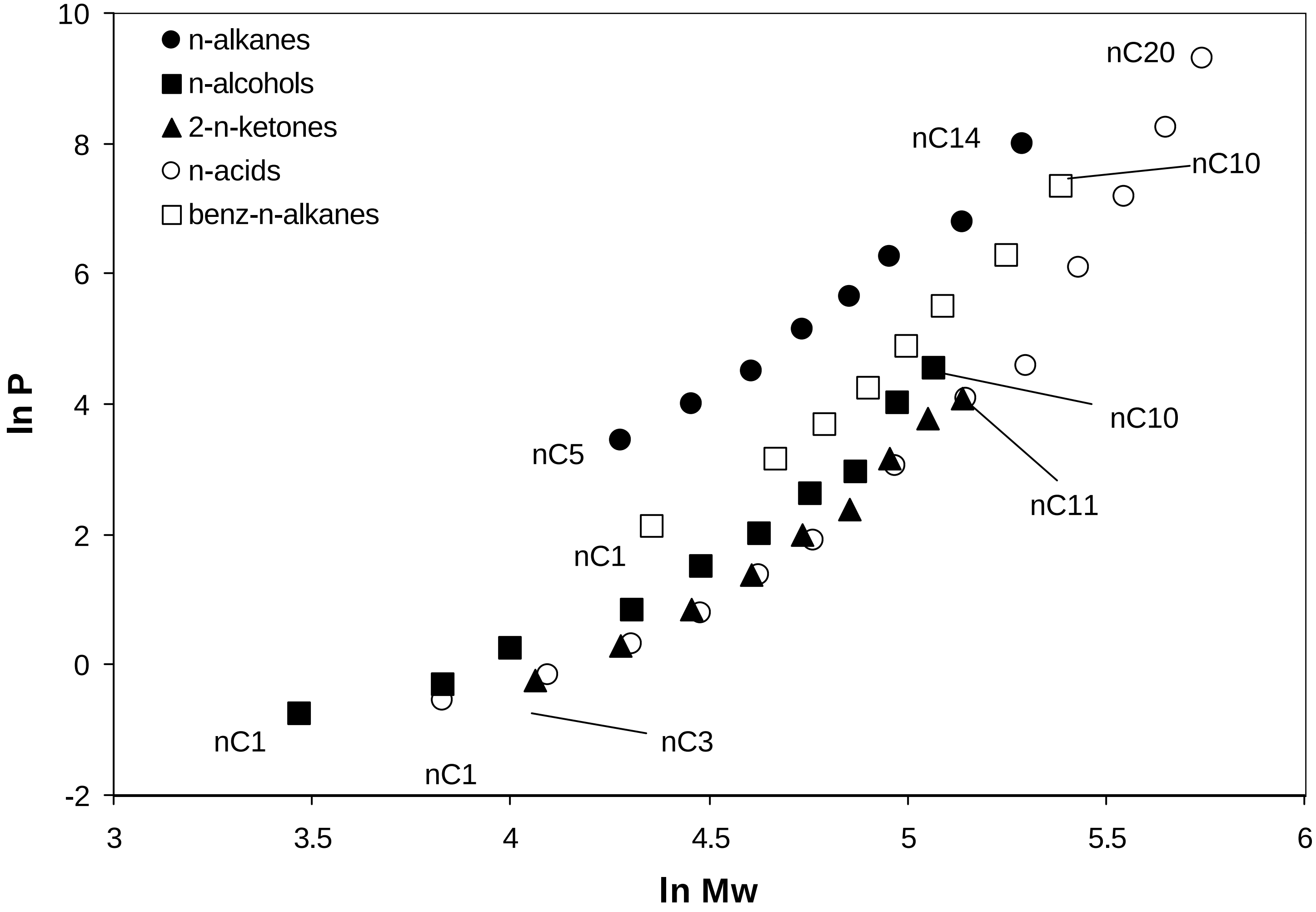

Figure 1. Dependence of partition coefficient on overall molecular weight for five series of molecular species related with n-alkanes.

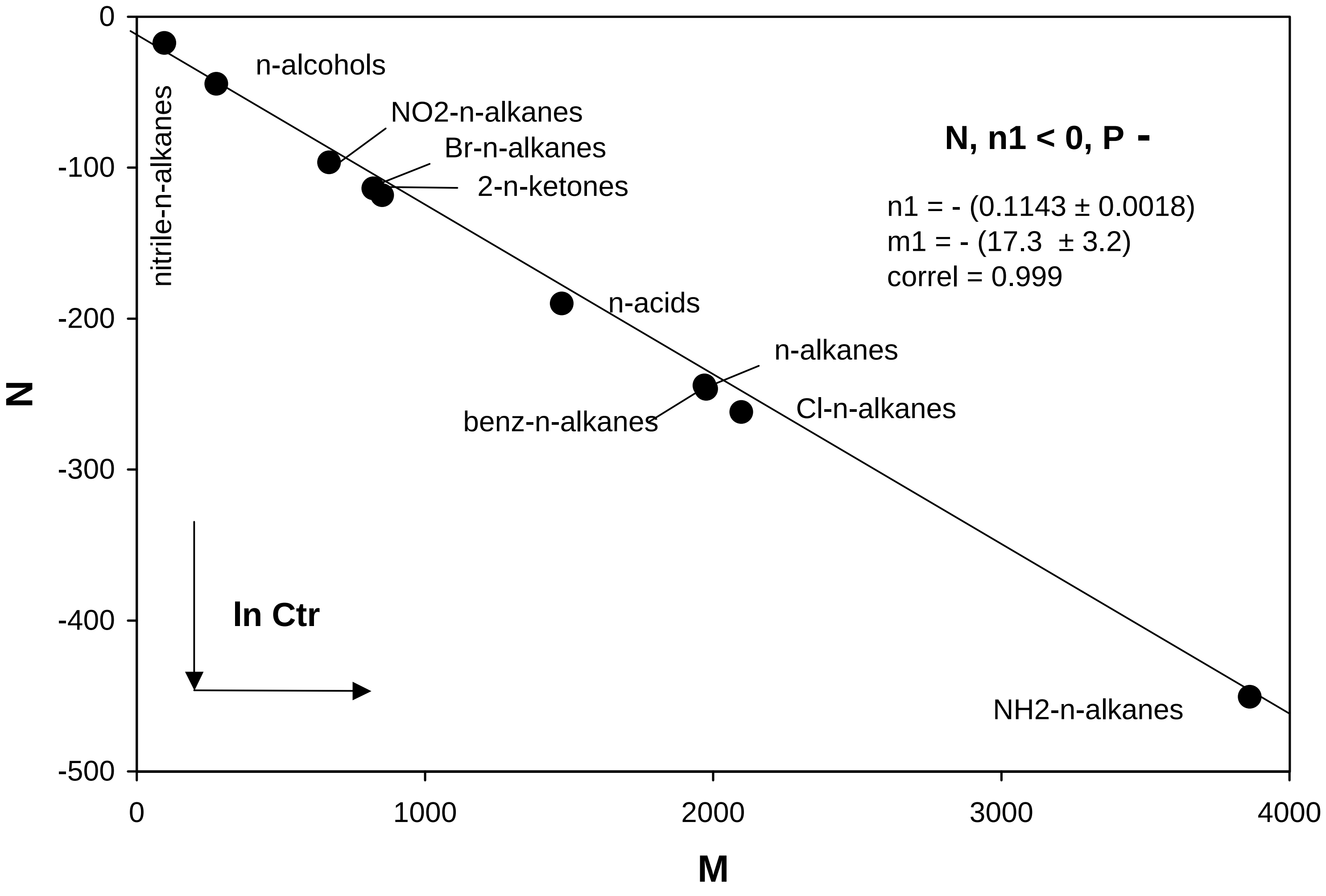

Figure 2. Amplitude phylogeny of isothermal (25 oC) partition behaviour driven by n-alkane molecular weight for ten n-alkane related series of compounds.

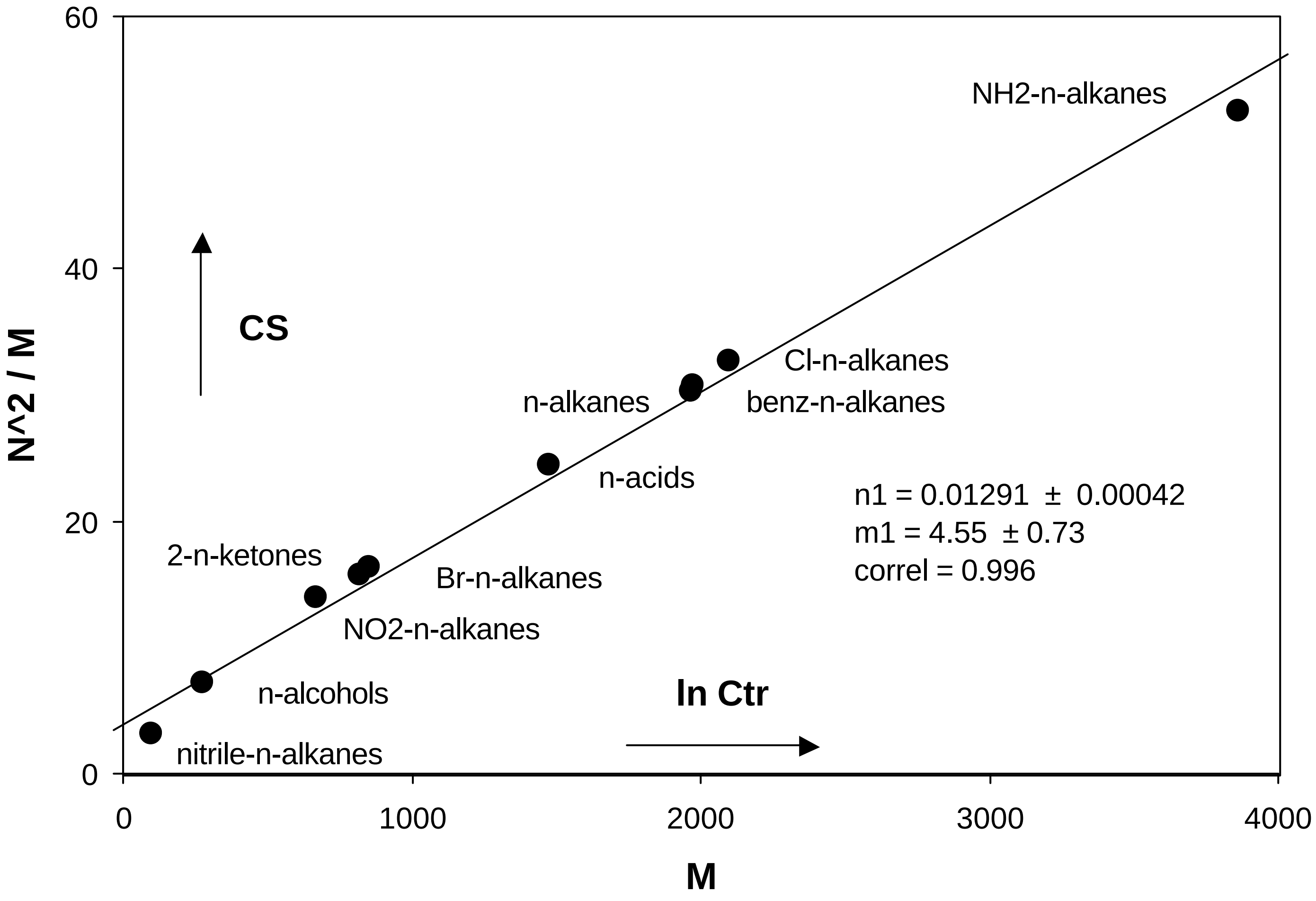

Figure 3. CS phylogeny for partition behaviour as driven by molecular weight for ten series of n-alkane related compounds.

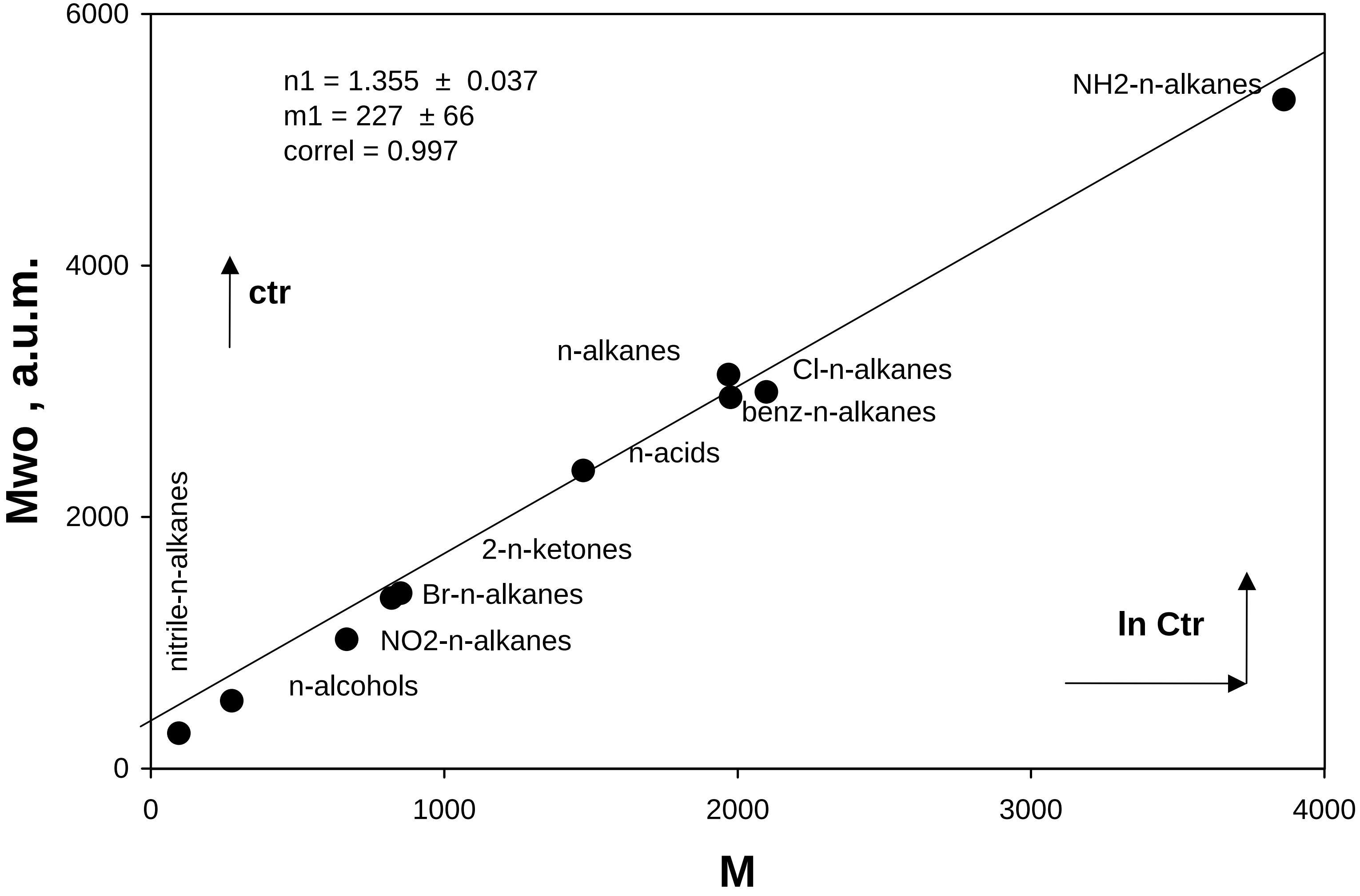

Figure 4. Phylogeny of threshold value Mwo for partition process as driven by molecular weight for the ten series of n-alkane related compounds.

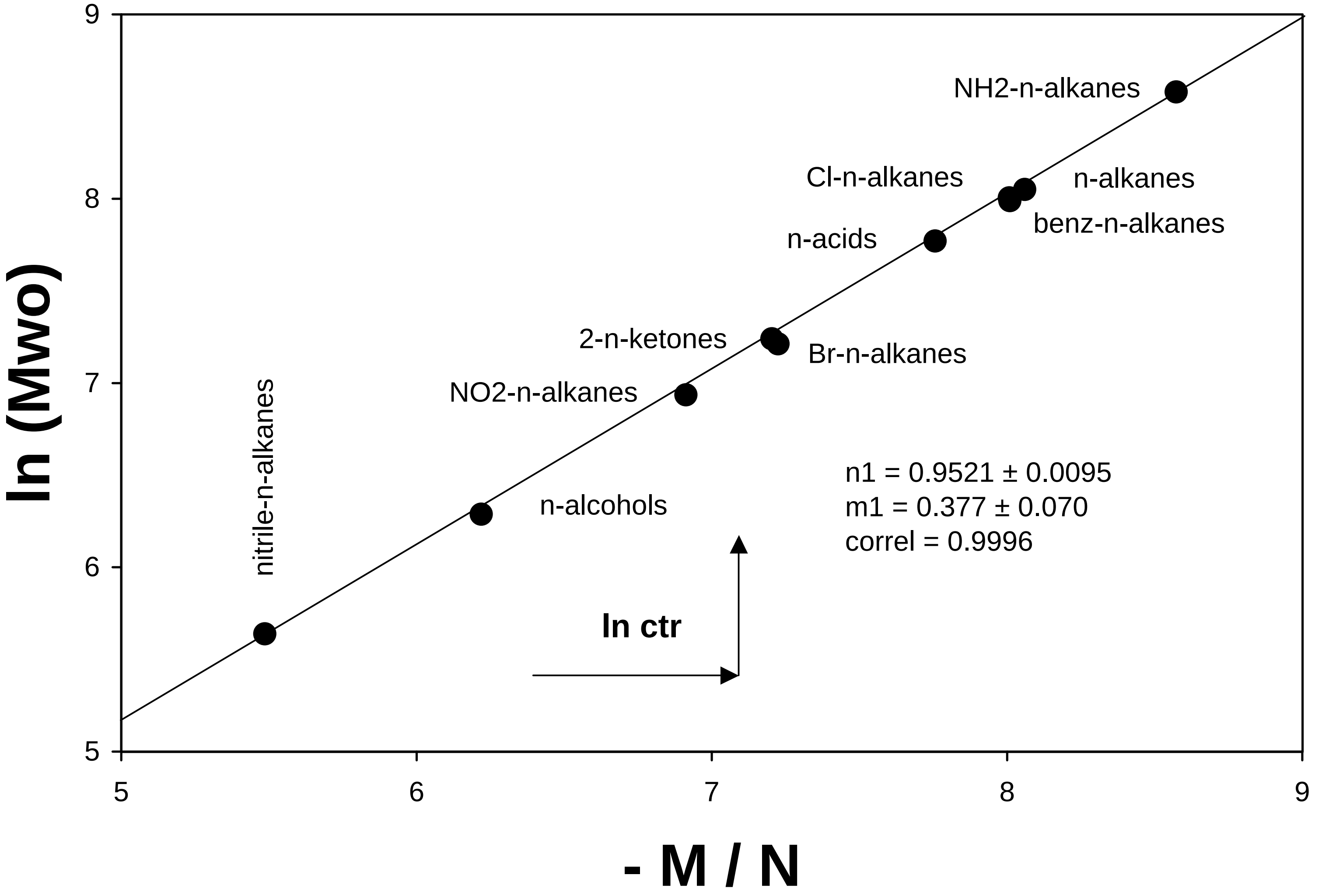

Figure 5. Dependence of threshold value Mwo on kinetic entity for partition process as driven by molecular weight for ten series of n-alkane related compounds.