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Limitations of additivity of Kováts retention indices

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Abstract

It is shown that the Kováts retention index is not a fully additive property. For the prediction of retention indices, a correlation method should be used instead of additivity. The value of the additivity parameter for a given group depends on the structure of the remainder of the molecule.

1. Introduction

It is assumed that retention index is an additive property, *i.e.*, the introduction of a certain substituent into molecules of similar structure changes their retention indices by the same value, called the additivity parameter or additivity increment. The additivity method, although not very precise, is often used in chromatographic practice on account on its simplicity. A retention index is calculated by addition of the increment for a substituent to the retention index of the unsubstituted compound.

However, in many instances, considerable differences between calculated and experimental values have been encountered. Budahegyi *et al.* [1], in a review on applications of the retention index system concluded, "Of the various methods available . . . the increment method is one of the most favourable. At present . . . a universal increment method fails for the retention index system, and its elaboration is a task for the near future". Hawkes [2,3] later showed that in some instances, "The rule that addition of a CH_2 group to a molecule increases the retention index by 100 ± 3 is subject to a greater uncertainty". Therefore, a new approach to the problem of retention index prediction was necessary.

2. Retention index prediction

It has been pointed out [4] that the prediction of any parameter for a compound belonging to one group based on the parameter of a corresponding compound belonging to another group is a typical problem of correlation analysis, where the parameters (P^1) of the compounds of one series are expressed as a function, usually linear, of the parameters (P^2) of compounds in another series:

$$P^1(x_i) = aP^2(x_i) + b \qquad (1)$$

Any additivity scheme is a very particular case of the linear Eq. 1, namely one in which the slope of the correlation line (a) is by definition equal to unity, and only then does the term b become an additivity parameter. Therefore, before making any attempts at calculating additivity parameters for a group of compounds, an attempt at linear regression should be made, as only when a appears to be equal to unity will the additivity method yield reliable results.

The first attempts at the application of the correlation method instead of additivity rules for the prediction of retention indices were made less than 10 years ago [4–9]. In our laboratory,

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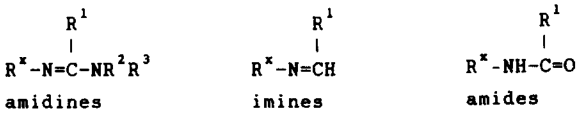
structure–retention relationships have been investigated for several series of compounds containing amidino (–N=CR–N⟨) or imino (–N=C⟨) groups (amidines and imines). The retention indices of these compounds were in the wide range between 800 and 2800 index units (i.u.).



$R^x\text{-}N{=}\overset{R^1}{C}\text{-}NR^2R^3$ amidines

$R^x\text{-}N{=}\overset{R^1}{C}H$ imines

$R^x\text{-}NH\text{-}\overset{R^1}{C}{=}O$ amides

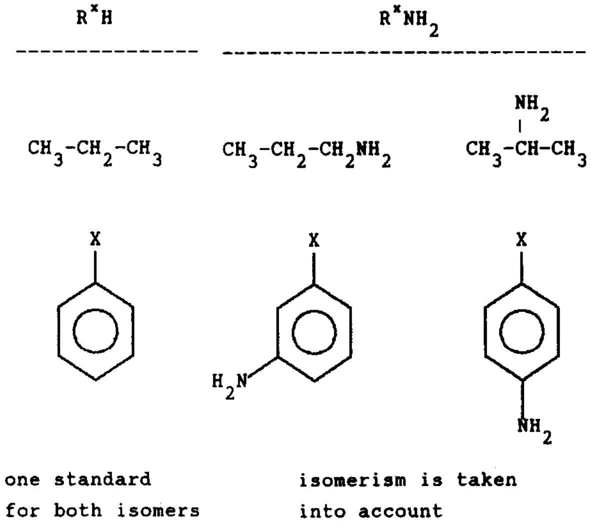
As the variable substituents R^x in the series, C_3–C_{10} *n*-alkyl groups, isopropyl, isobutyl, cyclohexyl and benzyl were chosen, and as aryl groups both *meta* and *para* methyl-, methoxy-, ethoxy-, fluoro-, chloro-, bromo- and nitrophenyl isomers were chosen.

Accordingly to additivity rules, the retention index of a compound containing a given functional group is calculated by addition of the increment of this group to the retention index of the unsubstituted compound. Amidino ($-N{=}CR^1{-}NR^2R^3$), imino ($-N{=}CHR^1$) or acylamino ($-NH{-}CO{-}R^1$) groups are the substituents whose increments should be added to the retention indices of the corresponding hydrocarbons R^xH taken as the reference compounds (standards). In the correlation method, retentions of compounds with a given substituent are linearly related to the retention indices of unsubstituted compounds. The relationship has the form

$$I(\mathrm{Cpd}_i) = aI(\mathrm{Std}_i) + b \qquad (2)$$

where I = Kováts retention index, Cpd = compound and Std = reference compound (standard).

In spite of the common practice, the use of hydrocarbons or substituted hydrocarbons R^xH as the basis for the prediction of retention data for compounds containing their moieties in the molecule does not seem to be the best choice, because isomerism is not taken into account. Hence we have assumed that better, more accurate results might be obtained if other simple compounds, containing some functional group at the corresponding carbon atom, were taken as the references. For the studied series, primary amines (R^xNH_2; see formulae) seemed to be the most appropriate, because they are available as the substrates for the synthesis of all the types of compounds studied. Correlation would show the change in the retention index when the NH_2 group is replaced by an amidino, imino or amido group.



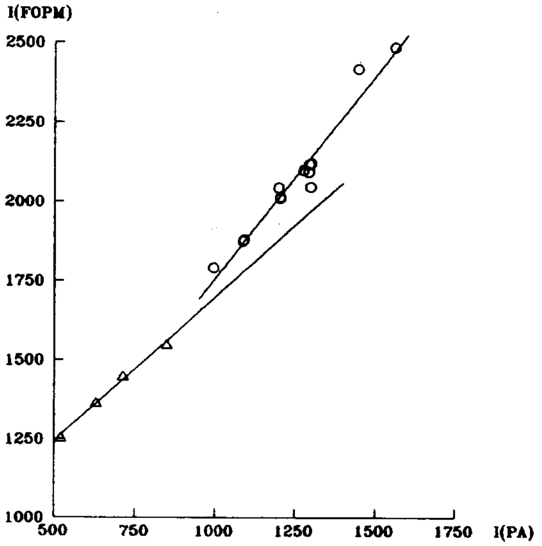


Fig. 1. Correlation of retention indices of N^1,N^1-(3-oxapentamethylene)formamidines (FOPM) with those of corresponding primary amines (PA).

The proper choice of model compounds for the prediction of retention indices appears to be very important. For each series of compounds the correlation with the retention indices of primary amines is of higher quality than that with unsubstituted hydrocarbons, and therefore is of greater predictive value. However, correlations with the retentions of hydrocarbons are still satisfactory.

Attempts at correlation for all the series studied revealed that in each instance there are at least two regression lines, one for compounds containing purely aliphatic substituents and the other for those with a substituted phenyl ring, as shown by the two examples in Figs. 1 and 2. Therefore, for compounds with aliphatic and aromatic substituents separate correlations were calculated. The amidines can be divided into series depending on the substituents at the amidino carbon atom and further at the amino nitrogen atom.

The regression coefficients *a* with confidence intervals calculated at a significance level of 0.05 for the series with an alkyl group at the amidino carbon atom are given in Table 1. For most of the series the slopes of the correlation lines (*a*) are not significantly different from unity, but for two series, alkyl derivatives of dimethylacetamidines (ADM) and aryl derivatives of amidines containing a morpholine moiety (FOPM), they are undoubtedly different from unity. The best example is provided by alkyl derivatives of acetamidines, where the correlation is of excellent quality, as shown by the correlation coefficient *r*.

Table 1

Parameters of correlations[a] of retention indices of amidines[b] and tetramethylguanidines[b] with those of primary amines

Series[c]	*a*	*b*	*r*
Alkyl derivatives			
FDM	0.91 ± 0.22	400	0.997
ADM	0.86 ± 0.04	553	0.9999
FTM	0.91 ± 0.30	737	0.994
FPM	0.94 ± 0.23	788	0.997
FHM	0.90 ± 0.23	915	0.997
FOPM	0.92 ± 0.24	782	0.997
TMG	1.07 ± 0.53	462	0.987
Aryl derivatives			
FDM	1.05 ± 0.11	337	0.986
ADM	0.99 ± 0.11	470	0.986
FTM	0.99 ± 0.09	760	0.989
FPM	0.99 ± 0.09	826	0.990
FHM	1.02 ± 0.10	885	0.989
FOPM	1.28 ± 0.19	477	0.976
TMG	1.09 ± 0.13	421	0.982

[a] $I(\text{amidine}) = aI(\text{amine}) + b$.

[b] On the basis of refs. 4 and 6.

[c] For abbreviations, see formulae in text.

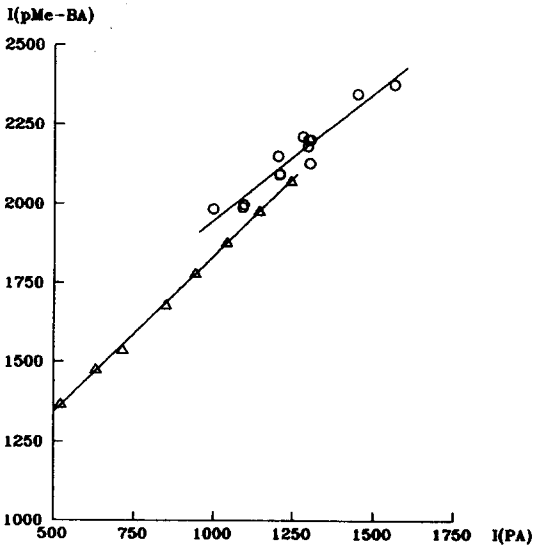
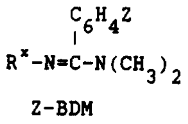


Fig. 2. Correlation of retention indices of *p*-methylbenzylideneanilines (pMe-BA) with those of corresponding primary amines (PA).

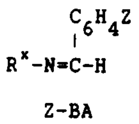
It should be mentioned that even when *a* can be taken as equal to unity, the terms *b* are not identical for alkyl and aryl series. The difference between "additivity parameters" for alkyl and aryl derivatives are as high as 300 i.u. in some instances. In all correlations isoalkyl and cyclohexyl derivatives do not fit the corresponding correlations, and for such compounds other "additivity parameters" are obtained.

Non-additivity is much more evident for benzamidines (Z-BDM) and benzylideneamines (imines, Z-BA) (see formulae). Parameters of the linear regressions for these compounds are summarized in Table 2. For all series of alkyl



$$R^x\text{-N=}\overset{C_6H_4Z}{\overset{|}{C}}\text{-N(CH}_3)_2$$

Z-BDM



$$R^x\text{-N=}\overset{C_6H_4Z}{\overset{|}{C}}\text{-H}$$

Z-BA

	Amidines	Imines
Z = H	H-BDM	H-BA
Z = p-Me	pMe-BDM	pMe-BA
Z = p-OMe	pOMe-BDM	pOMe-BA
Z = p-Cl	pCl-BDM	pCl-BA

derivatives of dimethylbenzamidines (BDM) and for *p*-methylbenzylideneanilines (pMe-BA), the regression coefficient *a* is distinctly different from unity. For other series, where *a* does not differ significantly from unity, other values of *b* are obtained for alkyl and aryl derivatives.

Non-additivity is observed also for monosubstituted amides of carboxylic acids. Analysis of the parameters of these correlations presented in Tables 3 and 4 lead to similar conclusions.

Amides of butyric acids may serve as a good example of the influence of the structure of an alkyl chain, such as exchange of an *n*-propyl for an isopropyl group, on the values of the retention indices in the series. Correlation of the retention indices of the amides of isobutyric acid with those of the straight-chain isomer (Table 5) clearly indicates that such a change does not involve a change in retention index by a constant value, thus providing further support for the conclusion that retention index is not fully additive property. It seems very likely that the main

Table 2

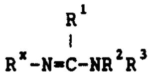
Parameters of correlations[a] of retention indices of dimethylbenzamidines[b] and corresponding imines[b] with those of primary amines

Series[c]	*a*	*b*	*r*
Alkyl derivatives			
H-BDM	0.84 ± 0.11	1021	0.991
pMe-BDM	0.83 ± 0.14	1098	0.986
pOMe-BDM	0.82 ± 0.11	1257	0.991
pCl-BDM	0.82 ± 0.11	1216	0.991
H-BA	0.97 ± 0.07	751	0.997
pMe-BA	0.99 ± 0.03	851	0.999
pOMe-BA	0.95 ± 0.03	1042	0.9995
pCl-BA	0.98 ± 0.09	1040	0.997
Aryl derivatives			
H-BDM	0.93 ± 0.23	907	0.950
pMe-BDM	0.91 ± 0.21	999	0.956
pOMe-BDM	0.89 ± 0.21	1162	0.954
pCl-BDM	0.91 ± 0.24	1098	0.946
H-BA	0.94 ± 0.24	840	0.948
pMe-BA	0.78 ± 0.24	1171	0.926
pOMe-BA	0.96 ± 0.25	1023	0.946
pCl-BA	0.89 ± 0.15	1224	0.971

[a] *I*(amidine) = *aI*(amine) + *b*.

[b] On the basis of ref. 5.

[c] BDM = Benzamidines; BA = benzylideneamines.



$$R^x\text{-N=}\overset{R^1}{\overset{|}{C}}\text{-NR}^2R^3$$

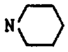
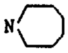
R^1	NR^2R^3	Series	Abbr.
H	NMe_2	N^1,N^1-dimethylformamidines	FDM
CH_3	NMe_2	N^1,N^1-dimethylacetamidines	ADM
H		N^1,N^1-tetramethyleneformamidines	FTM
H		N^1,N^1-pentamethyleneformamidines	FPM
H		N^1,N^1-hexamethyleneformamidines	FHM
H		N^1,N^1-(3-oxa-pentamethylene)-formamidines	FOPM
NMe_2	NMe_2	N^1,N^1,N^2,N^2-tetramethylguanidines	TMG

Table 3
Parameters of correlations[a] of retention indices of formamides[b], HCONHR^x (FA), and acetamides[b], $\mathrm{CH_3CONHR}^x$ (AA), with those of primary amines

Series	a	b	r
Alkyl derivatives			
FA	1.05 ± 0.06	359	0.999
AA	1.04 ± 0.07	665	0.998
Aryl derivatives			
FA	0.89 ± 0.10	588	0.988
AA	1.00 ± 0.07	425	0.995

[a] I(amide) = aI(amide) + b.
[b] According to ref. 10.

Table 4
Parameters of correlations[a] of retention indices of monosubstituted amides of *n*-butyric acid[b] (A-nBtr) and isobutyric acid[b] (A-iBtr) with those of primary amines (PA)

Series	a	b	r
Alkyl			
A-nBtr	1.05 ± 0.11	509	0.992
A-iBtr	0.94 ± 0.06	569	0.997
Aryl			
A-nBtr	0.84 ± 0.15	746	0.969
A-iBtr	0.97 ± 0.12	506	0.987

[a] I(amide) = aI(amine) + b.
[b] According to ref. 11.

reason why the retention index system fails for some types of compounds is the assumption of additivity.

Table 5
Parameters of correlations[a] of retention indices of monosubstituted amides of isobutyric acid (A-iBtr) with those of amides of *n*-butyric acid (A-nBtr)

R	Series	a	b	r
Alkyl	A-iBtr	0.82 ± 0.13	238	0.99
Aryl	A-iBtr	0.91 ± 0.13	98	0.99

[a] I(A-iBtr) = aI(A-nBtr) + b.

3. Conclusions

The Kováts retention index is not a fully additive property. For prediction of the retention indices the correlation method (Eq. 2) should be used instead. The term b in this equation is a real additivity parameter only when a is equal to unity.

Series of compounds containing *n*-alkyl and aryl groups should be treated separately, because even when a is equal to unity, the b term for them may appear different, *i.e.*, another "additivity parameter" is obtained for each group.

Compounds with non-linear alkyl groups such as isopropyl, *tert.*-butyl or cyclohexyl do not belong to the same family as *n*-alkyl groups. It is not possible at present to determine whether they belong to one or to more groups, because insufficient experimental data are available.

4. Acknowledgement

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5. References

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