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AMIDINES

XXVI*. RETENTION INDICES OF N^1,N^1-DIMETHYLPROPIONAMIDINES, ISOBUTYRAMIDINES, PIVALAMIDINES AND PHENYLACETAMIDINES ON A NON-POLAR COLUMN

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SUMMARY

The retention indices of 92 compounds, comprising four series of N^2-substituted N^1,N^1-dimethylamidines, $R_xN=C(R_z)N(CH_3)_2$, each containing the same set of 23 variable substituents at the imino nitrogen atom, have been measured on a non-polar GE SE-30 silicone gum rubber column. The values obtained for each series were correlated with those of corresponding model compounds, such as primary amines, R_xNH_2, substituted hydrocarbons, R_xH, ethyl esters of corresponding carboxylic acids, $R_zCOOC_2H_5$, and dimethylamides, $R_zCON(CH_3)_2$. Support is provided for an earlier conclusion that for the prediction of retention indices the correlation method should be used instead of additivity rules.

It has been found that the regression parameter characterizing the influence of substitution at the imino nitrogen atom on the retention index depends on the type of substituent at the amidino carbon atom. On the basis of the retention indices of 115 compounds the parameters of an equation for the prediction of the retention indices of N^1,N^1-dimethylamidines containing an alkyl or aralkyl substituent at the amidino carbon atom were found.

INTRODUCTION

In the course of our studies of the gas chromatographic analysis of amidines[1–5], the relationship between their structures and retention indices on various stationary phases is being investigated.

The retention indices of compounds containing the amidino ($-N=\overset{|}{C}-N<$) group depend on substitution at three sites, the imino and the amino nitrogen atoms and the functional carbon atom. Therefore, the prediction of their retention indices is possible only if the influence of substituents at these sites is known.

We have found that the retention indices of amidines in the series with a vari-

* For Part XXV, see ref. 5.

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able substituent R_x at the imino nitrogen atom correlate very well with the retention indices of corresponding simple model compounds taken as standards (Std), such as substituted hydrocarbons, R_xH, or, better, primary amines, R_xNH_2:

$$I(\text{amidine}) = aI(\text{Std}) + b \quad (1)$$

where I are the Kováts retention indices[6,7] and a and b are regression coefficients. We have shown that for the prediction of the retention indices of amidines this type of correlation should be used instead of additivity rules. We have found that the retention indices of amidines containing variable substituents, R_y, at the amino nitrogen atom also obey eqn. 1, where the corresponding secondary amines $(R_y)_2NH$ are used as the model (standard) series. Thus the conclusion was drawn that for the prediction of the retention indices of N^2-substituted N^1,N^1-dialkylamidines a diparameter linear regression (eqn. 2) can be used:

$$I(\text{amidine}) = a_1I(\text{Std}_1) + a_2I(\text{Std}_2) + b \quad (2)$$

and generally for compounds (Cpd) containing more than two substituents a linear regression (eqn. 3):

$$I(\text{Cpd}) = \sum_i a_iI(\text{Std}_i) + b \quad (3)$$

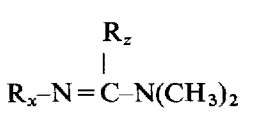
The regression coefficients a for several series of amidines containing variable substituents at the imino nitrogen atom appeared to be very similar and the differences between them were much lower than their confidence intervals, but for a few series it was considerably different. Hence it was assumed that a change in substituent at one site of the molecule may affect to some extent the parameter a for substitution at another site of the molecule[3]. Some support for this assumption was provided by the substantial difference between the regression coefficients for benzamidines, $R_xN=C(C_6H_4Z)N(R_y)_2$, and benzylideneamines, $R_xN=CHC_6H_4Z$.

The results obtained for benzamidines indicated[3] that their retention indices can be correlated with those of ethyl esters of corresponding benzoic acids, $ZC_6H_4COOC_2H_5$.

The question therefore arose of whether for the prediction of retention indices of trisubstituted amidines a linear three-parameter regression (eqn. 4) can be applied, or whether a more complex equation should be used, taking into account changes in the coefficients a_i caused by the substitution at various sites of the amidino group, and how far the structure of the substituents at these sites may be changed without discernible changes in the regression parameters, so that the error in the prediction of retention indices is within acceptable limits.

$$I(\text{amidine}) = a_1I(R_xNH_2) + a_2I[(R_y)_2NH] + a_3I(R_zCOOC_2H_5) + b \quad (4)$$

In this work the retention indices of four series of N^1,N^1-dimethylamidines, each containing the same set of 23 variable substituents R_x at the imino nitrogen atom, were determined on a non-polar GE SE-30 column. The compounds investigated have the following general formula:



R_z	*Series*
CH_2CH_3	N^1,N^1-dimethylpropionamidines (PrpDM)
$CH(CH_3)_2$	N^1,N^1-dimethylisobutyramidines (iBtrDM)
$C(CH_3)_3$	N^1,N^1-dimethylpivalamidines (PivDM)
$CH_2C_6H_5$	N^1,N^1-dimethylphenylacetamidines (PhADM)

Using the same column, the retention indices of N,N-dimethylamides and ethyl esters of corresponding carboxylic acids were determined for comparative purposes.

EXPERIMENTAL

Materials

All compounds studied were synthesized in our laboratory. Propionamidines, isobutyramidines and pivalamidines were synthesized as described elsewhere[8]. Phenylacetamidines were obtained according to Scoggins[9] by the reaction of primary amines, R_xNH_2, with dialkylphenylacetamide dimethyl acetal, $(CH_3)_2NC(CH_2C_6H_5)(OCH_3)_2$, also synthesized in our laboratory by a known procedure[10].

The amines were commercial samples. C_{12}–C_{20} alkanes were purchased from Applied Science Labs. (State College, PA, U.S.A.).

Gas chromatography

A Chromatron Model GCHF 18.3.4 gas chromatograph (VEB Chromatron, Berlin, G.D.R.) equipped with a flame ionization detector and a 3 m × 3 mm I.D. column filled with 15% GE SE-30 silicone gum rubber on Chromosorb W AW (60–80 mesh) was used. The column temperature was maintained at 240°C for PrpDM, iBtrDM and PivDM, at 280°C for PhADM and at 180°C for amides and esters. The carrier gas (nitrogen) flow-rate was 25 ml/min. Samples of 0.1 μl of 0.1 *M* solutions in methanol (or pentane for hydrocarbons) were injected by means of a 10-μl Hamilton syringe.

Retention indices and dead times were determined by regression analysis by the method of Grobler and Bálizs[11], as improved by Haken *et al.*[12], using the series of nine C_{12}–C_{20} *n*-alkanes, under the same conditions as for the studied samples. The retention times were recorded by means of a KB 5503 electronic integrator (COBRABID, Warsaw, Poland) with an accuracy of 0.5 s.

RESULTS AND DISCUSSION

The retention indices of the investigated amidines, with confidence intervals at a significance level of 0.05, calculated from at least five measurements, are given in Table I and those of the ethyl esters and N,N-dimethylamides of carboxylic acids in Table II.

TABLE I

RETENTION INDICES OF DIMETHYLPROPIONAMIDINES (PrpDM), DIMETHYLISOBUTYRAMIDINES (iBtrDM), DIMETHYLPIVALAMIDINES (PivDM) AND DIMETHYLPHENYLACETAMIDINES (PhADM) ON A NON-POLAR GE SE-30 COLUMN

R_x	*Retention index*					
	R_xH (180°C)	*PA (180°C)*	*PrpDM (240°C)*	*iBtrDM (240°C)*	*PivDM (240°C)*	*PhADM (280°C)*
n-C_3H_7	300*	521 ± 2**	1065 ± 6	1065 ± 0	1093 ± 0	1605 ± 0
n-C_4H_9	400*	629 ± 2**	1161 ± 5	1176 ± 7	1204 ± 0	1697 ± 0
n-C_5H_{11}	500*	712 ± 3**	1220 ± 5	1230 ± 5	1229 ± 7	1739 ± 0
n-C_6H_{13}	600*	848 ± 7**	1366 ± 4	1374 ± 2	1393 ± 4	1881 ± 2
n-C_7H_{15}	700*	939 ± 3***	1447 ± 3	1485 ± 1	1483 ± 3	1975 ± 3
n-C_8H_{17}	800*	1038 ± 2***	1550 ± 0	1581 ± 2	1586 ± 3	2072 ± 0
n-C_9H_{19}	900*	1141 ± 2***	1652 ± 0	1685 ± 3	1687 ± 4	2172 ± 1
n-$C_{10}H_{21}$	1000*	1241 ± 1***	1752 ± 1	1789 ± 2	1786 ± 3	2271 ± 1
Cyclo-C_6H_{11}	658 ± 0***	857 ± 1**	1389 ± 5	1473 ± 3	1410 ± 2	1926 ± 2
$C_6H_5CH_2$	788 ± 1**	1035 ± 6**	1617 ± 5	1561 ± 2	1607 ± 2	2148 ± 1
C_6H_5	681 ± 2**	995 ± 0**	1510 ± 1	1541 ± 4	1539 ± 1	2056 ± 1
3-$CH_3C_6H_4$	788 ± 1**	1088 ± 5**	1590 ± 1	1615 ± 2	1590 ± 0	2118 ± 2
4-$CH_3C_6H_4$	788 ± 1**	1092 ± 5**	1595 ± 0	1626 ± 1	1614 ± 5	2134 ± 1
3-$CH_3OC_6H_4$	927 ± 1**	1229 ± 6**	1741 ± 1	1761 ± 1	1746 ± 1	2272 ± 1
4-$CH_3OC_6H_4$	927 ± 1**	1199 ± 5**	1742 ± 1	1769 ± 1	1765 ± 1	2281 ± 1
3-$C_2H_5OC_6H_4$	995 ± 2**	1293 ± 1**	1793 ± 0	1811 ± 0	1792 ± 1	2314 ± 2
4-$C_2H_5OC_6H_4$	995 ± 2**	1277 ± 1**	1804 ± 2	1819 ± 3	1810 ± 2	2333 ± 1
3-ClC_6H_4	875 ± 2**	1204 ± 1**	1713 ± 1	1740 ± 0	1725 ± 1	2250 ± 1
4-ClC_6H_4	875 ± 2**	1204 ± 3**	1729 ± 1	1760 ± 1	1745 ± 3	2272 ± 1
3-BrC_6H_4	964 ± 2**	1295 ± 5**	1807 ± 1	1834 ± 1	1812 ± 1	2351 ± 1
4-BrC_6H_4	964 ± 2**	1300 ± 3**	1826 ± 1	1856 ± 1	1843 ± 3	2374 ± 1
3-$NO_2C_6H_4$	1103 ± 6**	1446 ± 3**	1969 ± 1	2000 ± 1	1984 ± 1	2511 ± 1
4-$NO_2C_6H_4$	1103 ± 6**	1560 ± 1**	2076 ± 1	2107 ± 1	2120 ± 1	2630 ± 3

* By definition.
** According to ref. 1.
*** According to ref. 2.

As the retention index depends to a small extent on temperature, for higher accuracy of the correlations we determined the retention indices of propionamidines, isobutyramidines and pivalamidines at the same temperature as for previously studied formamidines[2,4], *i.e.*, at 240°C, and of phenylacetamidines at 280°C as for benzamidines[3].

TABLE II

RETENTION INDICES OF ETHYL ESTERS AND N,N-DIMETHYLAMIDES OF CARBOXYLIC ACIDS, R_zCOOH, ON A NON-POLAR GE SE-30 COLUMN AT 180°C

Compounds	R_z				
	CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$	$C_6H_5CH_2$
Esters	572 ± 1	678 ± 0	737 ± 0	772 ± 0	1239 ± 2
Amides	766 ± 6	854 ± 4	978 ± 0	1023 ± 1	1535 ± 1

We correlated the retention indices of the amidines with those of corresponding primary amines, R_xNH_2, and substituted hydrocarbons, R_xH, used previously for correlations with the retention indices of other amidines[2–4].

Calculations were made by means of the least-squares method. The regression coefficients a and b in eqn. 1, with confidence intervals calculated at a significance level of 0.05, and the correlation coefficients r and Exner's Ψ functions[13] are given in Table III.

TABLE III

REGRESSION PARAMETERS OF RETENTION INDICES OF AMIDINES *VS.* RETENTION INDICES OF STANDARDS (EQN. 1)

Standard	*Series*	*a*	*b*	*r*	Ψ	*n*
R_xH	PrpDM	1.162 ± 0.096	673	0.9839	0.187	23
	iBtrDM	1.183 ± 0.096	679	0.9844	0.184	23
	PivDM	1.147 ± 0.103	704	0.9812	0.202	23
	PhADM	1.172 ± 0.116	1197	0.9772	0.222	23
R_xNH_2	PrpDM	0.983 ± 0.032	540	0.9975	0.075	23
	iBtrDM	1.000 ± 0.036	544	0.9969	0.083	23
	PivDM	0.972 ± 0.036	570	0.9966	0.086	23
	PhADM	0.997 ± 0.041	1057	0.9959	0.054	23

The values of the two estimators r and Ψ indicate that, as in our previous studies[2–4], the correlations with the retention indices of primary amines, R_xNH_2, are of higher quality than those with the retention indices of hydrocarbons, R_xH. The regression coefficients a for correlations with amines are close to unity, but for correlation with hydrocarbons they are considerably higher. This provides further support for the conclusion that for the prediction of retention indices the correlation method should be used instead of additivity rules[2].

The results obtained were compared with those for other series of N^1,N^1-dimethylamidines, $R_xN=C(R_z)N(CH_3)_2$, studied in our laboratory, namely formamidines[2] (FDM; R_z = H), acetamidines[2] (ADM; R_z = CH_3), benzamidines[3] (H-BDM; R_z = C_6H_5), *p*-methylbenzamidines[3] (*p*-Me-BDM; R_z = $C_6H_4CH_3$), *p*-methoxybenzamidines[3] (*p*-OMe-BDM; R_z = $C_6H_4OCH_3$); and *p*-chlorobenzamidines[3] (*p*-Cl-BDM; R_z = *p*-C_6H_4Cl).

We have found that the regression coefficients a for all studied series of amidines containing alkyl or aralkyl substituents at the amidino carbon atom (ADM, PrpDM, iBtrDM, PivDM and PhADM) are indistinguishable within the confidence intervals. For amidines containing a phenyl ring bonded directly to the amidine carbon atom (H-BDM, *p*-Me-BDM, *p*-MeO-BDM and *p*-Cl-BDM) the a values are about 10% lower, whereas for amidines unsubstituted at this atom (FDM) the a value is about 10% higher. This provides clear support for the assumption mentioned in the Introduction, that the value of a for substituents at the imino nitrogen atom depends on the substitution at the functional carbon atom. The results obtained indicate, however, that it depends mainly on the type of substituent (*i.e.*, alkyl, aryl or hydrogen atom) and only to a negligible extent on its detailed structure. This leads

to the conclusion that for the prediction of the retention indices of N^1,N^1-dimethylamidines containing an alkyl or aralkyl group at the amidino carbon atom a diparameter linear regression in the form of eqn. 2 may be used.

As one standard series, for substituents at the imino nitrogen atom, we chose primary amines, R_xNH_2, because in this instance, and also with other series of amidines[2–4], they yield correlations of higher quality than those with hydrocarbons, R_xH. As the second standard series, for substitution at the amidino carbon atom, we used derivatives of corresponding carboxylic acids, such as ethyl esters, $R_zCOOC_2H_5$, and N,N-dimethylamides, $R_zCON(CH_3)_2$. For the diparameter regression we used five series: ADM, PrpDM, iBtrDM, PivDM and PhADM (115 compounds). The regression parameters are given in Table IV.

TABLE IV

MULTIPLE REGRESSION PARAMETERS OF RETENTION INDICES OF AMIDINES *VS.* RETENTION INDICES OF STANDARDS (EQN. 2)

Std_1	Std_2	a_1	a_2	b	r	Ψ	n
R_xNH_2	$RCOOC_2H_5$	0.991 ± 0.031	0.934 ± 0.033	−115	0.9923	0.126	115
R_xNH_2	$RCON(CH_3)_2$	0.991 ± 0.039	0.793 ± 0.036	−186	0.9874	0.160	115

The correlations with both types of derivatives of carboxylic acids, esters and dimethylamides are of the same quality as indicated by both estimators, correlation coefficients r and Exner's Ψ function. The regression coefficients a_2 are different in both instances, and far from the unity (0.934 for esters and 0.793 for amides), indicating that for substituents at the amidino carbon atom also additivity rules should not be applied.

A good quality of the diparameter correlation eqn. 2 and the good correlation observed formerly for amidines containing variable substituents at both nitrogen atoms[4] indicate that it will be possible to find a general equation in the form of eqn. 4 for the prediction of the retention indices of trisubstituted amidines.

The questions remain of whether the parameter for substitution at the amino nitrogen atom (a_2 in eqn. 4) depends on the type of substituent at the amidino carbon atom, and whether and how far the parameters a_1 and a_2 in eqn. 4 depend on substitution at the second nitrogen atom. These questions require further study on appropriate series of compounds.

CONCLUSION

The results indicate that the retention indices of trisubstituted amidines can be predicted with satisfactory accuracy using a two-parameter linear regression equation (eqn. 2). The regression parameters a_1 depend on the type of substituent at the amidino carbon atom. The retention indices of N^1,N^1-dimethylamidines containing an alkyl carbon atom bonded to the amidino carbon atom are calculated as follows:

$$I(\text{amidine}) = 0.99I(R_xNH_2) + 0.93I(R_zCOOC_2H_5) - 115$$

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