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STRUCTURE-RETENTION STUDIES OF MODEL KETONES BY CAPILLARY GAS CHROMATOGRAPHY

J. RAYMER, D. WIESLER and M. NOVOTNY*

Department of Chemistry, Indiana University, Bloomington, IN 47405 (U.S.A.)

(First received August 15th, 1984; revised manuscript received February 6th, 1985)

SUMMARY

The retention indices (I) for a number of ketones were determined using linear temperature-programmed capillary gas chromatography. 2-Ketones were used as standards for the index calculations. The 95% confidence interval for triplicate determinations was found to be ± 0.13 index unit. These retention indices and the zero-, first-, and second-order molecular connectivity factors for each compound were treated with multiple regression to yield equations to predict I . An interesting trend in the retention of symmetric ketones was noticed and rationalized on the basis of shielding of the carbonyl oxygen.

INTRODUCTION

The use of a numerical descriptor of gas chromatographic retention can be of great help in the identification of chemical compounds in a complex mixture. One of the most popular descriptors is the retention index introduced by Kováts in 1958¹ in which the retention is determined relative to a series of homologous n -hydrocarbons. This index, as proposed, can sometimes be inconvenient as isothermal operation is required, limiting the molecular weight range of the solutes in any given analysis. In 1963, Van den Dool and Kratz² extended the Kováts system, to allow the use of linear temperature programming which resulted in eqn. 1:

$$I = 100 \frac{t_{R(\text{substance})} - t_{R(C_z)}}{t_{R(C_{z+1})} - t_{R(C_z)}} + 100z \quad (1)$$

where $t_{R(\text{substance})}$ is the retention time of the substance for which the retention index is to be determined, $t_{R(C_z)}$ and $t_{R(C_{z+1})}$ are the retention times for the n -alkane standards which bracket the substances of interest, and z is the number of carbon atoms in the n -alkane standard that elutes just prior to the compound of interest. Such index values determined for compounds dissimilar in nature from alkanes are often subject to much variability for a number of reasons, including the changing chemical nature of the stationary phase on the column due to aging, the degree of support deactivation, batch-to-batch variations in the chemical composition of a particular stationary phase, and even the temperature of the column³.

The reproducibility of such retention data has been improved by choosing the standard reference compounds to be very similar in chemical nature to those compounds under investigation³⁻⁶. Since the object of our attention was a collection of ketones, mainly methyl ketones, synthesized in our laboratory in connection with the elucidation of the structures of some ketones of biological origin⁷, we chose to use the series of normal aliphatic 2-ketones as reference compounds for retention index determination. The use of 2-alkanones as the retention standards was already reported by Ackman⁵ to minimize difficulties arising from the polarity differences between sample and reference compounds.

In addition to simply calculating a retention index for a given compound, we wanted to make use of some molecular descriptors in order to predict retention. In this manner, time may best be utilized in structural elucidation work by avoiding the synthesis of compounds that do not have the desired predicted retention. Many investigators have correlated various parameters with retention indices, including Van der Waals' volume⁸, magnitudes of energy and charge of molecular orbitals⁹, solution-of-groups concept¹⁰ and molecular connectivity¹¹⁻¹⁴. Some workers have combined topological (connectivity) information with physicochemical and/or quantum chemical parameters to predict retention in both gas¹⁵ and liquid chromatography¹⁶. For the sake of simplicity, we chose the molecular connectivity approach, because success had been achieved for different molecules by others¹¹⁻¹⁴.

Molecular connectivity

Briefly stated, the concept of molecular connectivity permits the representation of a molecular structure as a graph. Each atom becomes a "vertex" and each bond becomes an "edge". Molecular connectivity factors (see below) can be calculated from the zeroth order, where only the atoms (vertices) are taken into account, to the n th order where n represents the maximum number of bonds (edges) that can form a connecting path. If all possible orders of connectivity factors are calculated for a given molecule, each factor contributes unique information towards the graphical representation of the molecule as a whole. Higher order terms contain cluster, path/cluster, and chain types of subgraphs which have been described elsewhere¹⁷ and were not used in the present study.

Molecular connectivity factors (χ) were calculated from the zero order through second order for each ketone according to the method of Kier and Hall¹⁷. We chose to use the valence deltas (δ^v) resulting in a connectivity factor indicated by χ^v . The χ^v values can be considered to be the difference between the number of valence electrons Z^v and the number of hydrogen atoms h_i (which are suppressed in the graph):

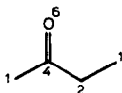
$$\delta_i^v = Z^v - h_i$$

Therefore, a methyl group δ^v is $4 - 3 = 1$, a methylene $\delta^v = 4 - 2 = 2$, etc. For oxygen in a carbonyl group, the $\delta^v = 6 - 0 = 6$. Consequently, each atom (except the hydrogens) is assigned a valencie. Once this is done, the calculation of the χ^v values can begin. For purposes of illustration, the connectivity factors for 2-butanone will be calculated. Each unsaturation is treated as two separate bonds.

The zero order term (${}^0\chi^v$) is defined as:

$${}^0\chi^v = \sum_{i=1}^n (\delta_i^v)^{-1/2}$$

Thus, for 2-butanone



$${}^0\chi^v = 2(1)^{-1/2} + 2^{-1/2} + 4^{-1/2} + 6^{-1/2} = 3.61$$

The first order term (${}^1\chi^v$) takes the bonds (edges) into account and is defined as

$${}^1\chi^v = \sum_{s=1}^{N_e} (\delta_i^v \delta_j^v)_s^{-1/2}$$

where edge e_s terminates on vertices v_i and v_j . The number of edges in the graph is N_e . Thus for 2-butanone:

$${}^1\chi^v = 2(1.4)^{-1/2} + 2(4.6)^{-1/2} + (2.4)^{-1/2} + (2.1)^{-1/2} = 1.97$$

The second order term (${}^2\chi^v$) contains all possible combinations of two connected (adjacent) edges and is defined as

$${}^2\chi^v = \sum_{s=1}^{n_m} (\delta_i^v \delta_j^v \delta_k^v)_s^{-1/2}$$

where n_m is the number of subgraphs with two adjacent edges and s identifies a particular subgraph. Again, for 2-butanone:

$${}^2\chi^v = 2(1.4.6)^{-1/2} + 2(2.4.6)^{-1/2} + 1(4.2.1)^{-1/2} = 1.05$$

where the first term represents the path formed by carbon number one and the carbonyl bonds, the second represents carbon number three and the carbonyl bonds, the third term corresponds to the path formed by carbon atoms one through three, while the last term represents the path formed by carbon atoms two through four. All connectivity factors in this work were calculated to four decimal places. Higher order terms can be calculated, but these become increasingly complicated without the aid of a computer.

Many of the ketones in this study contained one or more chiral centers yielding multiple peaks that result from the separation of the diastereoisomers. The enantiomers, of course, were not separated since SE-30 (the stationary phase used here) is not a chiral phase. It has been stated that stereoisomerism is an intrinsically non-topological subject¹⁸. Consequently, the retention indices of the diastereoisomers of any given chiral compound were averaged before the data treatment, as described later. Initially, a reasonable (but by no means exact) estimation of the retention was hoped for. Even approximate figures could have some use in structural elucidation work.

EXPERIMENTAL

Retention indices were calculated using eqn. 1 from data obtained by co-chromatographing a number of ketone standard compounds with the series of methylketones. Ketone (of Table I) numbers 2, 3, 4, 7, 9, 14, 17, 18, 19, 23, 24, 26, 28, 35, 38, 40, and 41 were synthesized in our laboratory. All others were obtained from commercial sources. The column was a 45 m \times 0.25 mm I.D. glass capillary column coated statically with a 0.4% (wt./vol) solution of SE-30 methyl silicone stationary phase, resulting in a film thickness of 0.5 μ m. The column was drawn from Pyrex borosilicate glass, leached with 6 N hydrochloric acid¹⁹, and deactivated using the alkylpolysiloxane decomposition approach of Schomburg *et al.*²⁰. After the column was coated statically with 0.4% SE-30 in pentane, it was filled with nitrogen, sealed and heated to 450°C for 22 h, then washed with pentane and again statically coated as described above. A Perkin-Elmer Sigma 3 gas chromatograph modified for use with capillary columns was employed for all measurements. Helium was used as the carrier gas at a linear velocity of 32 cm/sec at 30°C. Data acquisition was accomplished with a Perkin-Elmer Sigma 10 chromatography data station. Mass spectral information was obtained with a Hewlett-Packard 5982A combined gas chromatograph-dodecapole mass spectrometer.

Sample introduction into the gas chromatograph was accomplished by either splitless injection or use of a small Tenax GC pre-column. Splitless injection was used for the determination of retention indices used in conjunction with the molecular connectivity work. A volume of 0.2 μ l of a hexane solution was injected with the oven at room temperature. After 2.0 min the oven was brought to 50°C and the program to 250°C at 2°C per min begun. For the comparative study involving changes in retention index based on *n*-alkane or 2-ketone standards, an aliquot of a methanol solution containing the compounds of interest was deposited onto the Tenax bed of a pre-column and the methanol removed by purging the pre-column with helium at a flow-rate of 100 ml per min for 60 sec at room temperature. Methanol was used as the solvent because it has a relatively low affinity for the Tenax adsorbent, facilitating its complete removal from the pre-column. The retained alkanes and/or ketones were subsequently desorbed from the pre-column in the heated injection port and swept onto the capillary column where they were thermally focussed with liquid nitrogen for a period of 10 minutes. The column was then subjected to a temperature program of 2°C per min from 30 to 250°C. In this manner, the solvent peak was eliminated from the chromatogram. This was important in this work because some of the early-eluting compounds appeared on the tail of the solvent peak. By eliminating the solvent, it was assured that the measured retention time was indicative only of the interaction between the compound and the stationary phase and not shifted by solvent effects²¹.

RESULTS AND DISCUSSION

The compounds examined in this study and their respective retention indices are presented in Table I. Each index was determined in triplicate with the resulting 95% confidence interval being equal to ± 0.13 index unit. Molecular connectivity factors were calculated as described in the introduction and linear regression was

TABLE I

KETONES STUDIED ALONG WITH THE EXPERIMENTALLY DETERMINED RETENTION INDEX AS WELL AS THAT PREDICTED FROM EQN. 3 OF TABLE II

<i>Number</i>	<i>Compound</i>	<i>Observed I</i>	<i>Predicted I</i>	<i>Residual</i>
1	2-Hexanone	600.00	588.31	11.68
2	3,5-Dimethyl-4-hepten-2-one	616.07	670.37	-54.30
3	4-Hexen-3-one	633.28	597.49	35.79
4	3-Methyl-3-penten-2-one	639.36	572.52	66.83
5	4-Heptanone	681.47	686.64	-5.17
6	2-Heptanone	700.00	686.74	13.26
7	3,4-Dimethyl-3-penten-2-one	711.61	664.49	47.12
8	2,5-Hexanedione	713.95	622.09	91.86
9	4-Hepten-3-one	728.70	694.04	34.65
10	6-Methyl-5-hepten-2-one	793.48	1017.30	-223.82
11	2-Octanone	800.00	785.17	14.82
12	Acetophenone	858.60	846.07	12.52
13	5-Nonanone	882.53	883.50	-0.97
14	3,4,4-Trimethyl-2-heptanone	885.92	944.24	-58.32
15	2-Nonanone	900.00	883.61	16.39
16	3,5-Dimethyl-2-octanone	903.89	930.50	-26.61
17	3,4,5-Trimethyl-2-heptanone	914.67	905.33	9.34
18	5,6-Dimethyl-3-octanone	933.15	958.31	-25.17
19	3-Methyl-2-nonanone	953.20	969.52	-16.32
20	3-Decanone	995.91	979.14	16.77
21	2-Decanone	1000.00	982.03	17.96
22	Phenylacetone	1031.30	1042.24	-10.94
23	3,5,7-Trimethyl-2-nonanone	1050.91	1150.87	-99.96
24	6-Methyl-5(6)-decen-2-one	1061.08	1124.91	-63.84
25	6-Undecanone	1080.06	1080.37	-0.31
26	3,5-Dimethyl-2-decanone	1094.96	1144.13	-49.17
27	2-Undecanone	1100.00	1080.47	19.53
28	3,7-Dimethyl-2-decanone	1108.48	1158.73	-50.25
29	3,5,7-Trimethyl-2-decanone	1137.80	1250.74	-112.94
30	2-Dodecanone	1200.00	1178.90	21.10
31	7-Tridecanone	1277.91	1277.23	0.68
32	β -Ionone	1283.41	1176.76	106.65
33	2-Tridecanone	1300.00	1277.33	22.67
34	2'-Acetonaphthone	1383.26	1326.39	56.87
35	2-Tetradecanone	1400.00	1375.76	24.24
36	8-Pentadecanone	1476.50	1474.09	2.41
37	2-Pentadecanone	1500.00	1474.19	25.81
38	2-Hexadecanone	1600.00	1572.61	27.39
39	9-Heptadecanone	1675.19	1670.95	4.24
40	2-Heptadecanone	1700.00	1671.05	28.95
41	2-Octadecanone	1800.00	1769.47	30.53
42	10-Nonadecanone	1873.72	1867.81	5.91
43	2-Nonadecanone	1900.00	1867.91	32.09

carried out between *I* and each of the individual connectivity factors. Finally, all three connectivity factors were treated with a multiple regression program with *I* as the dependent variable. The resulting equations are shown in Table II. The predicted retention indices obtained from the equation incorporating all three connectivity

TABLE II

EQUATIONS OF BEST FIT AS DETERMINED BY REGRESSION ANALYSIS OF THE CONNECTIVITY FACTORS AGAINST I

r^2 = Correlation coefficient; s = uncertainty estimate.

Equation	r^2	s
$I = 130.2516 {}^0\chi^v - 28.22$	0.907	111.4
$I = 194.5274 {}^1\chi^v + 28.20$	0.969	64.4
$I = 261.2743 {}^2\chi^v + 16.71$	0.894	119.1
$I = 192.0812 {}^1\chi^v + 65.22791 {}^2\chi^v - 29.23485 {}^0\chi^v + 24.58$	0.976	57.74

factors are presented in Table I along with the residuals. The data of Table I are depicted graphically in Fig. 1.

In general, the predicted index gives a reasonable idea as to where a given ketone will elute. There are, however, some large residuals for which we seek explanations other than those offered by connectivity considerations. The most striking examples are seen in the ketones with methyl substitution on alternate carbons. Based on observations during our efforts to synthesize some naturally occurring ketones⁷ it was noted that branching on alternate carbons of a ketone significantly reduces the boiling point from one that might be expected. We speculate that eclipsing of the methyl groups in the otherwise favored molecular conformation may be somehow responsible for the anomaly. This effect is illustrated effectively for 3,7-dimethyl- and 3,5,7-trimethyl-2-decanone (compounds 28 and 29 of Table I). Note the relatively small increase in the observed index and the greatly increased residual resulting from the addition of the methyl group at carbon number five. This clearly illustrates the non-topological aspects of molecular conformation. The predicted retention index for 3,4,5-trimethyl-2-heptanone (compound 17) is very close to the observed value. Apparently, then, this type of substitution decreases the effect on retention exhibited by compounds with branching on alternate carbons. It is interesting to contrast the residuals for 3,4,5-trimethyl-2-heptanone and 3,4,4-trimethyl-2-heptanone (com-

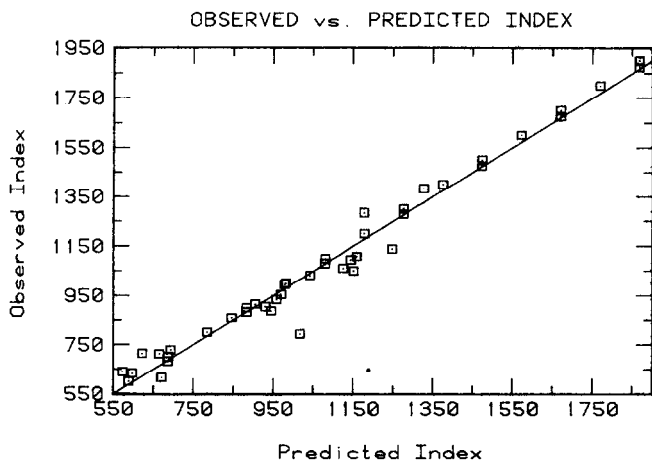


Fig. 1. Plot of observed retention index versus predicted retention index.

pounds 17 and 14, respectively). Rendering carbon number four quaternary in the 3,4,4-trimethyl compound has the same effect on retention as does the branching on alternate carbons.

Some other compounds worth discussing include certain unsaturated ketones, most notably 6-methyl-5-hepten-2-one (number 10) which elutes much earlier than predicted, perhaps because the connectivity calculations ascribe misleading emphasis upon the contribution of an isolated carbon-carbon double bond. The most favored conformations indicate a methyl group on carbon six eclipsed with the carbonyl oxygen, providing again some amount of shielding. Beta-ionone exhibits a longer retention than predicted but, then, it, unlike the other compounds studied, contains a six-membered ring. This would result in the carbonyl oxygen being more exposed in the most stable conformation, yielding a molecule with a higher effective polarity. The longer retention of 2,5-hexanedione (compound number 8) perhaps is noteworthy, but the likely interaction of two polar groups in the same molecule can be expected to introduce complications. It is worth noting that the molecular connectivity approach taken here does very well in predicting the retention index of many compounds in our data set including acetophenone, phenylacetone, and the entire series of symmetric ketones.

Once armed with retention data, one can speculate on the branching of an unknown ketone by utilizing the equations of Table II and "chemical intuition". The prediction of the retention index of a known compound is obviously less of a problem. The practicing analytical chemist usually has at least one more piece of information about the molecule under study. Most likely, this information is contained in the mass spectrum. Much work has been done with regard to the mass spectra of ketones, explaining the loss of $[H_2O + R]$ as a function of branching at some distance from the carbonyl group²², unusual fragmentations involving McLafferty rearrangements²³, and fragmentation in ketones with remote unsaturation²⁴. In addition, our work has resulted in some generalizations regarding the fragmentation of aliphatic ketones as a function of branching and carbonyl position. These trends are shown in Table III.

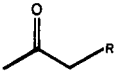
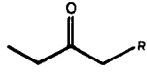
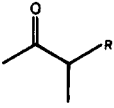
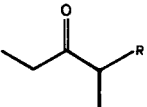
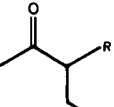
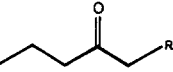
Additionally, an interesting trend was noticed upon examination of the observed retention indices of the symmetric ketones (compound numbers 5, 13, 25, 31, 36, 39 and 42). There is an initial increase in the index value (relative to the methyl ketone eluting before) between 4-heptanone and 5-nonanone ($I = 681.47$ and 882.53 , respectively) and then a steady relative decrease in I with increasing carbon number until a value of 1873.72 is observed for 10-nonadecanone. Since 4-heptanone eluted on the tail of the solvent peak, we chose to eliminate the solvent, as described in the experimental section, and in the process were able to add 2-pentanone and 3-pentanone to the mixture. In this manner, we could study the behavior of the five-carbon symmetric ketone as well. In addition, the retention indices for the C_5 - C_{19} symmetric and 2-ketones were determined using n -alkanes (C_6 - C_{24}) in order to see if the apparent discontinuity was observed when alkanes were used as the reference compounds. In order to accomplish this, we defined a term ΔI to be

$$\Delta I = I_{(2\text{-ketone})} - I_{(\text{symmetric ketone})}$$

In this manner, a ΔI value can be calculated for the case when either 2-ketones or n -alkanes are the reference compounds. By graphing ΔI vs. carbon number when

TABLE III

TYPICAL MASS SPECTRAL FRAGMENT IONS PRODUCED BY KETONES OF THE INDICATED STRUCTURES

<i>Structure of ketone</i>	<i>Significant m/e values (70 eV)</i>
	43, 58
	57, 72
	43, 72
	57, 86
	43, 86
	43, 58, 71, 86

both the alkanes and methyl ketones are used as references (Fig. 2), we indeed observe a discontinuity in the curve exhibited when 2-ketones are used as reference compounds. With alkanes as the reference, there is an always increasing ΔI . The negative values simply indicate that for 5 carbons the 2-ketone elutes before the 3-ketone.

The above results can again be interpreted in light of the shielding of the carbonyl oxygen by the aliphatic side chain. Retention is of course a function of both the number of carbon atoms and the effective polarity of the molecule. For 3-pentanone and 4-heptanone, a significant portion of the chemical characteristics contributing towards increased retention is derived from the polarity of the carbonyl oxygen; but for 5-nonanone, the aliphatic side chains are capable of wrapping back upon the carbonyl group, thus significantly reducing the contribution to retention by the oxygen atom. Since the carbonyl oxygen of 5-nonanone is shielded to a very great extent, further increases in the length of the side chain probably cannot increase the shielding further, for the result, contrary to observation, would be a continued decrease in retention with increasing carbon number relative to isomeric 2-ketones where the polarity of the oxygen atom is still contributing significantly to retention. This discontinuity in retention characteristics between four- and five-carbon chains attached to the carbonyl group is supported by the work of Dippy from 1938²⁵ who

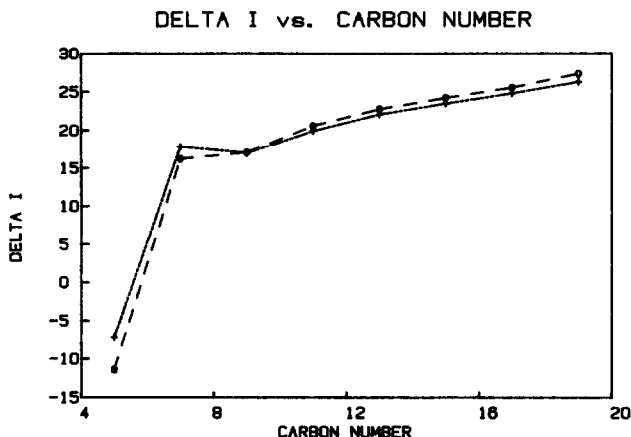


Fig. 2. Plot of ΔI versus carbon number when *n*-alkanes (O) or 2-alkanones (+) were used as reference compounds for the retention index determinations of the symmetric ketones.

demonstrated that there is a discontinuity in acid strength for straight-chain aliphatic carboxylic acids. Acid strength decreases as one goes from acetic to propanoic but increases at butanoic acid. Dippy hypothesized that the carbon chain length of four is sufficient for the chain to wrap around so as to permit the carboxylate anion to become stabilized through hydrogen bonding between the oxygens and the hydrogens of the terminal carbon atom. As the chain length is increased further, the original trend of decreasing acid strength is restored. Similar effects have been demonstrated for aliphatic primary amines²⁶. All this suggests that by using 2-ketones as standards, subtle polarity changes in a series of compounds might be brought to light.

Further evidence supporting our shielding argument is found in the retention characteristics of 2- and 3-pentanone. Normally, the symmetric ketone elutes before the methyl ketone. However, with the five-carbon ketones, the reverse is observed. Using the last equation of Table II, it is predicted that 3-pentanone should elute before 2-pentanone ($I_{\text{predicted}} = 484.19$ and 489.88 , respectively) as in the higher homologues. One notices here that 2-pentanone has a three-carbon chain attached to the carbonyl group as do 4-heptanone and butanoic acid. Since the oxygen of 2-pentanone would be shielded to a greater extent than the oxygen of 3-pentanone, we would expect 2-pentanone to be less polar, hence giving rise to an earlier elution than for the 3-keto compound. This, again, demonstrates the failure of molecular connectivity to take molecular conformation into account and supports our explanation of the original retention anomaly.

CONCLUSION

Molecular connectivity combined with mass spectrometry and a general familiarity with the types of compounds being studied provides substantial information leading to structural elucidation. Much time can be saved in solving a structural unknown if the means of predicting retention and mass spectral characteristics exist. In addition, by properly choosing the reference compounds for the determination of

retention indices (in this case, while using a temperature program) various molecular characteristics can be probed.

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