

# Quantitative Structure–Odor Relationships of Aliphatic Esters Using Topological Indices

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Quantitative structure–activity relationships (QSAR) were used in this study to relate the structural parameters (electronic, topological, etc.) to the odor of 27 aliphatic esters previously evaluated by Rossiter. Rossiter used the Hansch approach, principal component analysis and comparative molecular field analysis (CoMFA) to predict the odor of these esters. Different structural parameters were selected, such as topological, physicochemical, and quantum-chemical indices, to find an equation to predict the molecular factors that determine the fruit odor of these compounds and to compare such results with those obtained by Rossiter. Two significant correlation equations were obtained with the following molecular descriptors: one with the electrotopological-state index related to the carbon atom of the carbonyl group ( $S_{C=O}$ ), the Kappa index ( $^2K$ ), and the topological-state index related to the oxygen on the alcoholic side of the molecule ( $T_{O-}$ ), and the other with  $^2K$ ,  $S_{C=O}$ , and the energy of the highest occupied molecular orbital ( $E_{HOMO}$ ). The model found had a good predictive ability as established by cross-validation  $r^2_{cv}$  values and thus can be used to help in the prediction of odor of similar compounds. This method is simpler than the methods used by Rossiter and represents a reliable QSAR alternative in predicting the fruit odor of such aliphatic esters.

**Keywords:** QSAR; aliphatic esters; odor; topological indices

## 1. INTRODUCTION

The great majority of the aromatic substances that have been investigated in the past 100 years were synthesized at random. Now, with the application of QSAR, the synthesis of new substances can be rationalized, avoiding a waste of time and money. Different QSAR methods have been used to investigate the relationship between chemical structure and odor. For example, the Hansch and Fujita approach (1964) was applied satisfactorily for 16 compounds with bitter aroma (Kubinyi, 1986). Also, Kier et al. (1977) used the molecular connectivity topological method in structure–property studies for groups of molecules with similar aromas.

Quantitative odor–structure relationships were used in this study to relate the structural parameters of a molecule (electronic, topological, etc.) to its odors. Topological technique is founded on the assumption that the characteristic of the molecular structure can be interpreted mathematically and that the mathematically determined parameters of molecules can be correlated with their experimentally measured properties (Rouvray, 1986). The term “topological index” indicates a characterization of a molecule (or a corresponding molecular graph) by a single number. The need to represent molecular structure by a single number arises from the fact that most molecular properties are recorded as single numbers. Therefore, QSAR modeling is reduced to a correlation between the two sets of numbers via an algebraic expression—one set of numbers represents the properties, and the other set represents the structures of molecules under study (Mihalic and Trinajstić, 1992). This method becomes, then, an

important tool that aids in the identification and prediction of new compounds.

The main problems in the application of structure–activity relationships to odor are as follows: our limited understanding of the mechanism of olfaction and difficulties associated with precise odor measurement. However, such problems have been minimized with recent progress in the biological sciences and the development of more sophisticated computer programs applied to QSAR (Rossiter, 1996a).

There is no doubt that the main group of fruity odorants are esters, and as a result, this class of compounds has been the center of several SAR studies. Boelens (1983) rated the fruity odor aspect strengths of 106 esters against ethyl phenylglycidate and then attempted to correlate these ratings with features of the molecular structure by multiple regression analysis. Following on from this work, Sell (1986, 1988) investigated the effects of steric hindrance of the ester function, and also the presence of unsaturation in the proximity to the ester function, for a series of aliphatic esters.

Rossiter (1996b) studied the quantitative fruity odor–structure relationships of 27 aliphatic esters using three different approaches: regression analysis (Hansch Approach), principal component analysis (PCA), and comparative molecular field analysis (CoMFA) and concluded that these techniques can be used to identify sensible relationships between structure and fruity odor and that they can therefore be applied, with some degree of confidence, to more complicated problems where this relationship is not so obvious.

In this study, our aim was to use molecular and topological descriptors as an alternative approach in the

prediction of the molecular factors that determine the fruit odor of this same series of compounds and to compare the results with those obtained by Rossiter (1996b).

## 2. METHODS

The fruit scores of 27 aliphatic esters were obtained by Rossiter (1996b) through a sensorial analysis carried out by a panel of 28 trained assessors.

The structural descriptors used in the present study were topological, physicochemical, and quantum-chemical indices. The molecular connectivity indices of different orders ( $X_i$  and  $X_i^v$ ) (Kier and Hall, 1976, 1986; Heinzen and Yunes, 1992, 1993), electrotopological-state indices ( $S_i$ ) (Hall and Kier, 1991; Hall et al., 1991; Georgakopoulos et al., 1991; Heinzen and Yunes, 1996; Heinzen et al., 1999), topological state indices ( $T_i$ ) (Hall and Kier, 1990), and indices of molecular shape, kappa values ( $^kK$ ) (Kier, 1987; Heinzen and Yunes, 1996), were calculated using the computational program Molconn-X, developed by Hall and Kier (1991). These indices express, in a general way, the topological environment of each atom, the linearity and the branching of the molecule, the presence of heteroatoms, the charge distribution, and the electronic effects in molecules (Kier and Hall, 1976, 1986; Hall and Kier, 1991; Hall et al., 1991; Georgakopoulos et al., 1991; Kier, 1987; Heinzen and Yunes, 1992, 1993, 1996; Heinzen et al., 1999).

The molecules were drawn using the PcModel version 3.01 computer program, and the figures were geometrically energy-minimized by use of the PM3 quantum mechanical method (Santos and Almeida, 1995). Subsequently, the energy-minimized molecular structure was used for generating a number of molecular parameters utilizing the semiempirical molecular orbital MOPAC 6.0 program (Stewart, 1990). The following quantum mechanical molecular properties were chosen for this study: the highest occupied molecular orbital energy ( $E_{\text{HOMO}}$ ), the lowest unoccupied molecular orbital energy ( $E_{\text{LUMO}}$ ), the total surface area (TA), saturated area (ST), polar area (PA), molecular volume (VMOLEC), molar volume (VMOLAR), and total energy (TE).

**2.1. Selection of Descriptors.** In this work, we made single linear correlations between the fruit scores of the esters and the structural descriptors in order to identify, through the correlation coefficient values, those best related to the esters' odors.

The descriptor combinations that presented the highest correlation coefficient values with the fruit scores, smaller standard deviation values, and larger overall  $F$  value were considered, taking into consideration the low collinearity between them.

The best regression equations were selected on the basis of the multiple correlation coefficient,  $r$ , the standard deviation,  $s$ , the overall  $F$  value, and the value of the difference between the experimental fruit score and the calculated fruit score for this group of compounds. Finally, to estimate the predictive power of the equations, the cross-validation ( $r^2_{\text{cv}}$ ) following the "leave-one-out" scheme was performed (Muresan et al., 1995; Wagener et al., 1995). All the single and multiple linear regression analyses, as well as the calculation of the cross-validation coefficient, were carried out using the Bilin computer program (Kubinyi, 1993).

The model was also evaluated through the prediction of fruit scores of four test esters, which were assessed by a panel of fragrance chemists and ranked as weak, moderate, or strong (Rossiter, 1996b).

## 3. RESULTS AND DISCUSSION

The ester fruit scores obtained by Rossiter (1996b) are presented in Table 1.

In accordance with previous reviews (Kier et al., 1977; Rossiter, 1996a) the parameters used in this study were

**Table 1. Fruit Scores of the 27 Esters (Rossiter, 1996b)**

no.	ester	fruit score (%)
1	hexyl methanoate	24
2	pentyl ethanoate	100
3	butyl propanoate	92
4	propyl butanoate	47
5	ethyl pentanoate	85
6	methyl hexanoate	81
7	pent-2-yl ethanoate	34
8	2-methylbut-2-yl ethanoate	0
9	propyl 2-methylpropanoate	44
10	ethyl 2,2-dimethylpropanoate	32
11	pentyl 2,2-dimethylpropanoate	31
12	2-methylhex-2-yl ethanoate	25
13	2-methylhex-2-yl 2,2-dimethylpropanoate	11
14	pentyl pentanoate	65
15	pent-2-yl pentanoate	40
16	2-methylbut-2-yl pentanoate	22
17	2-methylbutyl pentanoate	56
18	2,2-dimethylpropyl pentanoate	72
19	3-methylbutyl pentanoate	80
20	pentyl 2-methylbutanoate	79
21	pentyl 3-methylbutanoate	66
22	2,2-dimethylpropyl 2-methylbutanoate	19
23	2,2-dimethylpropyl 3-methylbutanoate	37
24	2-methylbutyl 3-methylbutanoate	55
25	2-methylbutyl 2-methylbutanoate	54
26	pent-2-yl 3-methylbutanoate	36
27	pent-2-yl 2-methylbutanoate	32

chosen according to their probable capacity to contribute to the understanding of some of the mechanisms of olfaction (odor-sense interaction of smell). The values of some of the molecular descriptors used in the correlations are given in Table 2.

The best single linear regressions were obtained with descriptors related to the lowest unoccupied molecular orbital energy ( $E_{\text{lumo}}$ ),  $r = 0.712$ , to the molecular topology of the carbon atom attached to the oxygen on the alcoholic side ( $T_{\text{C-O}}$ ),  $r = 0.673$ , to the electrotopological state of the first carbon on the alcoholic side, attached to the oxygen ( $S_{\text{C-O}}$ ),  $r = 0.669$ , to the highest occupied molecular orbital energy ( $E_{\text{HOMO}}$ ),  $r = 0.571$ , and to the topological state index in relation to the oxygen on the alcoholic side of the molecule ( $T_{\text{O-}}$ ),  $r = 0.562$ . The descriptors related to the electrotopological and topological state of the molecule have high collinearity to each other. These equations are not able to describe a good odor-structure relationship for these compounds. This led us to test two-variable regression equations. Different combinations of the variables representing each of the two terms described above were tried in order to obtain the best equation. However, the linear regression equations of two variables produced correlation coefficients with low values:  $r = 0.744$  with  $S_{\text{C=O}}$  and  $E_{\text{lumo}}$ ,  $r = 0.662$  with  $T_{\text{O-}}$  and  $^2K$ , and  $r = 0.651$  with  $E_{\text{HOMO}}$  and  $^2K$ .

Thus, the odor of the series of esters studied was tested by an equation consisting of three variables. The best equations were obtained with the Kappa index ( $^2K$ ),  $T_{\text{C-O}}$ , and the electrotopological-state index related to the carbon atom of the carbonyl group ( $S_{\text{C=O}}$ ), or with the kappa index ( $^2K$ ),  $S_{\text{C=O}}$ , and  $E_{\text{HOMO}}$ . The relative importance of the three variables used in the equations was estimated by regression analysis. Due to the fact that the topological index  $T_{\text{C-O}}$  had high collinearity with the topological state index in relation to the oxygen on the alcoholic side of the molecule ( $T_{\text{O-}}$ ), it was the only one introduced into eq 1, because it reflected better the introduction of substituents on both sides of the chain (alcoholic and acid). Thus, the best multiple linear

**Table 2.** Polar Area ( $A_p$ ), Total Surface Area ( $A_{\text{total}}$ ), Energy of the Lowest Unoccupied Molecular Orbital ( $E_{\text{LUMO}}$ ), Topological State Indices ( $T_i$ ), Electrototopological State Indices ( $S_i$ ) for the Carbon Attached to the Oxygen of Ester Group ( $S_{(-C-O)}$  and  $T_{(-C-O)}$ ), for the Carbon of Carbonyl Group ( $S_{(C=O)}$ ) and for the Oxygen Atom on the Alcoholic Side ( $T_{-O}$ ), Kappa Index ( $^2K$ ), and the Highest Occupied Molecular Orbital ( $E_{\text{HOMO}}$ )

no.	$A_p$ (Å <sup>2</sup> )	$A_{\text{total}}$ (Å <sup>2</sup> )	$E_{\text{LUMO}}$ (eV)	$S_{(-C-O)}$	$S_{(C=O)}$	$T_{(-O)}$	$T_{(-C-O)}$	$^2K$	$E_{\text{HOMO}}$
1	38.043	183.95	1.0771	0.5868	0.5059	9.1505	4.4492	8.0000	-11.326
2	31.911	183.85	1.0444	0.5865	-0.1749	9.6378	4.6087	6.1250	-11.251
3	31.257	184.51	1.0854	0.5865	-0.0940	9.8132	4.6499	6.1250	-11.157
4	30.050	181.43	1.0862	0.5683	-0.0700	9.8311	4.5805	6.1250	-11.171
5	30.525	183.30	1.0895	0.5025	-0.0700	9.7082	4.3136	6.1250	-11.165
6	30.335	181.14	1.0479	1.4249	-0.0940	9.2561	2.5609	6.1250	-11.178
7	31.091	184.28	1.1196	0.0903	-0.1843	10.1225	6.4060	4.8395	-10.814
8	29.858	178.38	1.1462	-0.2859	-0.2066	10.5617	8.1647	3.2397	-10.893
9	28.995	184.20	1.1082	0.5526	-0.1001	9.9583	4.6363	4.8395	-11.049
10	28.634	182.59	1.1446	0.4684	-0.1343	10.0232	4.4569	3.2397	-10.989
11	29.001	245.00	1.1435	0.5734	-0.0985	10.4129	5.0202	5.6122	-10.977
12	30.011	221.56	1.1475	-0.2759	-0.1888	10.7740	8.4511	4.7929	-10.927
13	26.951	277.16	1.2470	-0.3191	-0.1124	11.5492	8.9266	5.1856	-10.714
14	31.295	249.19	1.0804	0.6075	-0.0343	10.0979	4.8769	9.0909	-11.171
15	29.801	246.59	1.1536	0.0966	-0.0437	10.5826	6.6953	7.6389	-10.760
16	28.357	241.99	1.1605	-0.2869	-0.0660	11.0218	8.4699	5.6122	-10.821
17	29.823	242.66	1.0961	0.5824	-0.0443	10.2499	5.1450	7.6389	-11.098
18	30.997	243.71	1.0891	0.5234	-0.0632	10.3511	5.3338	5.6122	-11.155
19	30.212	244.60	1.0824	0.5835	-0.0440	10.1445	4.9471	7.6389	-11.009
20	30.198	246.92	1.0877	0.5943	-0.0476	10.2861	4.9643	7.6389	-10.950
21	30.707	246.60	1.0627	0.5966	-0.0545	10.1537	4.9067	7.6389	-11.012
22	27.540	236.14	1.0928	0.5101	-0.0764	10.5394	5.4212	4.8889	-10.972
23	30.034	240.99	1.1070	0.5124	-0.0834	10.4069	5.3636	4.8889	-10.853
24	30.795	246.24	1.0762	0.5715	-0.0645	10.3057	5.1748	6.5089	-11.058
25	29.963	243.24	1.0584	0.5691	-0.0576	10.4382	5.2324	6.5089	-10.963
26	29.048	241.24	1.1434	0.0845	-0.0639	10.6385	6.7278	6.5089	-10.697
27	29.116	243.85	1.1309	0.0801	-0.0570	10.7709	6.7917	6.5089	-10.971

regressions with three variables for the 26 esters studied were as follows:

Fscore =

$$12.94^2K - 143.8S_{C=O} - 34.60T_{-O} + 313.6 \quad (1)$$

$$N = 26; r = 0.882; s = 13.3; F = 25.6; r_{cv}^2 = 0.546$$

Fscore =

$$14.45^2K - 150.5S_{C=O} - 109.4E_{\text{HOMO}} - 1252 \quad (2)$$

$$N = 26; r = 0.865; s = 14.3; F = 21.7; r_{cv}^2 = 0.605$$

The position of the ester group in the aliphatic chain can be predicted by the electrototopological indices ( $S_i$ ). These indices give information about the electronic and topological state of an atom according to the presence of other atoms in the molecule (Hall et al., 1991; Georgakopoulos et al., 1991; Heinzen and Yunes, 1996; Heinzen et al., 1999). The resulting electrototopological state of any atom is a numerical value that describes the availability of that atom to interaction across space with some reference atom or group (Hall et al., 1991; Heinzen and Yunes, 1996; Heinzen et al., 1999).  $S_{C=O}$  is related to odor in the following way: the higher the number of branches in the cetonic group (acid side of the molecule), the lower its value will be, and this contributes to the decrease in the fruit score in eq 1. In a general way, it is observed that when the ester group is placed toward the center of aliphatic chain, the index  $S_{C=O}$  is decreased and the fruity character is reduced. The degree of linearity or starlikeness of bonding patterns and the presence of branching in the molecule are directly related to the value of  $^2K$ . Its value increases with the growth of the linear aliphatic chain, and it decreases with the growth of the branching in accordance to the odor.  $T_{-O}$  is related to the molecular topology and to the degree of substitution (number of

branches and size of the substituent) in the oxygen atom on the alcoholic side, being inversely proportional to the odor, according to eq 1. For isomeric esters with the same number of carbon atoms in the main aliphatic chain, the  $T_{-O}$  value increases when the ester group is placed toward the center of the chain and also with the decrease in the number of carbon atoms on the alcoholic side of the linear aliphatic chain. Another fact to be observed in relation to  $T_{-O}$  is that its value increases with the degree of branching.

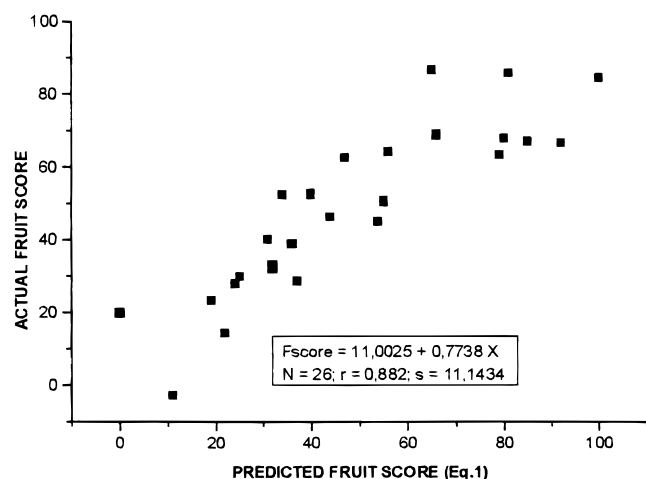
It can be observed by eq 1 and by the descriptors used that the introduction of substituents on to the alcoholic side of the molecule ( $T_{-O}$ ) has a stronger negative effect on the fruity character than the introduction of substituents to the acid side. These results are in agreement with those obtained by Rossiter (1996b).

Considering the coefficient values in eq 1, it appears that the main factor that describes the odor is  $S_{C=O}$ , the second-most significant is  $T_{-O}$ , and the least significant parameter is  $^2K$ .

The third parameter introduced in eq 2 was the energy of the highest occupied molecular orbital of the esters,  $E_{\text{HOMO}}$ .  $E_{\text{HOMO}}$  is related to the energy necessary to remove an electron from a molecule. The sign of this coefficient in eq 2 is negative; this signifies that the more electron-donating molecules contribute to increase the fruit score of esters. Thus,  $E_{\text{HOMO}}$  should correct the values of  $S_{C=O}$  considering that  $E_{\text{HOMO}}$  is a global molecular value and not localized to an atom as is  $S_{C=O}$ .

Although the predictive abilities of the found model ( $r_{cv}^2 = 0.546$  for eq 1 and  $r_{cv}^2 = 0.606$  for eq 2) are slightly higher than those obtained by Rossiter (1996b) by the Hansch Approach ( $r_{cv}^2 = 0.50$ ) and CoMFA ( $r_{cv}^2 = 0.52$ ), the model applied in this study explains 78% (eq 1), and 75% (eq 2) of the variation of the observed fruit score, against 67% and 84% explained by the Hansch and CoMFA models, respectively. The predicted





**Figure 1.** Graph of predicted vs actual fruit score.

**Table 3. Fruit Scores Predicted by the Model Found by the Bilin Computer Program (Kubinyi, 1993) and the Observed Fruitiness of the Four Test Esters**

test compound	Fscore predicted by eq 1 (%)	Fscore predicted by eq 2 (%)	obsd fruitiness
but-2-yl propanoate (AB)	37	42	moderate
propyl propanoate (AC)	60	59	strong
cyclohexyl propanoate (AD)	2	23	strong
cyclopentyl propanoate (AE)	0	21	strong

versus actual fruit score is indicated in Figure 1. For an ideal model, the points would fall on a diagonal line from left to right. Points which deviate from this line correspond to compounds that are poorly modeled by the QSAR. These graphs show visually that the model is good. In fact, an  $r^2$  of 0.78 (eq 1) and  $r^2$  of 0.75 (eq 2) are relatively good for correlations between odor and structure because the odor measurement generally gives rise to a 10–15% variation in the individual odor scores (Rossiter, 1996b).

As compound **18** (Table 1) exhibited a significantly large  $s$  in the eq 1, it was eliminated and the correlation coefficient is improved ( $r$  with outlier = 0.849, and  $r$  without outlier = 0.882). For the eq 2, the outlier was the compound **14** (Table 1) ( $r$  with outlier = 0.825, and  $r$  without outlier = 0.865).

The equations obtained by Rossiter (1996b) using the Hansch and PCA models were applied for 24 compounds using four variables:  $\nu_R$ , the Charton substituent for the alkyl group attached to C=O;  $\nu_{OR}$ , Charton substituent for the alkyl group attached to the ether oxygen atom;  $L$ , molecular length; and  $L_{comb}$ , descriptor for the position of the ester group in the chain. The Charton parameter is related to measured rates of hydrolysis of esters and, as such, is a measure of intramolecular steric effects around nearby reaction centers (Rossiter, 1996a). In this study, the model was developed for 26 compounds with just three general variables ( $S_{C=O}$ ,  $T_{O-}$ ,  $^2K$ , and  $S_{C=O}$ ,  $E_{HOMO}$ ,  $^2KK$ ) which did not involve the introduction of a specific random variable such as the molecular length in the case of Rossiter (1996b).

To verify the model's applicability, the equations obtained were used to predict the odor of four test esters previously evaluated sensorially (Rossiter, 1996b). The predicted scores of these esters are in Table 3. It can be noted that this method was valid for the esters AB and AC, classified as moderate and strong odor, respectively, but that it was not valid for the esters AD and AE. This

is explained by the fact that the structures of the compounds AD and AE are different from the structures of the esters of the data set (Table 1) that were used in this study. This was expected, because studies of QSAR that use topological indices are only valid for compounds of similar structures. It was verified that the presented model had a similar predictive ability to the model of CoMFA, while the Hansch model proposed by Rossiter (1996b) had predictive ability for all the test esters.

#### 4. CONCLUSIONS

The suggested model, using molecular and topologic descriptors, was able to predict the fruit odor of 26 aliphatic esters, as well as two of the test compounds whose structures were similar to those of the data set used in the model. It may be observed through the topological indices used, related fundamentally to the carbon of the carbonyl and secondarily to the oxygen of the ester group, that the functional group has great influence on the fruit odor of the esters. Our model was found to have good predictive ability as established by cross-validation  $r^2_{cv}$  values and thus is of potential use in the prediction of odor of similar compounds.

This method is simpler than the methods used by Rossiter, and represents a reliable QSAR alternative in predicting the fruit odor of such aliphatic esters. Besides, these indices can be used for other types of molecules, while the descriptors used by Rossiter (1996b) such as the molecular length and the Charton substituent constant, are specific for the esters in this study.

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