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Short communication

Chromatographic retention behaviour of *n*-alkylbenzenes and pentylbenzene structural isomers on porous graphitic carbon and octadecyl-bonded silica studied using molecular modelling and QSRR

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ABSTRACT

The retention behaviour of a series of 15 *n*-alkylbenzenes and pentylbenzene structural isomers and benzene were investigated using porous graphitic carbon (PGC) and octadecyl-bonded silica (ODS) stationary phases. Shorter chain *n*-alkylbenzenes and benzene (n = 0–6), and all the pentylbenzene isomers were more strongly retained on ODS, although the selectivity was greater with PGC. For the pentylbenzene analytes the degree of branching in the alkyl chain at the position adjacent to the aromatic ring affects retention on PGC, with higher retention in less branched molecules. Molecular modelling studies have provided new insights into the geometry of aromatic π–π stacking interactions in retention on PGC. For alkylbenzenes with high branching at the position adjacent to the ring, the preferred geometry of association with the surface is with the branched chain directed away from the surface, a geometry not seen in the other alkylbenzenes. The most energetically favoured orientation for interaction between analytes and the PGC surface was found to be cofacial for toluene and ethylbenzene, whereas for other analytes this interaction was in a face-edge orientation. The alternative geometry of association observed with both toluene and ethylbenzene may explain the enhanced retention of these two analytes on PGC compared with their longer chain analogues. Quantitative structure–retention relationships revealed the importance of compactness in analyte structure during retention on PGC, with decreased compactness (associated with longer chain length and reduced chain branching) improving retention.

1. Introduction

Porous graphitic carbon (PGC) is an established stationary phase for high-performance liquid chromatography, originally intended as a substitute for reversed-phase silica in areas where this bonded phase is inadequate (e.g. at extremes of pH) [1–6]. However PGC has been found to possess a number of unexpected properties which have not been fully explained, and which have expanded its area of application and opened up new avenues for research [7]. The chemistry of the graphite surface plays a significant role in analyte retention [8,7], an effect greater than originally expected by the developers of PGC [1], who had predicted a near perfect reversed-phase mechanism [2,7].

A number of studies have shown the importance of hydrophobicity, polarity, size and topology on retention behaviour at PGC [9–16]. One key aspect of retention on PGC is the rigid planar graphite surface which results in strong retention of large planar molecules [10,13,17,18] and reduced retention in very branched molecules, where steric hindrance limits the degree of contact between the analyte and PGC surface [19]. The surface of PGC is crystalline and made up of flat sheets of hexagonally arranged sp^2 hybridised carbon atoms [16,20]. As such it is structurally similar to large polycyclic aromatic molecules, which are also flat and have high degrees of electron delocalisation. It is well established that aromatic rings adopt two preferred dimeric structures, these being the cofacial and face-edge geometries [21,22], but no studies have been carried out to probe the role of such geometries in separations on PGC. Clearly the three dimensional geometric and electronic properties of the PGC surface are likely to strongly influence retention on this material.

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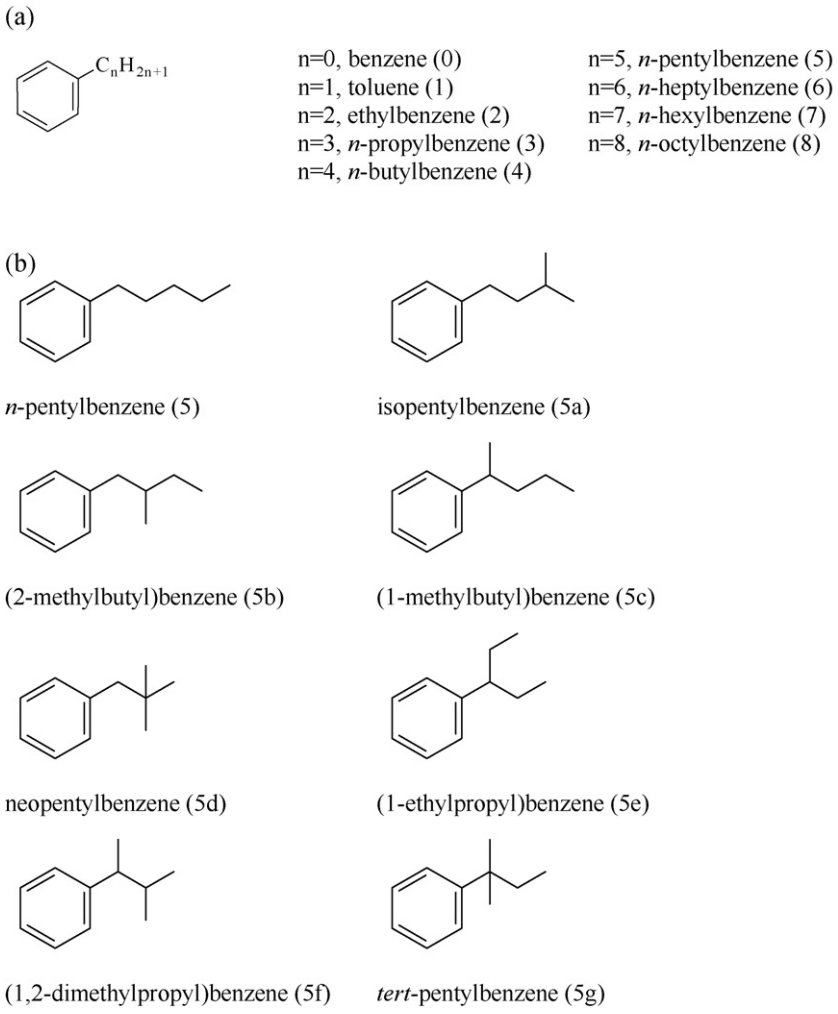


Fig. 1. Structures of (a) *n*-alkylbenzenes (*n* = 0–8) and (b) pentylbenzene structural isomers, with compound numbering in parentheses.

Whilst extensive studies have been carried out exploring the role of key aspects of analyte structure on separation on PGC, less is known about the combined effect of these structural features to retention. The aim of this work was to use both chromatographic and computational approaches to investigate the mechanisms of retention of a series of *n*-alkylbenzenes and pentylbenzene structural isomers on PGC. Benzene and 15 derivatives were chosen (Fig. 1) so that the contribution to retention of different structural features could be explored, and their combined contribution to retention assessed. In particular, the role of aromaticity, planarity, topology and hydrophobicity in retention on PGC were explored. This simple series of non-polar benzene derivatives is ideal in this context since a planar aromatic moiety is present in all the analytes, with different molecular topologies depending on the extent of branching in the alkyl substituent, and with a minimal polar retention effect on graphite (PREG), as described by Knox and Ross [15,16]. Molecular modelling calculations, i.e. simulations of 3D molecular structure, have been used, for the first time, to explore the aromatic π–π stacking interactions between aromatic analytes and the PGC surface.

The retention characteristics of the benzene derivatives were measured on both PGC and ODS, a comparison thought to be relevant, since ODS represents the standard stationary phase used in these separations. Molecular modelling calculations were designed to explore the geometries of interaction between the analytes and a model PGC surface, and to provide hitherto unavailable insights into the role of aromatic stacking interactions in separations on PGC. Given the difficulties in modelling aromatic π–π stacking interactions using molecular mechanics methods, and the likely involvement of electronic effects in the interaction between the analyte and PGC, semi-empirical molecular orbital methods were chosen as the preferred computational model. Whilst some modelling studies have previously been reported, where analyte-PGC surface interactions have been explored [23], no modelling has been reported of aromatic π–π stacking interactions. Quantitative structure–retention relationship (QSRR) studies were used to explore the structural features of most importance to retention, with particular emphasis on topological features, given the likely influence of molecular branching and topology on the geometry of association between the aromatic moieties in the analyte and surface.

2. Materials and methods

2.1. Chromatography

2.1.1. Materials

Details are provided in the supplementary material.

2.1.2. Instrumentation

HPLC analysis was performed on an Integral Micro-Analytical 100Q Workstation (PerSeptive Biosystems, now part of Applied

Biosystems, Foster City, USA) with a variable wavelength UV detector set at 220 nm.

2.1.3. Analysis conditions

HPLC was performed using a Hypersil ODS column (150 mm × 4.6 mm i.d.) 5 μm particle size and Hypercarb PGC column (100 mm × 3.0 mm i.d.) 5 μm particle size (ThermoQuest, Runcorn, UK). Conditions used were 90:10 (unbuffered) methanol:water (v/v) mobile phase, and flow rates of 1.0 ml min^{-1} and 0.42 ml min^{-1} for ODS and PGC systems respectively. The flow rates were set to maintain comparable column linear flow velocities. Chromatography was performed at ambient temperature. Samples were dissolved in methanol (100 μg ml^{-1}) and were injected in triplicate. Sample injections were 10 μl volumes.

2.1.4. Data treatment

The chromatographic retention factor, k, was calculated by the computerised integration software within the Integral Workstation. The retention time of the unretained analyte (solvent) peak was taken as the time interval from the moment of injection to the time when the trace for the solvent disturbance crossed the baseline.

2.2. QSRR

QSRR analysis was performed on retention data obtained for the *n*-alkylbenzenes, the pentylbenzenes, and benzene, on the ODS and PGC phases. Analyte structural descriptors were selected to assess topology, geometry, polarity, size and hydrophobicity and were calculated using the TSAR 3.0, VAMP and COSMIC software packages (Oxford Molecular Ltd). More details are provided in the supplementary material. Correlations between the chromatographic log k measurements and the structural descriptors were assessed using bivariate linear regression analysis.

2.3. Molecular modelling

The energies of interaction between the benzene derivatives, and a model graphite surface were calculated using semi-empirical molecular orbital methods. Adsorption of analytes onto the surface of PGC was simulated using the AM1 method within MOPAC [24]. An extended polycyclic aromatic molecule ($C_{78}H_{22}$) was used to represent the PGC stationary phase (Fig. 2).

The energy of interaction between the analyte molecule and the model graphite surface molecule, termed E_I (in kcal/mol) was calculated as the difference in heat of formation of the analyte and the surface complex at a separation of 50 Å (i.e. no intermolecular interaction) and the analyte-surface complex at a small separation distance (3.6 Å). The separation distance of 3.6 Å was chosen since this represents a typical distance observed between carbon atoms in π–π stacked aromatic rings [21,22,25].

Five alternative geometries for alignment of the analyte with the model graphite surface were considered, and are shown in Fig. 2. The lowest value for the interaction energy, which represents the strongest interaction between analyte and model surface, was used to represent the optimal interaction energy ($E_{I(min)}$). More details are provided in the supplementary material.

3. Results and discussion

The values of log k, obtained for the 16 analytes on PGC and ODS, are given in Table S1. Retention data were reproducible to better than 1% from run to run.

3.1. Chromatographic retention data

3.1.1. n-Alkylbenzenes

The *n*-alkylbenzenes with shorter chain lengths were more strongly retained on ODS than PGC, however the longer chain heptylbenzene and octylbenzene showed stronger retention on PGC than ODS. Retention of this series of analytes on both ODS and PGC increased with increasing chain length; this is discussed further with the QSRR results. The average selectivity, α (where $\alpha = k_2/k_1$, and considering *n*-butylbenzene to *n*-octylbenzene) for a CH_2 unit addition when chromatographed on ODS was 1.38 and on PGC was 1.83. PGC therefore showed improved selectivity. Enhanced selectivity of PGC compared to ODS with *n*-alkylbenzenes, has previously been reported [10].

3.1.2. Pentylbenzenes

Chromatograms of a mixture of eight pentylbenzene structural isomers show that on ODS the analytes remained largely unresolved (Fig. 3a), whereas on PGC there was almost complete resolution of all peaks (Fig. 3b) and thus superior selectivity. Again, in comparison with PGC, ODS showed increased retention of pentylbenzene isomers. A number of previous studies have shown that PGC allows far greater resolution of structurally similar analytes, including alkylbenzenes and polymethylbenzenes than ODS [10,12,19].

With both stationary phases the straight chain isomer is most retained, but the order of elution then alters between the two phases. In the case of PGC, there appears to be some correlation between the degree of alkyl chain branching and retention, with the more branched isomers eluting at a lower retention time. For example, the three most retained isomers (*n*-pentylbenzene, isopentylbenzene and (2-methylbutyl)benzene) show no branching at the position adjacent to the aromatic ring, whilst the least retained isomer (*tert*-pentylbenzene) shows the highest degree of branching at this position.

3.2. QSRR analysis

3.2.1. n-Alkylbenzenes

The correlations obtained between log k values and a variety of structural descriptors are given in Fig. 4 (and Figs. S2 and Table S2).

A linear relationship between alkyl chain length (n = 0–8) and log k was observed for ODS, a result also observed by Kriz et al. [10], whilst on PGC, the linear relationship was only seen at alkyl chain length above *n*-butylbenzene (n = 4–8) (Fig. 4a), with similar results again previously reported [10,26]. Deviations from linearity in plots of log(retention data) against number of carbon atoms in homologous series of compounds is well known, with this deviation seen for the smaller members of the series [32]. At alkyl chain lengths below *n*-butylbenzene the data points deviate from this linear relationship, with this deviation being most pronounced in the cases of toluene and ethylbenzene, and in all cases this is associated with enhanced retention on PGC compared to the longer chain analytes. The position of benzene was anomalous for PGC when compared to the shorter chain *n*-alkylbenzenes, but approximately in line with the retention of the higher *n*-alkylbenzenes.

A strong linear relationship between log P_{calc} and log k was observed for ODS (Fig. 4b). This result is in agreement with chromatography results on ODS by Kriz et al. [10]. For PGC however, the linear relationship was only observed at and above *n*-butylbenzene. This strongly mirrors the correlation between log k and alkyl chain length (Fig. 4a), again suggesting a different or additional interaction between the analyte and PGC at shorter alkyl chain lengths. The position of benzene in the retention series was again anomalous. It is of note however, that other authors have reported little

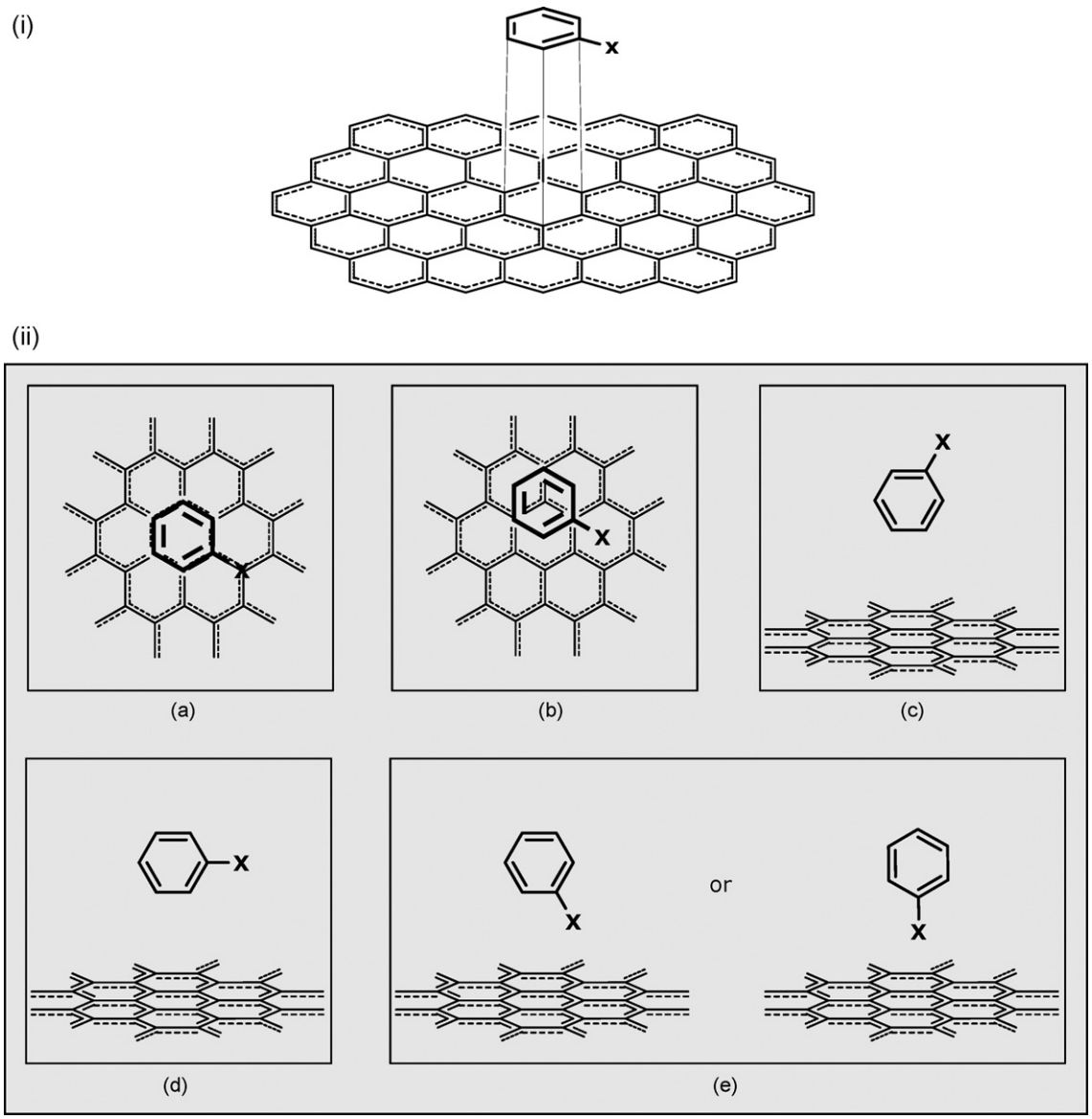


Fig. 2. Structure of the model graphite surface and geometries of alignment between the model surface and the alkylbenzene analytes. (i) The complete model graphite surface ($C_{78}H_{22}$), with an alkylbenzene analyte positioned in a cofacial geometry, and (ii) the five alternative geometries investigated in molecular modelling studies, showing part of the model surface with the analyte in bold; (a) cofacial geometry with no offset, (b) cofacial geometry with offset, (c) face-edge geometry with substituent directed away from the surface, (d) face-edge geometry with substituent directed parallel to the surface and (e) face-edge geometry with substituent directed towards the surface.

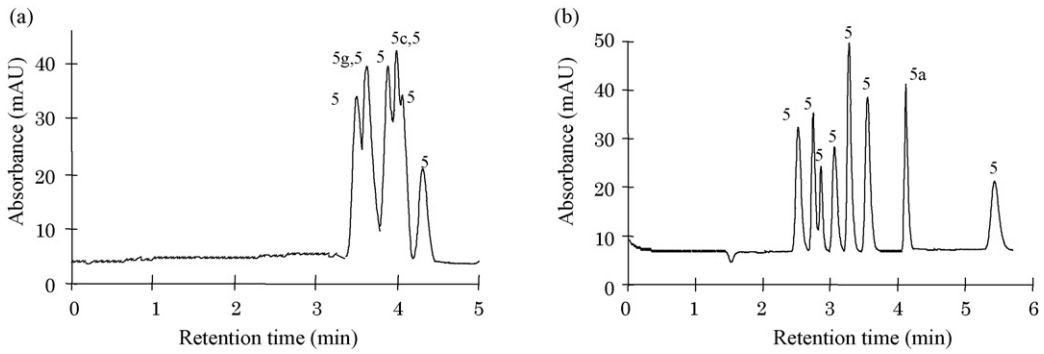


Fig. 3. Separation of pentylbenzene structural isomers on (a) ODS and (b) PGC. (analytes: 5, *n*-pentylbenzene; 5a, isopentylbenzene; 5b, (2-methylbutyl)benzene; 5c, (1-methylbutyl)benzene; 5d, neopentylbenzene; 5e, (1-ethylpropyl)benzene; 5f, (1,2-dimethylpropyl)benzene); 5g, *tert*-pentylbenzene.

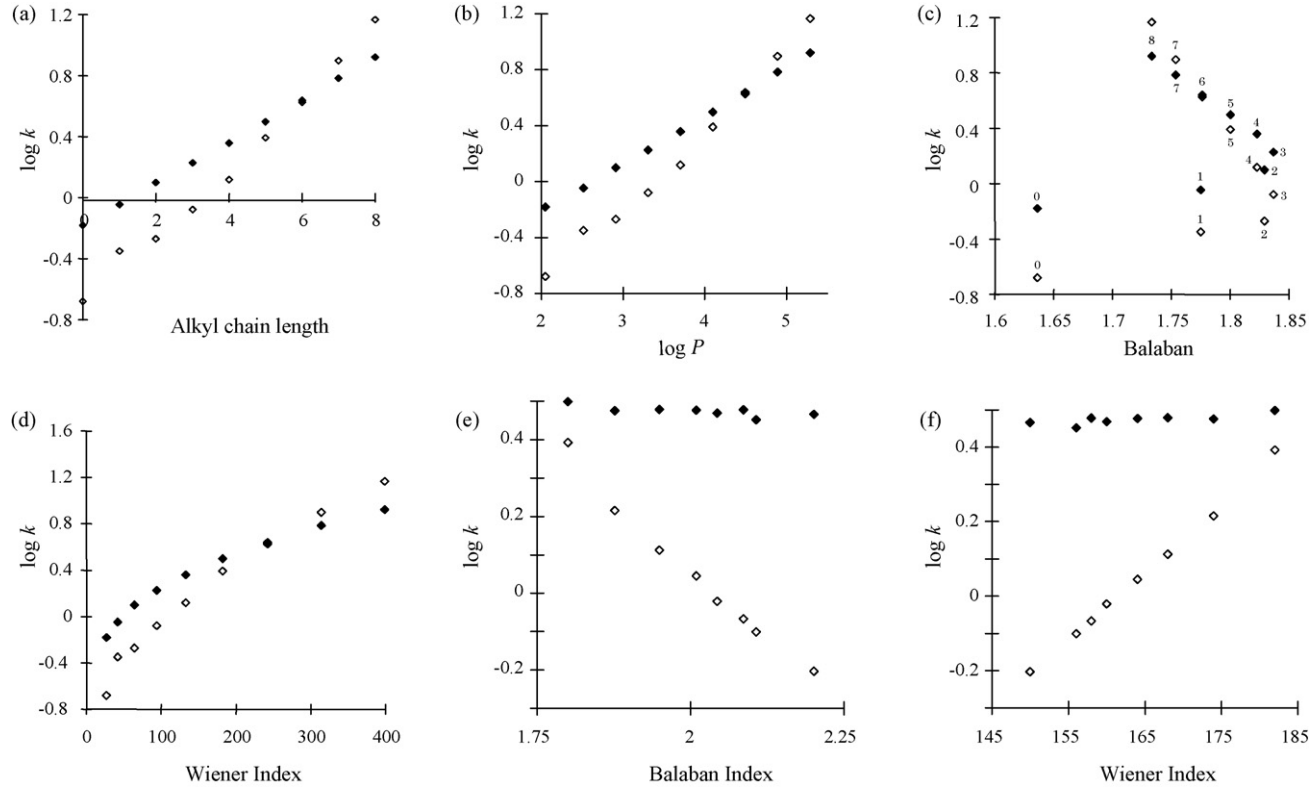


Fig. 4. The relationship between log k and (a) alkyl chain length, (b) log P_{calc}, (c) Balaban index (labels (0–8) indicate the length of the alkyl chain, e.g. 0 is benzene and 3 is n-propylbenzene), and (d) Wiener index for benzene and n-alkylbenzenes, and between log k and (e) Balaban index and (f) Wiener index for pentylbenzene structural isomers, on PGC (open diamonds) and ODS (solid diamonds).

correlation between retention on PGC and log P, when analytes of more varied polarity have been studied [11,6,27].

When considering all n-alkylbenzenes, the Balaban topological index [28,29] showed a low linear correlation coefficient with log k for both PGC and ODS (Fig. 4c and Table S2), although there was significant linearity for n-alkylbenzenes at or above n-propylbenzene on both stationary phases. The Wiener topological index [30,31] showed a high linear correlation coefficient with log k for both PGC and ODS (Fig. 4d), although a slight curvature in these relationships can be seen indicating a departure from the simple linear relationship. In both cases a lower Wiener index, which is associated with increased compactness and shorter alkyl chain length, was associated with decreased retention.

3.2.2. Pentylbenzenes

The correlations between structural descriptors and retention data for the pentylbenzene structural isomers are given in Fig. 4f and g, Fig. S3 and Table S3. The correlation between log P_{calc} and log k was poor for pentylbenzenes on PGC and ODS (Table S3), although slightly higher on ODS. A strong linear relationship was observed between log k and Wiener index on PGC, whilst on ODS the linear correlation is lower (Fig. 4f). Again a lower Wiener index, which is associated with increased compactness and increased branching of the pentyl group, was associated with decreased retention. A strong linear relationship was observed between log k and Balaban index on PGC, with again less linear correlation on ODS (Fig. 4e). A higher Balaban index, which indicates increased branching in the analyte, was associated with decreased retention. Wiener and Balaban indices are strongly related with a high cross-correlation coefficient ($r^2 = 0.992$).

Kriz et al. [10] found that whilst ODS could not distinguish between polymethylbenzenes and n-alkylbenzenes which were structural isomers, PGC offered complete resolution of these hydrocarbons. Details of bivariate linear regression analysis of log k values derived by Kriz et al. [10] with topological indices are provided in the supplementary material.

3.3. Molecular modelling

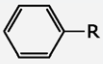
The energies of interaction between benzene and alkylbenzene analytes, and a model graphite surface are presented in Table 1. A more detailed treatment of the results is presented in the supplementary material.

3.3.1. n-Alkylbenzenes

The relationship between $E_{I(min)}$ and alkyl chain length, considering benzene and the 8 n-alkylbenzenes is shown in Fig. 5a, and shows striking similarities with the correlation observed between log k values on PGC and alkyl chain length (Fig. 4a). n-Alkylbenzenes below n-propylbenzene showed a stronger degree of association between analyte and model surface than might be expected by comparison with the longer chain analogues, which mirrors the retention observed for these analytes on PGC. Again, benzene behaviour is more in line with the longer chain analogues, than those smaller than n-propylbenzene. The data points for the two longest chain analogues show some departure from the linear central portion of the graph.

The geometry of strongest interaction between the analyte and the model surface shows some interesting trends. For benzene and for n-alkylbenzenes above n-propylbenzene, the face-edge geometry with the alkyl chain of the analyte directed towards the surface or parallel to the surface is most favourable (Fig. 2), whilst toluene and ethylbenzene have strongest interaction with the surface in a cofacial geometry. This different geometry of interaction may explain their relatively stronger retention on PGC as seen in chromatography studies.

Table 1
Interaction energies (E_I in kcal/mol) for a complex between a series of alkylbenzenes (including benzene) and a model graphite surface molecule. The E_I value which represents the strongest interaction of the given analyte with the surface, $E_{I(min)}$, is highlighted in bold.

Analyte	R = 	Cofacial		Face-edge			$E_{I(min)}$ (kcal/mol)
		No offset[a]	Offset[b]	x up[c]	x side[d]	x down[e]	
Benzene (0)	–H	0.068	−0.038	**−0.119**	**−0.119**	**−0.119**	−0.119
Toluene (1)	$-CH_3$	0.226	**−0.246**	0.682	−0.109	0.532	−0.246
Ethylbenzene (2)	$-CH_2CH_3$	**−0.262**	−0.216	0.175	−0.121	−0.259	−0.262
n-Propylbenzene (3)	$-CH_2CH_2CH_3$	0.152	−0.119	1.032	0.497	**−0.301**	−0.301
n-Butylbenzene (4)	$-(CH_2)_3CH_3$	−0.153	−0.006	0.475	−0.350	**−0.376**	−0.376
n-Pentylbenzene (5)	$-(CH_2)_4CH_3$	−0.050	0.021	−0.356	**−0.440**	−0.421	−0.440
Isopentylbenzene (5a)	$-(CH_2)_2CH(CH_3)_2$	0.349	0.187	0.402	0.513	**−0.197**	−0.197
(2-Methylbutyl)benzene (5b)	$-CH_2CH(CH_3)CH_2CH_3$	0.709	0.777	0.631	**0.068**	0.165	0.068
(1-Methylbutyl)benzene (5c)	$-CH(CH_3)CH_2CH_2CH_3$	0.628	0.292	**0.208**	0.824	0.523	0.208
Neopentylbenzene (5d)	$-CH_2C(CH_3)_3$	0.094	**−0.047**	0.371	2.357	0.835	−0.047
(1-Ethylpropyl)benzene (5e)	$-CH(CH_2CH_3)_2$	1.210	0.756	0.426	1.295	**0.041**	0.041
(1,2-Dimethylpropyl)benzene (5f)	$-CH(CH_3)CH(CH_3)_2$	0.342	0.352	0.411	**0.327**	1.012	0.327
tert-Pentylbenzene (5g)	$-C(CH_3)_2CH_2CH_3$	0.312	0.328	**0.251**	0.934	2.133	0.251
n-Hexylbenzene (6)	$-(CH_2)_5CH_3$	−0.134	−0.023	−0.366	**−0.487**	−0.478	−0.487
n-Heptylbenzene (7)	$-(CH_2)_6CH_3$	−0.201	−0.009	−0.136	−0.506	**−0.567**	−0.567
n-Octylbenzene (8)	$-(CH_2)_7CH_3$	−0.328	−0.098	−0.116	**−0.576**	−0.548	−0.576

[a–e]Geometries as shown in Fig. 2.

The relationship between $E_{I(min)}$ and $\log k$ is explored in Fig. 5b and shows a strong linear correlation ($r^2 = 0.979$), suggesting that $E_{I(min)}$ is able to predict and describe the experimentally observed retention of benzene and simple *n*-alkylbenzene analytes on PGC.

3.3.2. Pentylbenzenes

The relationship between $E_{I(min)}$ and $\log k$ for the 8 pentylbenzene structural isomers is shown in Fig. 5c, where a linear relationship can be seen but with lower correlation ($r^2 = 0.756$) than that seen with the *n*-alkylbenzenes.

All pentylbenzene isomers, with the exception of neopentylbenzene, have the strongest interaction with the model surface in a face-edge alignment. The isomers with the highest $E_{I(min)}$ values and hence lowest predicted interactions are 1,2-dimethylpropylbenzene, followed by *tert*-pentylbenzene and (1-methylbutyl)benzene. When compared with the experimental data, *tert*-pentylbenzene was the least retained isomer, with 1,2-dimethylpropylbenzene the second least retained, whilst (1-methylbutyl)benzene was fifth least retained. The preferred geometry with alkyl group pointed away from the surface in *tert*-pentylbenzene and (1-methylbutyl)benzene is of interest given the high degree of branching adjacent to the aromatic ring in these compounds. It is likely that in order to allow successful aromatic–aromatic interactions in these isomers, these bulky substituents are required to adopt this orientation.

The straight chain *n*-pentylbenzene and isopentylbenzene have the largest interactions with the model surface compared with the other pentylbenzenes, and this trend is reflected in the chromatography data, with these two isomers being the most retained. Despite the lower overall linear correlation observed between $E_{I(min)}$ and $\log k$ with the pentylbenzene structural isomers, the calculated $E_{I(min)}$ was able to predict the two most

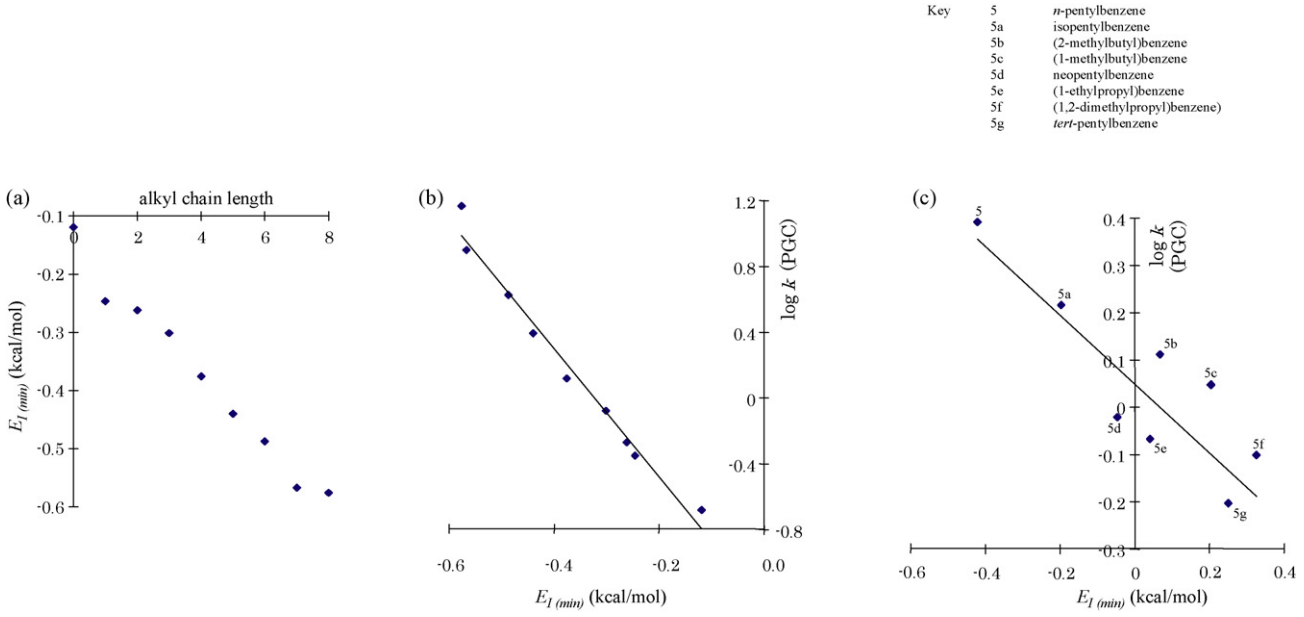


Fig. 5. The relationships between $E_{I(min)}$ and alkyl chain length and between $E_{I(min)}$ and $\log k$ on PGC; (a) and (b) for *n*-alkylbenzenes and (c) for pentylbenzene isomers.

retained isomers and two of the three least retained isomers correctly.

4. Conclusions

Novel molecular modelling calculations have provided interesting insights into the role of aromatic stacking interactions in retention on PGC. A strong linear correlation between retention of the *n*-alkylbenzenes on PGC and the calculated minimum interaction energy between the graphite surface and the analyte was observed, suggesting the ability of these energy values to predict retention behaviour in this structurally similar series of analytes; further studies would be required to assess whether similar trends occur with more structurally diverse molecules. For the pentylbenzenes a weaker correlation between log *k* and minimum interaction energy was observed, but interestingly the two most retained isomers and two of the three least retained isomers were correctly predicted from calculated minimum interaction energy values. Calculations have shown that for alkylbenzenes with high branching at the position adjacent to the ring, the preferred geometry of association with the surface is with the branched chain directed away from the surface, a geometry not seen in less branched structures. This supports the results from QSRR, where strong linear correlations between Wiener and Balaban indices, and retention on PGC, were observed for the pentylbenzene isomers, suggesting that more compact analytes, associated with increased branching of the alkyl chains, decreased retention. These results therefore suggest that steric/conformational factors that limit the degree of contact between the analyte and surface reduce retention. The most energetically favoured orientation for interaction between analytes and the PGC surface was found to be cofacial for toluene and ethylbenzene, whereas for other analytes (except neopentylbenzene) this interaction was in a face-edge orientation. The alternative geometry of association for both toluene and ethylbenzene may explain the relatively enhanced retention of these analytes on PGC compared with their longer chain analogues.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2010.08.023.

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