Topically resolved intramolecular CH-π interactions in phenylalanine derivatives†

W. Brian Jennings,*[a] Noel J. P. McCarthy,[a] Padraig Kelly[a] and John F. Malone*[b]

Received 4th August 2009, Accepted 24th September 2009
First published as an Advance Article on the web 27th October 2009
DOI: 10.1039/b916021n

NMR spectra of imines and nitrones derived from benzophenone and phenylalanine or tyrosine show clear evidence of an aromatic edge-to-face interaction in solution. At low temperatures the two *ortho* protons of the edge interacting phenyl ring become topically resolved with the *ortho* proton NMR signal involved in the CH-π interactions shifted well upfield (δ 5.4–5.8 at –88 °C) of the other *ortho* signal. Introduction of a *para* substituent into the phenylalanine ring has a modest effect on the upfield shift. The edge-to-face arrangement also manifests in the X-ray crystal structures of two of these compounds. Barriers to rotation around the *syn* phenyl-imino bond are also reported (10.5–11.1 kcal mol^{-1}).

Introduction

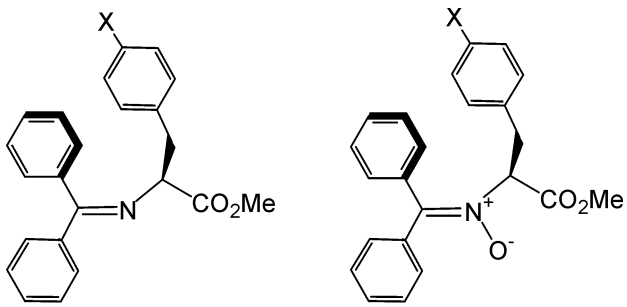
General interest in aromatic CH-π interactions was largely initiated in the 1980s by recognition of their importance in protein structure[1] and host binding in supramolecular systems.[2] These interactions are also important in crystal engineering,[3] molecular recognition[4] and some drug receptor binding interactions.[5,6] Further insight into the nature and strength of these weak interactions has been provided by molecular orbital calculations on the benzene dimer system.[7] Several model systems have been synthesised where single intramolecular aromatic CH-π interactions can be assessed in solution by NMR and/or in the solid state by X-ray crystallography.[8] These include the Grossel aryl cyclohexadiene model,[9] the conformationally restricted cyclophanes of Kim, Fukazawa and Gellman,[10] the Wilcox 'torsion balance',[11] the Gellman carboxylic acid and amides,[12] the Gung triptycene system,[13] and our own imino and biaryl systems.[14,15] Hunter and co-workers have devised an interesting alternative procedure involving mutant cycles for assessing intermolecular aromatic CH-π interactions.[16]

In previous model compounds where intramolecular edge-to-face interactions involving phenyl rings have been observed by NMR in solution, the edge orientated *ortho* (or *meta*) proton is in a fast dynamic exchange with the other *ortho* (or *meta*) proton due to rapid rotation of the phenyl ring about its two-fold axis. This leads to a single time averaged signal for these two protons, and any observed upfield shift due to ring current shielding from a face oriented aromatic ring is thereby reduced by 50%. In order to circumvent this problem, our previous investigations[14,15] in this area employed compounds where one *ortho* position was blocked by a substituent. Nevertheless the possibility remains that a significant population of a second conformation with the *ortho* substituent directed towards the second aromatic ring, and the single *ortho* proton directed away, could reduce the magnitude of the observed upfield shift.

We now report an improved 'topically resolved' model where rotation of the edge orientated phenyl ring is sufficiently restricted to enable the interacting *ortho* proton to be independently observed by NMR investigations at low temperature.

Results and discussion

Compounds **1–3** (Fig. 1) were prepared by a transimination procedure devised by O'Donnell and Polt.[17] Direct imination of benzophenone with amino acid esters is problematic due to the low reactivity of diaryl ketones and the tendency of amino acid esters to dimerise on heating in the presence of Lewis acid catalysts such as titanium tetrachloride.



1 X = H
2 X = OH
3 X = NO_2

4 X = H
5 X = OH
6 X = NO_2

Fig. 1 Structures of compounds **1–6**

The ^{1}H NMR spectra of these three compounds in deuteriochloroform at ambient temperature were in agreement with their structures except that an anomalous broadened doublet signal integrating for two protons was observed at δ 6.6–6.7 for imines **1**, **2**, and **3** (Table 1). Imines **1** and **2** have been reported previously,[18,19] but the broadening and unusual upfield shift of this signal was not

[a]*Department of Chemistry and Analytical & Biological Chemistry Research Facility, University College Cork, Cork, Ireland. E-mail: brianj@ucc.ie*
[b]*School of Chemistry & Chemical Engineering, The Queen's University of Belfast, Belfast, Northern Ireland, UK, BT9 5AG. E-mail: j.malone@qub.ac.uk*

† CCDC reference numbers 739741–739743. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b916021n

Table 1 Selected ^{13}C and ^{1}H chemical shifts for compounds **1–6**

Compd	$^{13}C{=}N$ (25 °C)[a]	$=N\text{-}^{13}C$ (25 °C)[a]	Ho + Ho′ (25 °C)[a]	Ho (−88 °C)[b]	Ho′ (−88 °C)[b]
1	170.9	67.2	6.60	5.52	7.14
2	171.3	67.4	6.64	5.78	7.14
3	171.6	66.3	6.69	5.71	7.17
4	147.5	73.8	6.58	5.26	7.45
5	148.0	73.8	6.65	5.45	7.41
6	148.0	72.9	6.70	5.49	7.50

[a] Solvent $CDCl_3$. [b] Solvent CD_2Cl_2 set at δ 5.32.

commented upon. A 2D-COSY spectrum of imine **1** confirmed that this broad signal was from aromatic protons as it was coupled to a signal at δ 7.27 in the normal aromatic envelope. A HMBC experiment on **1** was conducted at 70 °C in 1,1,2,2-tetrachloroethane-d_2, where the upfield aromatic signal was a well resolved doublet. The imino carbon signal at δ 170.7 gave a three-bond correlation with the upfield aromatic doublet (2H) at δ 6.72 and with a second 2H aromatic doublet at δ 7.61. Accordingly these doublet signals can be confidently assigned to the *ortho* protons on the imino phenyl rings. A third 2H doublet at δ 7.07 showed a three-bond HMBC correlation with the benzylic methylene carbon at δ 39.6, indicating that this 2H doublet belongs to the *ortho* protons on the N-terminal benzyl ring.

Previously reported imines derived from *ortho*-substituted acetophenones and phenylalanine esters also exhibit a similar upfield doublet signal in the *Z*-isomer where the aromatic ring is *syn* to the N-alkyl substituent.[14] Hence the upfield 2H doublet in the present series of compounds can be confidently assigned to the equivalent *ortho* hydrogens Ho and Ho′ on the phenyl ring located *syn* to the amino acid ester side chain (Fig. 2). The position of this signal is well upfield of the region (*ca.* δ 7.5–8.0) where *ortho* hydrogens would normally be expected for a phenyl ring attached to an electron withdrawing C=N moiety. Indeed the *ortho* hydrogens of the *anti* phenyl ring in imines **1–3** resonate at δ 7.56–7.59 in deuteriochloroform.

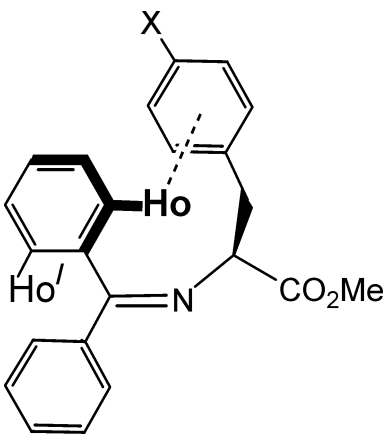


Fig. 2 Illustration showing the edge-to-face CH-π interaction involving close contact with Ho.

Abnormal signal broadening as observed for the upfield aromatic signal in compounds **1–3** can be indicative of an exchange process that is becoming slow on the NMR timescale. Accordingly a low temperature study was conducted on compounds **1–3** in dichloromethane-d_2. On lowering the temperature the upfield aromatic signal broadened further and below −30 °C it split into two widely separated broad components. These component signals were well resolved at −88 °C into an upfield doublet at δ 5.5–5.8 integrating for one proton, and a lower field signal at δ 7.14–7.17 also integrating for one proton (Table 1). The position of the latter signal was confirmed by a 2D EXSY spectrum on imine **1** at −88 °C as it lay underneath a doublet signal from the two *ortho* protons of the benzyl ring. Variable temperature spectra of imine **1** are depicted in Fig. 3.

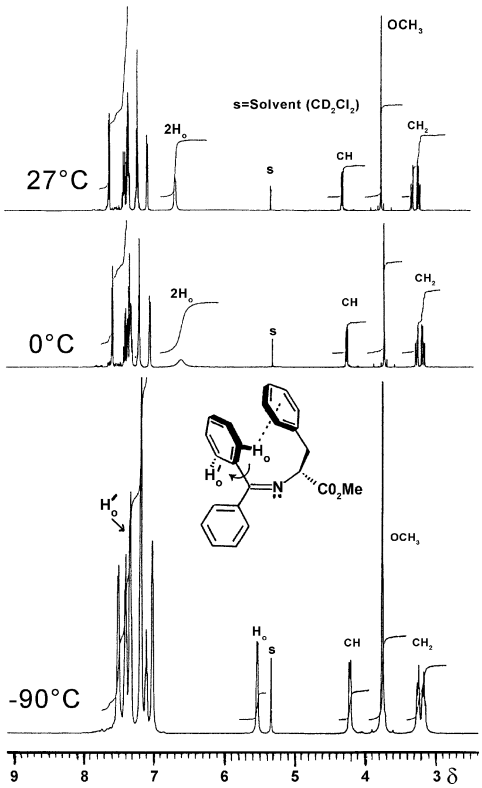


Fig. 3 Variable temperature ^{1}H NMR spectra of imine **1** in CD_2Cl_2 (**s** denotes the residual solvent signal).

Clearly the two *ortho* hydrogens (Ho and Ho′) on the *syn* phenyl ring (Fig. 2) have become diastereotopically resolved on the NMR timescale at low temperature due to slow rotation about the phenyl-imino bond combined with the stereogenic centre in the amino-ester moiety. These signals are unusually widely separated by 1.62, 1.36 and 1.46 ppm in **1**, **2** and **3**, respectively, and the higher field signal (Ho) is far outside the normal region for the aromatic signals. An upfield shift of this magnitude can only be rationalised by a well populated edge-to-face molecular conformation in solution where one *ortho* proton (Ho) in the *syn* imino phenyl ring is positioned above, and relatively close to, the face of the terminal phenyl ring of the phenylalanine moiety (Fig. 2). This does not necessarily mean that the edge-to-face conformer is the only populated conformation in solution. Indeed we believe that at least one other conformation is significantly populated especially at higher temperature. The signal position of the upfield Ho signal below coalescence moves steadily further upfield by *ca.* 0.06 ppm for each 10° decrease in temperature. This is consistent with a rapid dynamic conformational equilibrium between the 'closed'

edge-to-face conformer and a second higher enthalpy 'open' conformer where the phenylalanine moiety is remote from the *ortho* proton Ho.[8,14] There is considerable conformational freedom in solution about the sidechain N–CH, CH–CH_2 and CH_2–phenyl single bonds, and indeed more than one alternative conformer could be appreciably populated, especially at higher temperatures. The alternative 'open' conformation(s) are likely to be entropically favoured over the constrained edge-to-face conformation, and therefore more populated at higher temperatures.[8,14]

It is evident from Table 1 that the *para* substituent on the facially orientated benzylic ring has a modest effect on the chemical shift of the Ho signal at –88 °C. This signal moves further downfield by 0.26 and 0.19 ppm when the *para* hydrogen is replaced by an OH or NO_2 group respectively. A similar trend is present in the nitrones **4–6** (see below), indicating that this relatively small substituent effect is not an artefact. The effect can be attributed to a slight weakening of the edge-to-face interaction by both these *para* substituents. An alternative possibility that the chemical shift changes are primarily due to alterations in the ring current shielding of Ho can probably be excluded as the π-donating OH and electron withdrawing NO_2 substituents would have opposite effects on the ring current density. The weakening of the CH-π interaction is likely to be manifested in an increase of the population of the alternative open conformer(s) in dynamic equilibrium with the major closed form, or possibly a slightly increased contact distance between the phenyl rings. Molecular orbital calculations on model systems[20] indicate that introduction of a nitro group into the face orientated ring reduces the energy of the CH-π interaction by *ca.* 0.23–0.30 kcal mol^{-1} in chloroform solution which would be consistent with the present experimental observations. However the MO calculations also predict that an OH substituent should have a very small effect (< 0.1 kcal mol^{-1}) on the interaction energy in solution, in contrast to the present results. Experimental investigations on the Wilcox system by Diederich and co-workers also indicate that a nitro substituent on the face orientated ring appreciably weakens the CH-π interaction but a hydroxyl substituent has only a very minor weakening effect.[11] However the Wilcox system has an edge-tilted-T geometry with two intramolecular CH-π interactions whereas the present system has face-tilted-T geometry and a single intramolecular CH-π interaction. More recently Cockroft and Hunter have postulated that solvent effects play a significant role in determining the magnitude of substituent effects in the Wilcox, and possibly other systems.[11] Further experimental investigations of substituent effects on aromatic CH-π interactions may be required to clarify the situation.

The co-ordinates of Ho relative to the tyrosine ring centre, determined from X-ray crystallographic data (see below) for compound **2** and the Johnson–Bovey ring current tables,[21] gives a predicted estimate of a *ca.* 2.6 ppm upfield shift of proton Ho in the observed edge-to-face arrangement (see below). This is somewhat greater than the measured upfield shift of 1.36 ppm for Ho relative to Ho′ in imine **2** measured at –88 °C (Table 1). This could be due to inaccuracies in ring current model and/or a time averaged shift contribution from one (or more) open conformers in solution, even at this low temperature where entropy contributions ($T\Delta S$) to conformational free energies are reduced.

A single-crystal X-ray structure analysis of imine **2** showed that, in the solid state, the molecule adopts a closed conformation in which the *ortho* proton Ho (on C3, Fig. 4) of the benzophenone

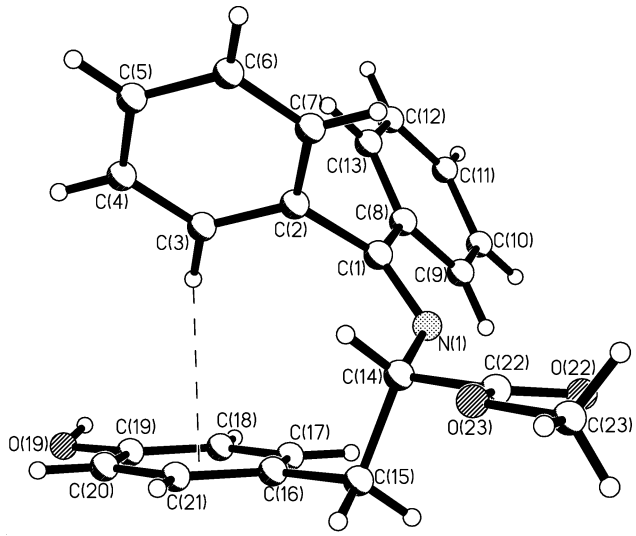


Fig. 4 X-Ray structure of imine **2**.

ring located *syn* to the amino acid ester side-chain lies above the face of the phenyl ring of the tyrosine moiety. With Ho positioned to give a C–H bond length of 1.083 Å (*i.e.* the standard value obtained from neutron diffraction determination of the position of the hydrogen nucleus, and used in earlier studies as a normalised distance[8]) the geometry of the edge-to-face interaction is as follows: the Ho to ring centroid distance is 2.60 Å; the perpendicular distance from Ho to the ring plane is 2.59 Å and the point of intersection of this perpendicular onto the ring plane is offset by 0.24 Å from the ring centroid. These distances are among the shortest found in previous edge-to-face contacts[8] and represent a substantial interaction. Moreover the dihedral angle between the interacting ring planes is 50°, typical of angles found in earlier examples of edge-to-face interactions with face-tilted-T geometry.[8]

Nitrones 4–6

Imines **1–3** were oxidised with *meta*-chloroperoxybenzoic acid or its complex with potassium fluoride. NMR spectra of the resulting crude products indicated the presence of some of the desired nitrone together with a mixture of diastereoisomeric oxaziridines. The more polar nitrones **4–6** (Fig. 1) were readily isolated from the mixture by flash column chromatography. The ^{1}H and ^{13}C NMR spectra of the nitrones showed broadly similar features to the parent imines except that the low field $^{13}C{=}N$ signal at δ 171 in the imines was absent in the nitrones. A HMBC spectrum was recorded on nitrone **4** at –88 °C in dichloromethane-d_2 (where the exchanging Ho and Ho′ doublet signals were well resolved). It exhibited cross peaks due to $^{3}J_{CCCH}$ coupling between a quaternary carbon at δ 147.5 and the *syn* phenyl Ho and Ho′ protons at δ 5.26 and δ 7.45, plus a 2H doublet signal at δ 7.78 assigned to the *ortho* protons on the phenyl ring *anti* to the N-alkyl moiety. Accordingly the quaternary carbon at δ 147.5 can be assigned to an unusually shielded C=N resonance in nitrones. It can also be seen (Table 1 and NMR data in the Experimental Section) that the N–^{13}C and NCH proton signals are shifted further downfield in the nitrones (by *ca.* 6.5 and 0.67 ppm respectively) due to the adjacent polar N-oxide moiety. As in the imines, the ^{1}H NMR spectra of nitrones

4–6 recorded at ambient temperature in deuteriochloroform displayed a broad upfield aromatic signal at δ 6.58–6.70 which integrated for two protons (Table 1). This signal was broader than that observed in the imines **1–3** due to a slightly higher barrier to rotation about the *syn* phenyl imino bond in the nitrones (see below).

On cooling samples of nitrones **4**, **5** and **6** in dichloromethane-d_2 this signal collapsed into the baseline, and below –30 °C it split into two equally intense components (Fig. 5). At –88 °C two new doublet signals were evident at δ 5.26–5.49 and δ 7.4–7.5 assigned to Ho and Ho′ respectively (Table 1). Unlike the situation in the imines the downfield Ho′ signal was not overlapped by other aromatic signals, but nevertheless the assignment of this signal as the exchanging partner of Ho was confirmed by a 2D EXSY experiment on nitrone **4** at –88 °C. The Ho signal in nitrones **4–6** is *ca.* 0.3 ppm upfield from the corresponding imines **1–3** while the Ho′ signal is 0.2–0.3 ppm further downfield in the nitrones (Table 1). Accordingly the chemical shift separation between Ho and Ho′ (1.96–2.19 ppm) in the nitrones is significantly larger than that in the imines. This could indicate a stronger edge-to-face interaction and/or a reduced population of alternative open conformers in the nitrones. The predicted ring current shielding of Ho for nitrone **6** using the Johnson–Bovey model[21] and the X-ray co-ordinates (see below) is 2.0 ppm. This is in excellent agreement with the measured chemical shift difference of 2.01 ppm (Table 1) between Ho and Ho′ in **6**. As discussed in the imine section, the presence of a *para*-nitro or *para*-hydroxy substituent on the terminal benzyl ring somewhat reduces the upfield shift of Ho′ in nitrones **5** and **6**. This may be due to a slight weakening of the CH-π interaction.

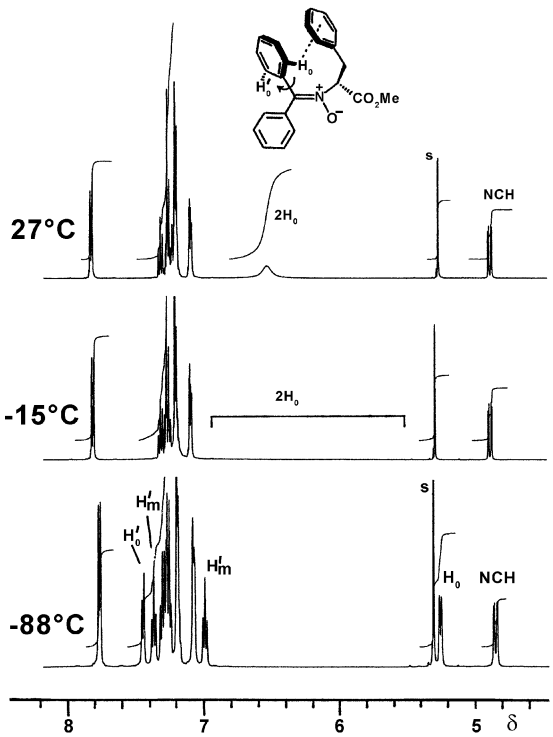


Fig. 5 Variable temperature ^{1}H NMR spectra of nitrone **4** in CD_2Cl_2 (**s** denotes the residual solvent signal).

Nitrone crystal structures

A single-crystal X-ray structure analysis of nitrone **6** showed that, in the solid state, the molecule adopts a closed conformation very similar to that of imine **2**. The *ortho* proton Ho (on C3, Fig. 6) of the benzophenone ring located *syn* to the amino acid ester side-chain lies above the face of the phenyl ring of the phenylalanine moiety. The Ho to ring centroid distance is 2.86 Å; the perpendicular distance from Ho to the ring plane is 2.85 Å and the point of intersection of this perpendicular to the plane is offset by 0.17 Å from the ring centroid. The inter-plane angle is 39°. While the distances are longer than those of imine **2**, and the inter-plane angle is shallower, these dimensions are still consistent with a face-tilted-T edge-to-face interaction.[8]

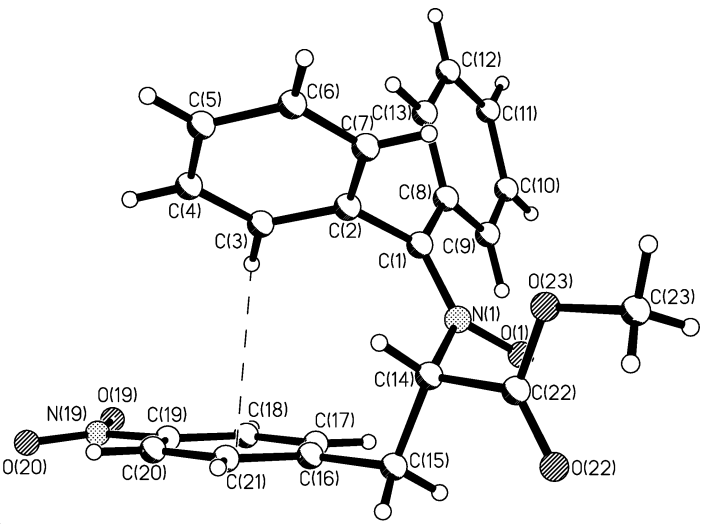


Fig. 6 X-Ray structure of nitrone **6**.

Nitrone **4** (Fig. 7), on the other hand, adopts a conformation in the solid state which puts the corresponding dimensions beyond the distances appropriate to an edge-to-face interaction. The conformational differences are illustrated by the torsion angles in Table 2 and by Fig. 4, 6 and 7 which show imine **2** and nitrones **6** and **4**, respectively, from a similar perspective with respect to the imine/nitrone planes.

Table 2 Selected bond angles and torsion angles from X-ray crystallographic data

Angle (°)	Imine **2**	Nitrone **6**	Nitrone **4**
C1-N1-C14	120.1	122.5	122.6
N1-C1-C2	125.7	119.1	121.6
N1-C1-C8	117.6	122.3	120.6
C1-N1-C14-C15	110.5	116.6	116.7
N1-C14-C15-C16	–60.3	–68.0	–48.7
N1-C1-C2-C3	–100.8	–96.3	–121.6
N1-C1-C2-C7	81.7	86.5	63.6
N1-C1-C8-C9	11.6	20.8	40.0
N1-C1-C8-C13	–169.1	–159.4	–144.5
C14-C15-C16-C17	83.3	93.5	121.7
C14-C15-C16-C21	–95.6	–87.0	–58.4

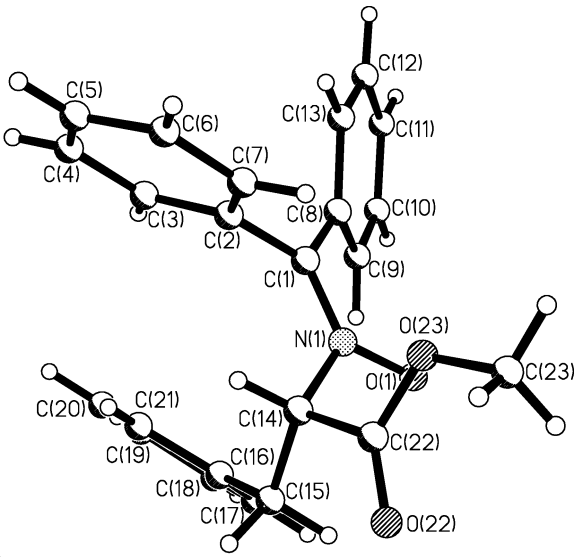


Fig. 7 X-Ray structure of nitrone **4**.

Phenyl-imino rotational barriers

Rates of rotation around the phenyl-imino bond *syn* to the N-alkyl group were determined for the representative imines **1** and **2** and nitrones **4** and **6** by computer assisted analysis of the coalescing Ho and Ho′ doublet signals. An additional signal collapse and eventual modest splitting involving triplet signals was also evident in the central aromatic region of the imines and nitrones at low temperature. This was due to the *meta* protons on the *syn* phenyl ring also becoming non-equivalent due to the slow phenyl-imino bond rotation.

The results (Table 3) show that the remote *para* substituents on the N-terminal benzylic ring have a negligible effect on the imino-phenyl rotational barrier. However, the rotational barrier in the nitrones **4** and **6** is appreciably higher (by 0.6 kcal mol^{-1}) than in the imines **1** and **2**. Buttressing effects from the N–O group in the nitrones and associated bond angle changes at the imino carbon are probably responsible for the increased rotational barriers in the nitrones. Thus the X-ray data (Table 2) show that the *syn* Ph–C=N bond angle (N1–C1–C2) is reduced in nitrones **4** and **6** by 4–6° compared with imine **2**. This places the *syn* phenyl group closer to the N-alkyl moiety thereby increasing the passing interactions in the rotational transition state.

The Ph_2C=X torsional system can be described as a two-bladed propeller. The rotational barriers in these compounds will be dominated by steric passing interactions between the *ortho* hydrogens Ho and Ho′ and the hydrogens on the *syn* N-alkyl moiety and the geminal *anti* phenyl ring as the *syn* phenyl ring rotates through the imino plane. The calculated phenyl rotational barrier (molecular mechanics and *ab initio* MO) in benzophenone (Ph_2C=O) is very small (1.3–1.6 kcal mol^{-1}),[22] hence the major contribution to the *syn* phenyl rotational barrier in compounds **1–6** is likely to be the passing interaction with the N-alkyl moiety The steric effects in the rotational transition state may be slightly offset by increased conjugation between the co-planar *syn* phenyl and imino systems, but this is likely to be reduced by a loss in conjugation involving the *anti* phenyl group which will probably twist out of plane to minimise steric contact with co-planar *syn* phenyl group. The CH-π interaction may make a minor contribution to the *syn* phenyl rotational barrier as this stabilising interaction is likely to be lost in the rotational transition state. The NMR data indicate that rotation about the much less hindered *anti* phenyl-imino bond in **1–6** remains fast on the NMR timescale down to −88 °C as the *ortho* proton doublet signal from this ring does not broaden and split into two components.

Table 3 Barriers to rotation around the *syn* phenyl-imino bond[a]

Compound	T/°C	k/s^{-1}	$\Delta G^{\neq}$/kcal mol^{-1}
1	−30[b]	1400	10.6
2	−42[c]	590	10.5
4	−15[b]	2400	11.1
6	−15[b]	2200	11.1

[a] Determined in CD_2Cl_2 by 500 MHz ^{1}H NMR lineshape analysis. [b] Coalescence temperature. [c] Lineshape analysis performed around 10° below coalescence due to overlap with tyrosinate ring signals.

Experimental

Preparation of imines 1–3

These imines were prepared from benzophenone imine and the appropriate phenylalanine methyl ester hydrochloride by the transimination methodology of O'Donnell and Polt,[17,18] and purified by flash column chromatography on silica gel using hexane–ethyl acetate as eluent (yields 75–90%).

Methyl *N*-diphenylmethylene-L-phenylalaninate 1. Previously characterised;[18] δ_H (500 MHz, $CDCl_3$) 3.18 (1 H, dd, J 13.3 and 9.4, H_A of CH_2), 3.28 (1H, dd, J 13.3 and 4.2, H_B of CH_2), 3.73 (3H, s, OCH_3), 4.27 (1H, dd, J 9.4 and 4.2, NCH_X), 6.60 (2H, br d, *o*-Ph *syn*), 7.03 (2H, d, *o*-benzyl), 7.2–7.4 (9H, m, *m*- and *p*-Ph/Bn), 7.57 (2H, d, *o*-Ph *anti*); δ_C (125.8 MHz, $CDCl_3$) 39.8 (CH_2), 52.2 (OCH_3), 67.2 (NCH), 126.3 (CH), 127.6 (2CH), 128.0 (2CH), 128.13 (2CH), 128.15 (2CH), 128.3 (CH), 128.8 (2CH), 129.8 (2CH), 130.3 (CH), 136.0 (Ph Cq), 137.9 (Ph Cq), 139.4 (Bn Cq), 170.9 (C=N), 172.3 (C=O).

Methyl *N*-diphenylmethylene-L-tyrosinate 2. Colourless crystals, mp 130–131 °C (from hexane–ether), (Found: C, 76.7; H, 5.9; N, 3.95. $C_{23}H_{21}NO_3$ requires C, 76.9; H, 5.9; N, 3.9); δ_H (500 MHz, $CDCl_3$) 3.10 (1H, dd, J 13.5 and 9.4, H_A of CH_2), 3.19 (1H, dd, J 13.5 and 4.3, H_B of CH_2), 3.72 (3H, s, OCH_3), 4.22 (1H, dd, J 9.4 and 4.3, NCH_X), 4.79 (1H, s, OH), 6.65 (2H, d, Bn *ortho* to OH), 6.66, (2H, d, *o*-Ph *syn*), 6.89 (2H, d, Bn *meta* to OH), 7.3–7.4 (6H, m, *m*- and *p*-Ph), 7.57 (2H, d, *o*-Ph *anti*); δ_C (75.5 MHz, $CDCl_3$) 38.8 (CH_2), 52.2 (OCH_3), 67.4 (NCH), 115.0 (2CH), 127.6 (2CH), 128.0 (2CH), 128.2 (2CH), 128.4 (CH), 128.8 (2CH), 129.5 (Bn Cq), 130.3 (CH), 130.9 (2CH), 136.0 (Ph Cq), 139.2 (Ph Cq), 154.4 (Bn Cq-OH), 171.3 (C=N), 172.5 (C=O).

Crystal data for 2

$C_{23}H_{21}NO_3$, M = 359.4, orthorhombic, a = 9.212(2), b = 10.822(3), c = 19.309(5) Å, U = 1924.9(9) Å^3, T = 150(2) K, Mo-Kα radiation, λ = 0.71073 Å, space group $P2_12_12_1$ (no. 19), Z = 4, $F(000)$ = 760, D_x = 1.240 g cm^{-3}, μ = 0.082 mm^{-1}, Bruker SMART CCD area detector diffractometer, ϕ/ω scans, 4.2° < 2θ < 52.8°, measured/independent reflections: 20 500/3936,

R_{int} = 0.038, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a different Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.035 for 3447 data with $F_o > 4\sigma(F_o)$, 246 parameters, wR_2 = 0.085 (all data), GoF = 1.05, $\Delta\rho_{min,max}$ = –0.14/0.15 e Å^{-3}. CCDC 739743.

Methyl *N*-diphenylmethylene-L-4-nitrophenylalaninate 3. Colourless crystals, mp 78–80 °C (from hexane), (Found: C, 71.25; H, 5.2; N, 7.1. $C_{23}H_{20}N_2O_4$ requires C, 71.1; H, 5.2; N, 7.2); δ_H (500 MHz, $CDCl_3$) 3.30 (1 H, dd, *J* 13.3 and 9.0, H_A of CH_2), 3.35 (1H, dd, *J* 13.3 and 4.3, H_B of CH_2), 3.75 (3H, s, OCH_3), 4.32 (1H, dd, *J* 9.0 and 4.3, NCH_X), 6.69 (2H, br d, *o*-Ph *syn*), 7.21 (2H, d, Bn *meta* to NO_2) 7.3–7.4 (6H, m, *m*- and *p*-Ph), 7.56 (2H, d, *o*-Ph *anti*) 8.06 (2H, d, Bn *ortho* to NO_2); δ_C (125.8 MHz, $CDCl_3$) 39.5 (CH_2), 52.5 (OCH_3), 66.3 (NCH), 123.3 (2CH), 127.5 (2CH), 128.2 (2CH), 128.4 (2CH), 128.8 (2CH), 128.8 (CH), 130.65 (2CH), 130.7 (CH), 135.7 (Ph Cq), 138.9 (Ph Cq), 146.0 (Bn Cq), 146.7 (Bn Cq-NO_2), 171.58 (C=N), 171.63 (C=O).

Preparation of nitrones. Nitrones **4** and **5** were obtained by stirring an equimolar mixture of the appropriate imine **1** or **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane for *ca.* 24 h. The required quantity of commercial 70–75% *m*-CPBA was first dissolved in dichloromethane and dried over $MgSO_4$ to remove the water present in the *m*-CPBA, followed by filtration and addition of the imine. After standing for 24 h the reaction mixture was washed with aqueous sodium sulfite (1.0 M), then aqueous sodium bicarbonate (1.0 M), water, and dried ($MgSO_4$). ^{1}H NMR spectra of the crude product indicated the presence of the desired nitrone together with a mixture of diastereoisomeric oxaziridines produced by epoxidation of the imino bond in competition with N-oxidation. Flash column chromatography on silica gel eluting with hexane-ether afforded the more polar nitrone as the last eluted material. Due partly to the formation of considerable oxaziridine co-products the isolated yield of nitrone was low (*ca.* 10%).

Methyl *N*-diphenylmethylene-L-phenylalaninate-*N*-oxide 4. Colourless crystals, mp 139–140 °C from hexane–EtOAc (Found: C, 77.35; H, 5.9; N, 3.9. $C_{23}H_{21}NO_3$ requires C, 76.9; H, 5.9; N, 3.9%); δ_H (500 MHz, $CDCl_3$) 3.16 (1 H, dd, *J* 13.8 and 3.6, H_A of CH_2), 3.69 (1H, dd, *J* 13.8 and 11.1, H_B of CH_2), 3.81 (3H, s, OCH_3), 4.93 (1H, dd, *J* 11.1 and 3.6, NCH_X), 6.58 (2H, br s, *o*-Ph *syn*), 7.14 (2H, d, *o*-benzyl), 7.2–7.4 (9H, m, *m*- and *p*-Ph/Bn), 7.87 (2H, d, *o*-Ph *anti*); δ_C (75.5 MHz, $CDCl_3$) 35.1 (CH_2), 53.2 (OCH_3), 73.8 (NCH), 127.1 (CH), 127.8 (2CH), 128.5 (2CH), 128.7 (2CH), 129.2 (CH), 129.5 (2CH), 129.6 (2CH), 129.9 (CH), 130.3 (2CH), 133.3 (Ph Cq), 135.0 (Ph Cq), 136.4 (Bn Cq), 147.5 (C=N), 167.8 (C=O); *m*/*z* (EI) 359.1498 (M^+), $C_{23}H_{21}NO_3$ requires 359.1521.

Crystal data for 4

$C_{23}H_{21}NO_3$, *M* = 359.4, orthorhombic, *a* = 9.729(2), *b* = 10.168(2), *c* = 18.965(4) Å, *U* = 1876.1(7) Å^3, *T* = 150(2) K, Mo-Kα radiation, λ = 0.71073 Å, space group $P2_12_12_1$ (no. 19), *Z* = 4, *F*(000) = 760, D_x = 1.272 g cm^{-3}, μ = 0.084 mm^{-1}, Bruker SMART CCD area detector diffractometer, ϕ/ω scans, 4.3° < 2θ < 52.8°, measured/independent reflections: 19 868/3843, R_{int} = 0.021, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a different Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.031 for 3457 data with $F_o > 4\sigma(F_o)$, 246 parameters, wR_2 = 0.080 (all data), GoF = 1.05, $\Delta\rho_{min,max}$ = –0.17/0.16 e Å^{-3}. CCDC 739741.

Methyl *N*-diphenylmethylene-L-tyrosinate-*N*-oxide 5. Colourless crystals, mp 79–81 °C from hexane–EtOAc; δ_H (500 MHz, $CDCl_3$) 3.13 (1 H, dd, *J* 14.1 and 3.5, H_A of CH_2), 3.72 (1H, dd, *J* 14.1 and 11.2, H_B of CH_2), 3.85 (3H, s, OCH_3), 4.90 (1H, dd, *J* 11.2 and 3.6, NCH_X), 6.65 (2H, br s, *o*-Ph *syn*), 6.72 (2H, d, Bn *ortho* to OH), 7.05 (2H, d, Bn *meta* to OH), 7.3–7.4 (6H, m, *m*- and *p*-Ph), 7.91 (2H, d, *o*-Ph *anti*); δ_C (75.5 MHz, $CDCl_3$) 34.2 (CH_2), 53.1 (OCH_3), 73.8 (NCH), 115.4 (2CH), 127.8 (2CH), 128.7 (2CH), 129.3 (CH), 129.5 (2CH), 130.0 (CH), 130.4 (2CH), 130.7 (2CH), 132.4 (Bn Cq), 133.2 (Ph Cq), 134.9 (Ph Cq), 155.2 (Bn Cq-OH), 148.0 (C=N), 167.7 (C=O); *m*/*z* (EI) 376.1551 ($M + H^+$), $C_{23}H_{22}NO_4$ requires 376.1549.

Methyl *N*-diphenylmethylene-L-4-nitrophenylalaninate-*N*-oxide 6. Was obtained by stirring freshly prepared solid *m*-CPBA/KF complex (1.07 g, 3.6 mmol) with imine **3** in dry dichloromethane (10 cm^3) at 0 °C for 12 h, followed by filtration and removal of solvent. Flash column chromatography on silica gel afforded nitrone **6** as colourless crystals (0.17 g, 29%), mp 142–143 °C (Found: C, 68.3; H, 4.9; N, 7.0. $C_{23}H_{20}N_2O_5$ requires C, 68.3; H, 5.0, N, 6.9%); δ_H (500 MHz, $CDCl_3$) 3.32 (1 H, dd, *J* 13.8 and 3.7, H_A of CH_2), 3.92 (1H, dd, *J* 13.8 and 11.0, H_B of CH_2), 3.88 (3H, s, OCH_3), 5.02 (1H, dd, *J* 11.0 and 3.8, NCH_X), 6.70 (2H, br d, *o*-Ph *syn*), 7.3–7.4 (8H, m), 7.90 (2H, d, *o*-Ph *anti*), 8.13 (2H, d, Ar *ortho* to NO_2); δ_C (75.5 MHz, $CDCl_3$) 34.9 (CH_2), 53.5 (OCH_3), 72.9 (NCH), 123.7 (2CH), 127.9 (2CH), 129.0 (2CH), 129.3 (2CH), 129.7 (CH), 130.3 (2CH), 130.4 (CH), 130.5 (2CH), 132.8 (Ph Cq), 134.7 (Ph Cq), 144.2 (Bn Cq), 147.2 (Bn Cq-NO_2), 148.1 (C=N), 167.2 (C=O).

Crystal data for 6

$C_{23}H_{20}N_2O_5$, *M* = 404.4, monoclinic, *a* = 9.094(2), *b* = 11.642(3), *c* = 9.371(2) Å, β = 91.370(4), *U* = 991.9(4) Å^3, *T* = 150(2) K, Mo-Kα radiation, λ = 0.71073 Å, space group $P2_1$ (no. 4), *Z* = 2, *F*(000) = 424, D_x = 1.354 g cm^{-3}, μ = 0.097 mm^{-1}, Bruker SMART CCD area detector diffractometer, ϕ/ω scans, 4.3° < 2θ < 52.8°, measured/independent reflections: 8232/3955, R_{int} = 0.009, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.030 for 3698 data with $F_o > 4\sigma(F_o)$, 272 parameters, wR_2 = 0.077 (all data), GoF = 1.06, $\Delta\rho_{min,max}$ = –0.17/0.13 e Å^{-3}. CCDC 739742.

NMR lineshape analysis. Exchange mediated low temperature 500 MHz ^{1}H NMR spectra of the *ortho*-proton signals in the phenyl ring *cis* to the *N*-phenethyl group at (or 10° below

in the case of **2**) the coalescence temperature in CD_2Cl_2 were analysed using the lineshape fitting programme INMR.[23] The doublet splitting of the exchanging *ortho* signals was included in the lineshape analysis as separate sites. Owing to partial overlap from other aromatic signals only the upfield section of the coalescing signal was analysed, but this was sufficient to afford a reasonably accurate rate constant (± 10%). The probe temperature at coalescence was calibrated using an external digital thermocouple with a fine copper-constantan lead inserted into the sample tube following acquisition of the spectra.

Acknowledgements

We thank Mr. Richard Murphy, Queen's University for assistance with the low temperature and 2D NMR experiments.

References

1 S. K. Burley and G. A. Petsko, *Science*, 1985, **229**, 23–28; S. K. Burley and G. A. Petsko, *Adv. Protein Chem.*, 1988, **39**, 125–189.
2 A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 1070–1072; P. R. Ashtona, E. J. T. Chrystal, J. P. Mathias, K. P. Parry, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Tetrahedron Lett.*, 1987, **28**, 6367–6370; F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 362–386.
3 M. Nishio, *CrystEngComm*, 2004, **6**, 130–158.
4 E. A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 1210–1250; A. K. Tewari and R. Dubey, *Bioorg. Med. Chem.*, 2008, **16**, 126–143.
5 D. Fattori, *Drug Discovery Today*, 2004, **9**, 229–238; V. Sukalovic, D. Andric, G. Roglic, S. Kostic-Rajacic, A. Schrattenholz and V. Soskic, *Eur. J. Med. Chem.*, 2005, **40**, 481–493; V. Sukalovic, M. Zlatovic, D. Andric, G. Roglic, S. Kostic-Rajacic and V. Soskic, *Arzneim. Forsch.*, 2005, **55**, 145–152; T. Sugimoto, K. Itagaki and K. Irie, *Bioorg. Med. Chem.*, 2008, **16**, 650–657.
6 For a general account of CH-pi interactions seeM. Nishio, M. Hirota, and Y. Umezawa, *The CH/pi Interaction. Evidence, Nature, and Consequences*, Wiley-VCH, New York, 1998; M. Nishio, *Top. Stereochem.*, 2006, **25**, 255–302; M. Nishio, Y. Umezawa, K. Honda, S. Tsuboyama and H. Suezawa, *CrystEngComm*, 2009, **11**, 1757–1788.
7 P. Hobza, H. L. Selzle and E. W. Schlag, *Chem. Rev.*, 1994, **94**, 1767–1785; K. Müller-Dethlefs and P. Hobza, *Chem. Rev.*, 2000, **100**, 143–167; S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami and K. Tanabe, *J. Am. Chem. Soc.*, 2002, **124**, 104–112; W. Wang, M. Pitonak and P. Hobza, *ChemPhysChem*, 2007, **8**, 2107–2111; T. Janowski and P. Pulay, *Chem. Phys. Lett.*, 2007, **447**, 27–32; S. Beg, K. Waggoner, Y. Ahmad, M. Watt and M. Lewis, *Chem. Phys. Lett.*, 2008, **455**, 98–102; P. C. Jha, Z. Rinkevicius, H. Agren, P. Seal and S. Chakrabarti, *Phys. Chem. Chem. Phys.*, 2008, **10**, 2715–2721.
8 For an overview see W. B. Jennings, B. M. Farrell and J. F. Malone, *Acc. Chem. Res.*, 2001, **34**, 885–894.
9 M. C. Grossel, A. K. Cheetham, D. A. O. Hope and S. C. Weston, *J. Org. Chem.*, 1993, **58**, 6654–6661.
10 D. H. Kim, S. S. Lee, D. Whang and K. Kim, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 263–268; Y. Fukazawa, S. Usui, K. Tanimoto and Y. Hirai, *J. Am. Chem. Soc.*, 1994, **116**, 8169–8175; K. D. Schladetzky, T. S. Haque and S. Gellman, *J. Org. Chem.*, 1995, **60**, 4108–4113.
11 S. Paliwal, S. Geib and C. S. Wilcox, *J. Am. Chem. Soc.*, 1994, **116**, 4497–4498; E. Kim, S. Paliwal and C. S. Wilcox, *J. Am. Chem. Soc.*, 1998, **120**, 11192–11193; F. Hof, D. M. Scofield, W. B. Schweizer and F. Diederich, *Angew. Chem., Int. Ed.*, 2004, **43**, 5056–5059; S. L. Cockroft and C. A. Hunter, *Chem. Commun.*, 2006, 3806–3808.
12 L. F. Newcomb and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 4993–4994; L. F. Newcomb, T. S. Haque and S. H. Gellman, *J. Am. Chem. Soc.*, 1995, **117**, 6509–6519; R. R. Gardner, L. A. Christianson and S. H. Gellman, *J. Am. Chem. Soc.*, 1997, **119**, 5041–5042; R. R. Gardner, S. L. McKay and S. H. Gellman, *Org. Lett.*, 2000, **2**, 2335–2338.
13 B. W. Gung, X. Xue and H. J. Reich, *J. Org. Chem.*, 2005, **70**, 3641–3644; B. W. Gung, X. Xue and H. J. Reich, *J. Org. Chem.*, 2005, **70**, 7232–7237.
14 T. A. Hamor, W. B. Jennings, L. D. Proctor, M. S. Tolley, D. R. Boyd and T. Mullan, *J. Chem. Soc., Perkin Trans. 2*, 1990, 25–30; D. R. Boyd, T. A. Evans, W. B. Jennings, J. F. Malone, W. J. O'Sullivan and A. Smith, *Chem. Commun.*, 1996, 2269–2270.
15 W. B. Jennings, B. M. Farrell and J. F. Malone, *J. Org. Chem.*, 2006, **71**, 2277–2282.
16 H. Adams, F. J. Carver, C. A. Hunter, J. C. Morales and E. M. Seward, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1542–1544; F. J. Carver, C. A. Hunter, P. S. Jones, D. J. Livingstone, J. F. McCabe, E. M. Seward and P. Tiger, *Chem.–Eur. J.*, 2001, **7**, 4854–4862.
17 M. J. O'Donnell and R. L. Polt, *J. Org. Chem.*, 1982, **47**, 2663–2666.
18 R. Polt, M. A. Peterson and L. DeYoung, *J. Org. Chem.*, 1992, **57**, 5469–5480; P. L. McGrane and T. Livinghouse, *J. Am. Chem. Soc.*, 1993, **115**, 11485–11489.
19 P. Roth and R. Metternich, *Tetrahedron Lett.*, 1992, **33**, 3993–3996; D. B. Berkowitz, S. Choi, D. Bhuniya and R. K. Shoemaker, *Org. Lett.*, 2000, **2**, 1149–1152.
20 E. C. Lee, B. H. Hong, J. Y. Lee, J. C. Kim, D. Kim, Y. Kim, P. Tarakeshwar and K. S. Kim, *J. Am. Chem. Soc.*, 2005, **127**, 4530–4537; see also M. O. Sinnokrot and D. Sherrill, *J. Am. Chem. Soc.*, 2004, **126**, 7690–7697.
21 The ring current shielding was determined from the tabular data given in J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford, 1965, vol. 1, pp. 595–604.
22 S. Grilli, L. Lunazzi, A. Mazzanti, D. Cassarini and C. Femoni, *J. Org. Chem.*, 2001, **66**, 488–495; Z. Rappoport, S. E. Biali and M. Kaftory, *J. Am. Chem. Soc.*, 1990, **112**, 7742–7748; R. J. Abraham and I. S. Haworth, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1429–1437.
23 W. B. Jennings, *J. Chem. Soc. D*, 1971, 867–868; J. Burdon, J. C. Hotchkiss and W. B. Jennings, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1052–1058.

