

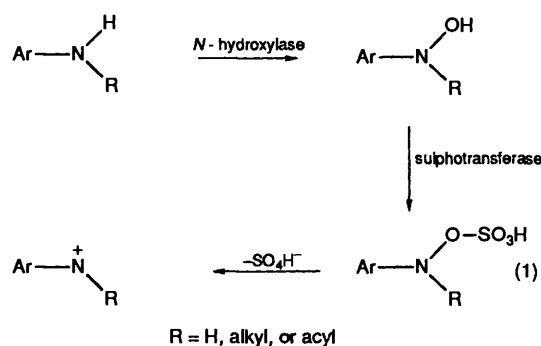
## Conformational Preferences and Energetics of N–O Heterolyses in Aryl Nitrenium Ion Precursors: *ab initio* and Semiempirical Molecular Orbital Calculations

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In the lowest energy conformations of *N*-hydroxyaniline and *N*-hydroxyacetanilide, *ab initio* HF/3-21G and semiempirical AM1 molecular orbital calculations predict that the NO bonds lie close to the planes of the aryl rings. However, the barriers to rotation about C<sub>Ar</sub>–N bonds *via* species in which the NO bonds are approximately orthogonal to the aryl planes are small. According to semiempirical AM1 calculations in the *N*-acetoxy analogues of these, and more complex arylamines, the orthogonal conformations are among the most stable. According to a previous suggestion NO heterolysis to the corresponding nitrenium ions should proceed most favourably from such conformations. NO heterolysis is calculated to be energetically less favourable in the arylamides due to the loss of amide resonance in their precursors. Regardless of the nature of the nitrogen substituents the heterolysis becomes progressively more favourable as the aryl group is varied in the series: Ph < 2-naphthyl < 1-naphthyl ≤ 2-fluorenyl.

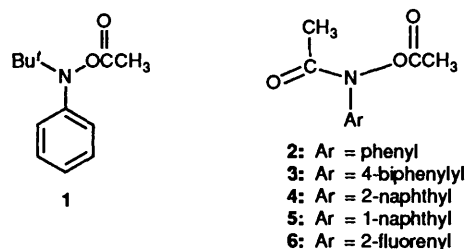
The aromatic amines and their derivatives constitute a large class of compounds, many of which are known to be carcinogenic.<sup>1</sup> According to prevailing ideas, the carcinogenicity of these compounds is associated with their enzymatic *N*-hydroxylation and subsequent esterification. The resulting esters are assumed to undergo unimolecular heterolysis to the highly reactive arylnitrenium ions which in turn react with critical cellular components including the nucleic acids.<sup>2</sup> The principal activation mechanism appears to be *via* the sulphuric acid esters shown in eqn. (1).<sup>3</sup> There is also evidence for the



intermediacy of the *N*-acetoxy-, and in some cases the *N*-glucuronyloxyamines, as well as for the analogous esters of serine and proline (reviewed in ref. 3). Because of difficulties in preparation of the sulphates many model studies in this area have focused on the *N*-acetoxyarylamines and amides.<sup>4</sup> More recently Novak and co-workers have carried out careful mechanistic studies using the *N*-pivaloyloxy derivatives.<sup>5</sup>

Two familiar examples of carcinogenic amines are 2-aminonaphthalene and benzidine, both of which are potent bladder carcinogens in humans.<sup>6</sup> The class also includes a number of arylamides. *N*-Acetylaminofluorene (AAF), originally intended for use as a pesticide, but never marketed because of its carcinogenicity,<sup>6</sup> is frequently employed as a positive control in aromatic amine carcinogenesis and has been one of the most thoroughly studied of all known carcinogens.<sup>7</sup>

The existence of a large number of carcinogenic arylamides is interesting. The presence of the strongly electron-withdrawing *N*-acetyl group might have been expected to militate against the



formation of a species in which the nitrogen atom formally bears a positive charge. This idea was clearly in the minds of Haberfield and DeRosa<sup>8</sup> who were surprised to find the *N*-acetoxy amine **1** unreactive under conditions in which a number of *N*-acetoxy-*N*-acetyl amines appeared to undergo ready solvolysis. Although product analyses were not carried out, Scribner *et al.* reported several cases of this kind where solvolysis occurred fairly rapidly in aqueous solutions.<sup>9</sup> Assuming that these compounds underwent solvolyses *via* NO heterolysis to the nitrenium ions, Haberfield and DeRosa proposed an ingenious explanation for the apparent facilitation of this reaction by the *N*-acetyl group.<sup>8</sup> They suggested that in the acetoxy amines [Fig. 1(a)] where R is alkyl, or hydrogen, the preferred conformation will be that in which the nitrogen lone pair is perpendicular to the ring. Loss of the acetoxy group in this conformation then leads to a nitrenium ion with an orbital occupancy corresponding to an excited state of the ion. The acetoxy amides, however, should adopt a conformation in which the nitrogen lone pair resides in the same plane as the benzene ring. Loss of the acetoxy group from this conformation then leads directly to the nitrenium ion in its ground state [Fig. 1(b)].

Subsequent work has shown that *N*-acetoxyacetanilide (**2**) does not undergo NO heterolysis under these conditions at all, but instead solvolyses *via* a simple ester hydrolysis.<sup>10</sup> The same also appears to be true for **3** and **4**, but not for **5** and **6**.<sup>10</sup> Thus, while Haberfield and DeRosa's suggestion is not relevant in the context in which it was made, it may be valid in others.

Although not couched in these terms, their argument was essentially an orbital symmetry one. Unimolecular loss of the

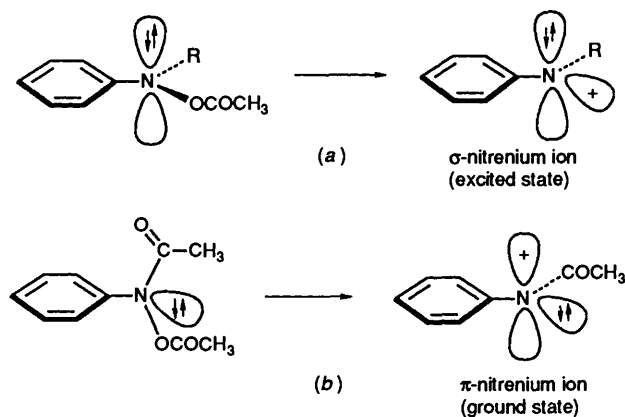


Fig. 1 Characteristics of NO heterolysis in *N*-acetoxyarylamines and amides proposed by Haberfield and DeRosa.<sup>8</sup> (a) Loss of acetate from the planar conformation of acetoxyarylamines; (b) loss of acetate from the perpendicular conformation of acetoxyarylamides.

acetoxy group in the plane of the molecule is formally a 'symmetry forbidden' process in which occupied orbitals in the reactant correlate with excited levels of the product.<sup>11</sup> In processes of this kind there is typically a symmetry-induced barrier in the vicinity of the orbital crossing. When the acetoxy group departs in a way that allows the nitrogen non-bonding electrons to remain in the molecular plane no such barrier is expected.\* Apart from certain special cases, for example where the nitrogen atom is part of a fused ring, the expected symmetry-imposed barrier in Fig. 1(a) can be circumvented simply by rotation about the N-C<sub>Ar</sub> bond. Thus the upper limit on the 'symmetry-induced' barrier should just be the barrier to the necessary rotation.

Intrigued by the notion that the ease of nitrenium ion formation *via* heterolysis of such esters might be simply related to their ground-state conformational preferences, we have undertaken a detailed study of the conformational energetics of some representative *N*-acetoxy arylamines and amides using semiempirical AM1 molecular orbital calculations,<sup>13</sup> supplemented by calculations on the rotational barriers in prototypical systems at the *ab initio* level. These results are reported below, together with an analysis of the effects of variations in the aryl group on the overall thermodynamics of NO heterolysis.

**Theoretical Procedures.**—Semiempirical calculations were carried out using version 5 of the MOPAC package<sup>14</sup> adapted for the Harris Corporation H800 minicomputer<sup>15</sup> or an IBM 3081.<sup>16</sup>

*Ab initio* calculations were carried out using either the GAUSSIAN 82 or GAUSSIAN 86 program packages<sup>17</sup> on IBM 3081 and 3090 series computers under the VM/CMS operating system. Geometry optimizations were carried out using the economical 3-21G basis set.<sup>18</sup> To obtain more reliable energetic comparisons single point calculations were carried out using the 6-31G(d) basis set<sup>19</sup> which includes a set of six d-type functions on all heavy atoms. Valence electron correlation was included using Møller-Plesset second-order perturbation theory.<sup>20</sup>

\* The orbital crossing and symmetry-imposed barrier is easily demonstrated in systems in which these geometrical constraints are artificially imposed. This was done early in this project while still working with MNDO,<sup>12</sup> the predecessor of the AM1.<sup>13</sup> Following the orbitals and state energies for loss of water from *O*-protonated phenylhydroxylamine in directions within, and perpendicular to, the molecular plane, using MNDO/CI calculations, revealed precisely the expected behaviour.

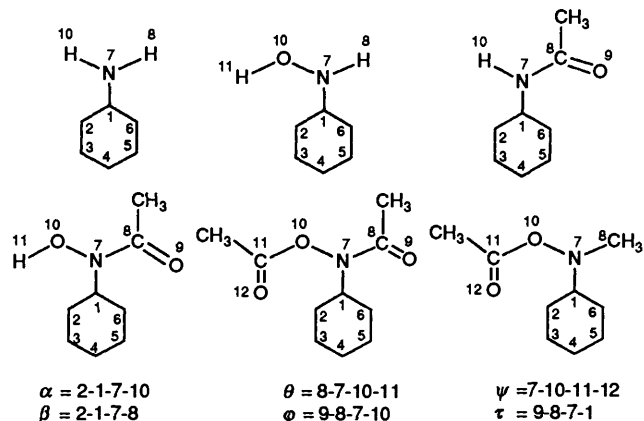


Fig. 2 Atom numbering and angle definitions used. For convenience, alternative conformations of the structures discussed in this work are identified as being approximately *syn* or *anti*, with respect to each of the dihedrals  $\theta$ ,  $\phi$  and  $\psi$ . The *syn* orientations were characterized by angles in the ranges  $60 \pm 19^\circ$ ,  $7 \pm 22^\circ$  and  $3 \pm 12^\circ$ , respectively. Values of  $\theta$ ,  $\phi$  and  $\psi$  in the ranges  $119 \pm 22^\circ$ ,  $167 \pm 6^\circ$  and  $184 \pm 5^\circ$ , respectively, are designated *anti*.

## Results

The atom numbering and the definition of some key dihedrals used in the following Tables are shown in Fig. 2. The dihedral angle between the NO bond and the aryl ring is of particular interest and is designated  $\alpha$ . A similar angle,  $\beta$ , refers to the related dihedral involving the second nitrogen substituent. Conformational relationships among the groups bound to the nitrogen atom are described by three dihedrals  $\theta$ ,  $\phi$  and  $\psi$  corresponding to rotations about the N-O, N-C<sub>acyl</sub> and O-C<sub>acyl</sub> bonds respectively. For convenience, conformational isomers are identified as being approximately either *syn* or *anti* with respect to each of the applicable variables  $\theta$ ,  $\phi$  and  $\psi$  (see legend to Fig. 2).

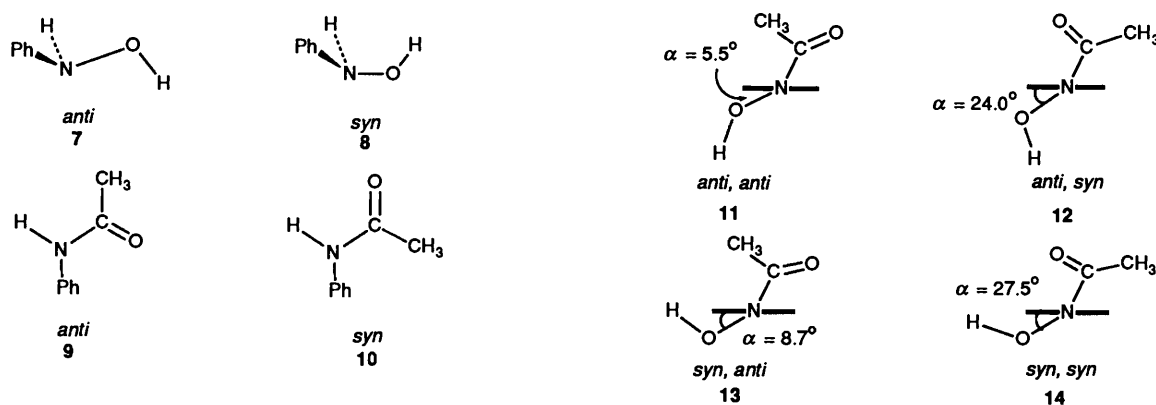
**Conformational Energetics of Aniline, Acetanilide and their *N*-Hydroxy Derivatives.**—The data calculated for various conformations of *N*-hydroxyacetanilide and its simpler relatives at the AM1 level are collected in Table 1. The geometry of aniline is very close to that deduced from microwave data.<sup>21</sup> AM1 makes the nitrogen atom somewhat too non-planar although the error is not large. The degree of non-planarity is conveniently quantified by the sum of the angles around the nitrogen atom ( $\zeta$  in Table 1). A value of  $360^\circ$  indicates that the nitrogen atom and the three substituents bound to it are coplanar, while  $\zeta = 328.4^\circ$  corresponds to a perfectly tetrahedral geometry. In the microwave structure of aniline  $\zeta = 345.0^\circ$ , while the AM1 calculation predicts a slightly smaller value of  $341.5^\circ$ . The distortion of the  $D_{6h}$  symmetry of the benzene nucleus, the shortening of the C(1)N bond relative to that in arylamines and the significant transfer of  $\pi$ -electron density to the ring are all consistent with the well-known resonance effect of the NH<sub>2</sub> substituent. Substitution of one of the NH bonds by OH gives rise to *anti* (7) and *syn* (8) conformers of *N*-hydroxyaniline. The former is calculated to be more stable by  $4.0 \text{ kcal mol}^{-1}$  which is similar to the corresponding difference calculated ( $5.8 \text{ kcal mol}^{-1}$ ) for hydroxylamine itself.† The presence of the polar OH group reduces  $\pi$ -donation into the aromatic ring by *ca.* 50% which is consistent with the relative magnitudes of the  $\sigma_r^\circ$  values of the NH<sub>2</sub> ( $-0.48$ ) and NHOH ( $-0.22$ ) groups.<sup>24</sup> Interestingly, and also consistent with the reduced resonance interaction with the ring, the

† NH<sub>2</sub>OH itself is known to exist entirely in the *syn* conformation,<sup>22</sup> with the most recent *ab initio* molecular orbital estimate of the *syn/anti* energy difference being  $5.6 \text{ kcal mol}^{-1}$ .<sup>23</sup>

**Table 1** Calculated data (AM1) for *N,N*-substituted anilines<sup>a</sup>

	<i>N</i> -Hydroxyaniline		Acetanilide		<i>N</i> -Hydroxyacetanilide				
	Aniline	7	8	9	10	11	12	13	14
$r[\text{C}(1)\text{-N}]$	1.400	1.441	1.439	1.404	1.404	1.442	1.444	1.435	1.449
$r[\text{C}(8)\text{-N}]$	—	—	—	1.389	1.389	1.444	1.445	1.433	1.451
$r[\text{C}(8)\text{-O}]$	—	—	—	1.244	1.248	1.238	1.241	1.239	1.240
$r(\text{N-O})$	—	1.341	1.326	—	—	1.339	1.343	1.324	1.328
$\zeta$	341.5	327.7	334.4	360.0	359.2	342.5	339.6	351.7	341.5
$\alpha$	-25.8	-22.0	-24.8	-0.2	31.2	5.5	24.0	8.7	27.5
$\beta$	-158.1	-139.6	-149.4	180.0	-138.4	-127.2	-106.1	-137.9	-105.1
$\theta$	—	-140.8	68.6	—	—	-125.5	-75.2	78.5	41.2
$\phi$	—	—	—	180.0	7.7	-166.3	21.5	-173.4	-4.2
$\Sigma q$	-40	-22	-21	65	59	75	86	80	49
$\Sigma q^\pi$	-119	-56	-57	-83	-64	-41	-26	-53	-31
$\mu$	1.542	0.422	2.779	3.322	3.353	2.367	3.147	2.630	3.669
$\Delta H_f$	20.5	12.3	16.3	-15.3	-14.7	-13.5	-12.9	-10.8	-11.8

<sup>a</sup> See Fig. 2 for atom numbering and definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$  and  $\phi$ . Bond lengths ( $r$ )/Å and angles/°.  $\Sigma q$  and  $\Sigma q^\pi$  are the total and  $\pi$ -charges associated with the aromatic ring ( $\times 10^3$ ). Other units: dipole moment  $\mu$ /D; heat of formation ( $\Delta H_f$ )/kcal mol<sup>-1</sup>; 1 kcal mol<sup>-1</sup> = 4.184 kJ mol<sup>-1</sup>,  $\zeta$  is the sum of the angles around the nitrogen atom/°.



**Scheme 1** Minimum energy conformations of *N*-hydroxyacetanilide. Views are along the N-C<sub>Ar</sub> bonds. Conformational designations refer to orientations about the NO and N-C<sub>acyl</sub> bonds (dihedrals:  $\theta$  and  $\phi$  in Fig. 2).

nitrogen is now predicted to be considerably less planar than in aniline.

The most stable conformer of acetanilide (**9**) is a C<sub>s</sub> structure in which the N-C<sub>Ar</sub> bond eclipses the carbonyl group. For consistency with our later usage this conformation is designated *anti*. Interestingly, the acetyl group is less effective than the OH group in reducing  $\pi$ -electron donation from the nitrogen atom into the ring. This is reflected both in the calculated data ( $\Sigma q^\pi$  in Table 1) and in the experimentally-determined  $\sigma_R^\circ$  values (-0.23 to -0.41<sup>24</sup>). In the second conformation **10** the acetyl group is rotated out of the plane of the aromatic ring by *ca.* 42°, and electron donation into the ring is *ca.* 23% less.

The four conformational isomers of *N*-hydroxyacetanilide (**11**–**14**) are shown in Scheme 1. These differ with respect to the conformations about the NO bonds ( $\theta$ ) and the orientations of the acetyl groups ( $\phi$ ). In the lowest energy conformation **11** both groups are in the *anti* relationship, although in no case do the conformational energies differ by more than 2.7 kcal mol<sup>-1</sup>. In every case the nitrogen atom is calculated to be pyramidal, although less so than in **7** and **8**. In each the NO bond was predicted to lie close to the plane of the phenyl ring ( $\alpha = 5$ –28°) with the N-C<sub>Ar</sub> bond approximately perpendicular to it ( $\beta = 105$ –138°).

**Rotational Barriers in N-Hydroxyaniline (7) and N-Hydroxyacetanilide (11).**—Next we located the transition states for rotation about the N-C<sub>Ar</sub> bonds in the most stable conformers of *N*-hydroxyaniline (**7**) and *N*-hydroxyacetanilide (**11**). Complete rotational profiles were constructed as functions of the dihedral angles  $\alpha$  at the AM1 level. The approximate energy maxima located in this way were refined by minimizing the squares of the gradient vectors in the usual way.

For comparison, the geometries of **7** and **11** were also optimized at the *ab initio* HF/3-21G level. Here the heavy atom skeleton of the ring as well as the hydrogen atoms attached to C(3)–C(5) were constrained to local C<sub>2v</sub> symmetry. The error introduced by this economical expedient is expected to be small.<sup>25</sup> For **7** a 'rigid rotational' pathway was generated by carrying out single point calculations for selected values of the angle  $\alpha$  and the approximate energy maximum located fully optimized as a saddle point (still with the local C<sub>2v</sub> constraint) using the BERNY algorithm.<sup>17</sup> For **11** an approximate energy maximum on the rotational pathway close to  $\alpha = 91 \pm 1^\circ$  was located by a judicious combination of single point minimizations and small rigid displacements. Unfortunately, our attempts to refine this transition state using the BERNY optimization algorithm in GAUSSIAN86 consistently failed. However, by quadratic interpolation of single point energies 1° on either side of the  $\alpha = 91^\circ$  point, we estimate the true maximum to lie at  $\alpha = 91.3^\circ$ . The relevant geometrical information is collected in Table 2. The AM1 and HF/3-21G energetic data are collected in Table 3 together with those for single point calculations at the HF/6-31G(d) and MP2/6-31G(d) levels for **7**.

Both the *ab initio* and semiempirical calculations predict rotation about the N-C<sub>Ar</sub> bonds in **7** and **11** to slightly increase the positive charge associated with the aromatic ring in each case, consistent with the reduction of the resonance interaction between the nitrogen lone pair and the aromatic ring in the

**Table 2** HF/3-21G and AM1 geometries for the C–N bond rotation in *N*-hydroxyaniline **7** and *N*-hydroxyacetanilide **11**<sup>a</sup>

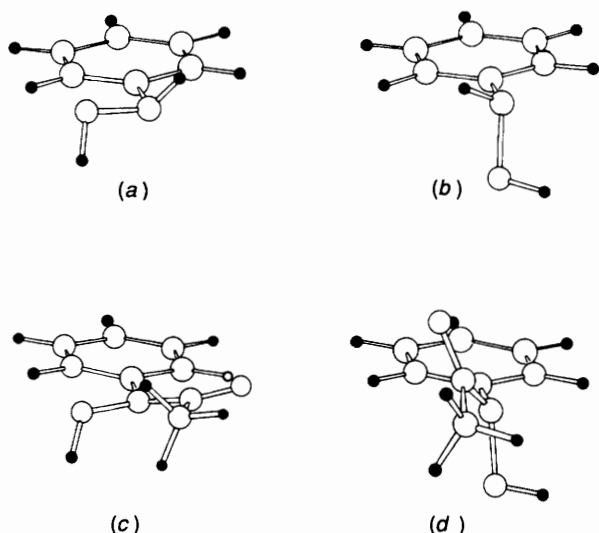
	HF/3-21G		AM1 7 <sup>‡</sup>	HF/3-21G		AM1 11 <sup>‡</sup>
	7	7 <sup>‡</sup>		11	11 <sup>‡</sup>	
<i>r</i> [C(1)–C(7)]	1.426	1.442	1.454	1.420	1.432	1.450
<i>r</i> [C(8)–N(7)]	—	—	—	1.380	1.390	1.442
<i>r</i> [C(8)–O(9)]	—	—	—	1.215	1.210	1.238
<i>r</i> [N(7)–O(10)]	1.451	1.470	1.345	1.429	1.442	1.341
<i>r</i> [C(1)–C(2)]	1.384	1.384	1.407	1.388	1.384	1.406
<i>r</i> [C(1)–C(6)]	1.388	1.383	1.407	1.391	1.382	1.408
<i>r</i> [C(2)–C(3)]	1.382	1.383	1.392 <sup>b</sup>	1.382	1.383	1.393 <sup>c</sup>
<i>r</i> [C(3)–C(4)]	1.384	1.384	1.395 <sup>b</sup>	1.383	1.384	1.394 <sup>c</sup>
C(1)–N(7)–O(10)	111.5	108.2	111.3	114.6	112.8	111.7
C(1)–N(7)–X(8)	113.4	111.9	106.8	129.0	123.4	116.7
X(8)–N(7)–O(10)	105.7	103.6	105.4	114.9	113.9	112.1
$\zeta$	330.6	323.7	323.5	358.5	350.1	340.5
$\alpha$	–11.5	83.1	75.0	3.5	91.3 <sup>d</sup>	80.0
$\beta$	–130.7	–30.3	–39.6	–161.6	–51.5	–50.8
$\theta$	–120.3	–125.5	–146.4	–104.9	–117.5	–125.2
$\phi$	—	—	—	–176.2	–160.6	–158.2
$\Sigma q$	301	330	15 <sup>e</sup>	430	450	121 <sup>e</sup>
$\mu$	0.792	0.822	1.000	3.390	3.257	3.376

<sup>a</sup> See Fig. 2 for atom numbering and definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$ ,  $\phi$  and  $\psi$ . Bond lengths (*r*)/Å and bond angles/°.  $\zeta$  is the sum of the angles around the nitrogen atom/°.  $\Sigma q$  is the total charge associated with the aromatic ring ( $\times 10^3$ ) and  $\mu$  is the dipole moment/D. <sup>b</sup> *r*[C(4)–C(5)] = *r*[C(5)–C(6)] = 1.394 Å. <sup>c</sup> *r*[C(4)–C(5)] = 1.394 Å; *r*[C(5)–C(6)] = 1.393 Å. <sup>d</sup> Estimated from a quadratic interpolation of points at  $91 \pm 1^\circ$ ; see text. <sup>e</sup> Given here as Mulliken charges for comparison with the *ab initio* results. The standard AM1 ZDO charges for 7<sup>‡</sup> and 11<sup>‡</sup> are 0 and 94, respectively.

**Table 3** Calculated energetics for C<sub>aryl</sub>–N bond rotation in *N*-hydroxyaniline and *N*-hydroxyacetanilide<sup>a</sup>

Method	<i>N</i> -Hydroxyaniline			<i>N</i> -Hydroxyacetanilide		
	7	7 <sup>‡</sup>	$\Delta H^\ddagger_{\text{rot}}$	11	11 <sup>‡</sup>	$\Delta H^\ddagger_{\text{rot}}$
HF/3-21G	–358.525 56	–358.519 74	3.65	–509.461 21	–509.452 29	5.60
HF/6-31G(d) <sup>b</sup>	–360.522 01	–360.518 40	2.27	—	—	—
MP2/6-31G(d) <sup>b</sup>	–361.620 95	–361.617 23	2.34	—	—	—
AM1	—	—	2.24	—	—	2.46

<sup>a</sup> Total energies in a.u.; relative energies in kcal mol<sup>–1</sup>. <sup>b</sup> Single point calculations on HF/3-21G geometries.



**Fig. 3** Calculated (HF/3-21G) geometries of the ground and transition states for rotation about the C<sub>Ar</sub>–N bond in *N*-hydroxyaniline (**7**) and *N*-hydroxyacetanilide (**11**). Ground and transition state of *N*-hydroxyaniline are shown in (a) and (b). Ground and transition states of *N*-hydroxyacetanilide are shown in (c) and (d).

transition state geometries (Fig. 3). According to this reasoning, and as might have been expected, the loss of such resonance is

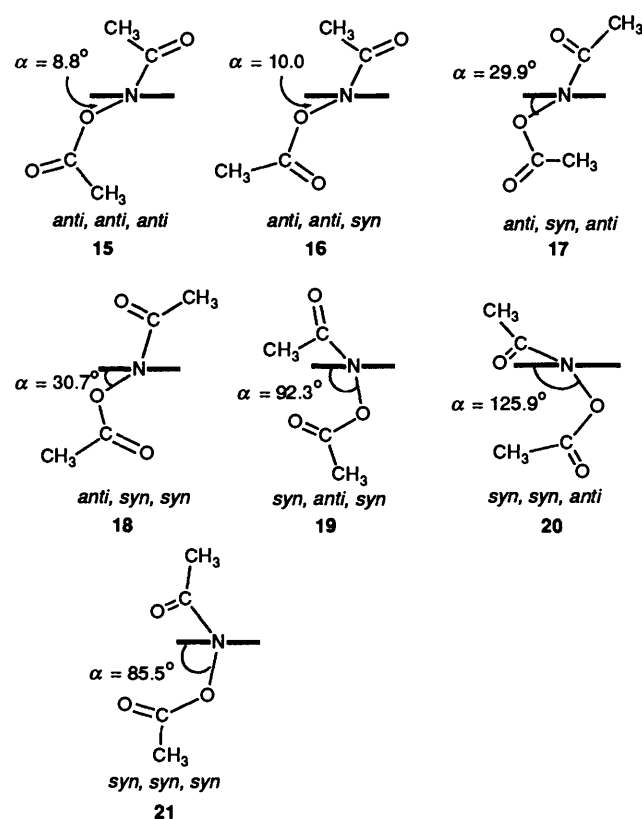
computed to be slightly greater for **7** than for **11**. Surprisingly, however, this did not translate into a smaller barrier for the *N*-acetylated molecule **11**. The *ab initio* HF/3-21G rotational barrier in **7** is 3.65 kcal mol<sup>–1</sup> but falls to a value very similar to that given by AM1 in single point calculations with the larger 6-31G(d) basis set. We were unable to carry out the higher level calculations for **11**. However, taken together, the HF/3-21G and AM1 calculations suggest the barrier in **11** is similar to, or slightly larger than, that in **7**.

*Conformational Energetics of N-Acetoxyacetanilide and N-Acetoxy-N-methylaniline.*—For *N*-acetoxyacetanilide seven of the eight distinct conformers corresponding to *syn* and *anti* relationships about bonds described by the dihedrals  $\theta$ ,  $\phi$  and  $\psi$  are shown in Scheme 2 (structures **15–21**). The *syn,anti,anti* conformer did not correspond to a stationary point and is therefore not shown. For **15–18**, where the *N*- and *O*-acetyl groups are in an *anti* relationship with respect to their orientations about the NO bond (the first conformational descriptor) the NO bond again lies close to the plane of the aromatic ring. However, in a second series (**19–21**), in which the two acetyl groups are in a *syn* relationship, the NO bonds are more nearly perpendicular to the ring. Indeed, the lowest energy conformer **21** is of this type although, with the exception of **20**, all fall within 2 kcal mol<sup>–1</sup> of one another (Table 4). Conjugation with the aryl ring appears to be of secondary importance here. In the most stable conformer **21** the nitrogen lone pair lies approximately in the plane of the ring and the nitrogen sub-

**Table 4** Calculated (AM1) data for *N*-acetoxyacetanilide<sup>a</sup>

	15	16	17	18	19	20	21
$r[\text{C}(1)\text{-N}]$	1.445	1.440	1.447	1.445	1.447	1.439	1.448
$r[\text{C}(8)\text{-N}]$	1.450	1.439	1.445	1.445	1.441	1.440	1.442
$r[\text{C}(8)\text{-O}]$	1.237	1.238	1.239	1.238	1.238	1.239	1.238
$r[\text{N-O}]$	1.347	1.347	1.349	1.351	1.334	1.328	1.334
$\alpha$	8.8	10.0	29.9	30.7	92.3	125.9	85.5
$\beta$	-121.8	-125.8	-100.0	-98.7	-49.4	-18.7	-53.4
$\theta$	-124.0	-101.9	-97.2	-107.5	69.7	74.3	61.7
$\phi$	-168.5	-161.3	29.0	13.6	-167.7	-15.3	6.6
$\psi$	177.5	15.1	-171.3	-3.0	-9.1	176.7	6.7
$\Sigma q$	88	99	97	85	113	86	95
$\Sigma q^\pi$	-36	-41	-18	-20	7	-22	5
$\mu$	1.768	4.238	5.481	3.331	3.924	6.203	2.910
$\Delta H_f$	-43.0	-42.7	-42.2	-43.1	-42.4	-39.4	-44.1
$\Delta\Delta H$	1.1	1.4	1.9	1.0	1.7	4.4	0.0

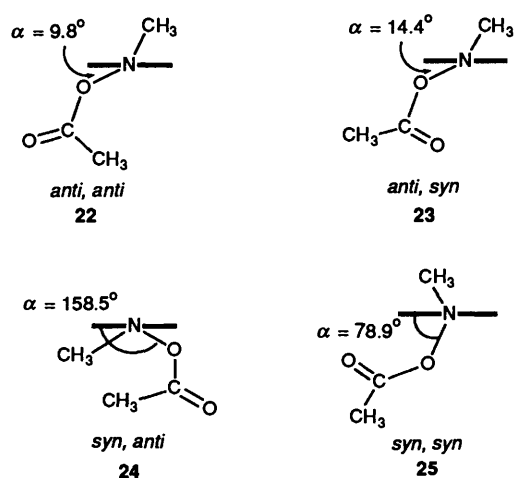
<sup>a</sup> See Fig. 2 for atom numbering and definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$ ,  $\phi$  and  $\psi$ . Bond lengths ( $r$ )/Å and bond angles/°.  $\Sigma q$  and  $\Sigma q^\pi$  are the total and  $\pi$ -charges associated with the aromatic ring ( $\times 10^3$ ). Other units: dipole moment  $\mu$ /D; heat of formation ( $\Delta H_f$ ) and relative enthalpies ( $\Delta\Delta H$ )/kcal mol<sup>-1</sup>.



**Scheme 2** Minimum energy conformations of *N*-acetoxy-*N*-acetanilide. Views are along the N-C<sub>Ar</sub> bonds. Conformational designations refer to orientations about the NO, N-C<sub>acyl</sub> and C-O bonds (dihedrals:  $\theta$ ,  $\phi$  and  $\psi$  in Fig. 2).

stituent as a whole is calculated to be slightly electron withdrawing. The principal conformational determinant appears to be the ability of acetoxy and acetyl groups to achieve orientations that minimize their mutual dipole-dipole repulsions. Indeed, there is a qualitative relationship between the energies of 15–21 and their overall dipole moments. On this basis, the absence of the *syn,syn,anti* conformation is consistent with the very unfavourable alignment of the two group dipoles that would be required, as well as with the serious steric conflict between the two methyl groups.

The situation for the *N*-acetoxy-*N*-methylaniline is much simpler. Alternative *anti* and *syn* conformations about the NO and C-O bonds give rise to four energy minima 22–25 (Scheme



**Scheme 3** Minimum energy conformations of *N*-acetoxy-*N*-methylaniline. Views are along the N-C<sub>Ar</sub> bonds. Conformational designations refer to orientations about the NO and C-O bonds (dihedrals:  $\theta$  and  $\psi$  in Fig. 2).

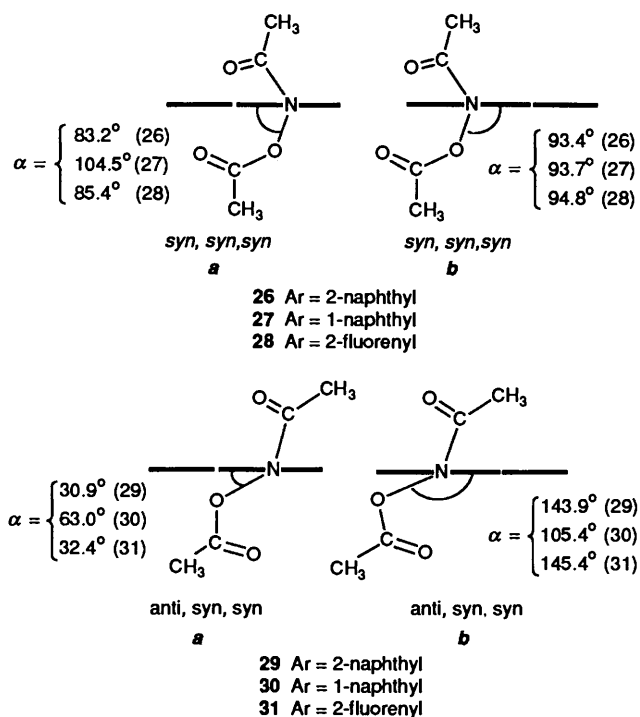
3). Again, where the orientations about the *N*- and *O*-substituents are in an *anti* relationship with respect to the NO bond (22 and 23), this bond itself lies close to the plane of the aromatic ring. In the second series (24 and 25), where the *N*- and *O*-substituents are *syn* the NO bond is more nearly perpendicular to the ring. The most stable of the four conformers, 25, is of this type, although all but 24 fall within 1.3 kcal mol<sup>-1</sup> of one another (Table 5).

*Conformational Energetics of the N-Acetoxy-N-acetyl Derivatives of 1-Aminonaphthalene, 2-Aminonaphthalene and 2-Aminofluorene.*—For the fused ring amines the situation is complicated by the alternative orientations of the aryl ring. Details of the *syn,syn,syn* and *anti,syn,syn* conformations analogous to 21 and 18, were calculated for the 1- and 2-aminonaphthalene and 2-aminofluorene derivatives. These are shown in Scheme 4. In 26a–31a fusion to the substituted phenyl ring is on the same side as the acetoxy group, and in 26b–31b on the other. Quantitative data are collected in Tables 6 and 7. Again the NO bond lies close to the plane of the aryl ring in the *anti,syn,syn* series and approximately perpendicular to the plane of the aryl ring in the *syn,syn,syn* series. Like the phenyl derivatives, the more stable conformations tend to be those in which the NO bonds are approximately perpendicular to the plane of the ring,

**Table 5** Calculated data (AM1) for *N*-acetoxy-*N*-methylaniline<sup>a</sup>

	22	23	24	25
$r[\text{C}(1)\text{-N}]$	1.454	1.453	1.444	1.457
$r[\text{NO}]$	1.360	1.364	1.335	1.342
$\alpha$	9.8	14.4	158.5	78.9
$\beta$	-109.7	-105.2	25.1	-51.4
$\theta$	-128.8	-123.4	65.7	53.8
$\psi$	178.9	1.9	178.6	-2.0
$\Sigma q$	22	19	13	38
$\Sigma q^{\pi}$	-32	-31	-48	4
$\mu$	3.663	2.881	4.987	0.739
$\Delta H_f$	-11.1	-10.5	-7.1	-11.8
$\Delta\Delta H$	0.7	1.3	4.7	0.0

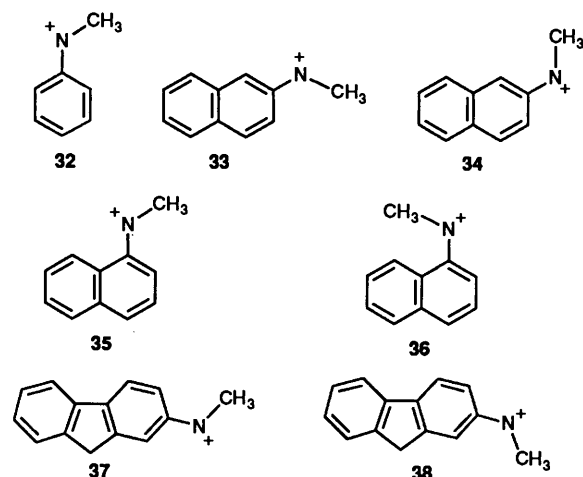
<sup>a</sup> See Fig. 2 for atom numbering and definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$  and  $\psi$ . Bond lengths  $r/\text{\AA}$  and bond angles/ $^{\circ}$ .  $\Sigma q$  and  $\Sigma q^{\pi}$  are the total and  $\pi$ -charges associated with the aromatic ring ( $\times 10^3$ ). Other units: dipole moment  $\mu/\text{D}$ ; heat of formation ( $\Delta H_f$ ) and relative enthalpies ( $\Delta\Delta H$ )/kcal mol<sup>-1</sup>.



**Scheme 4** Minimum energy conformations of *N*-acetoxy-*N*-acetylaminonaphthalenes and aminofluorenes. Views are along the N-C<sub>Ar</sub> bonds. Conformational designations refer to orientations about the NO, N-C<sub>acetyl</sub> and C-O bonds (dihedrals:  $\theta$ ,  $\phi$  and  $\psi$  in Fig. 2). In **26** and **29** the unsubstituted ring is fused at the 3-4 bond (Fig. 2) and at the 2-3 bond in **27** and **30**. In **28** and **31** the indene ring is fused at the 3-4 bond, with the methylene attached at C-3.

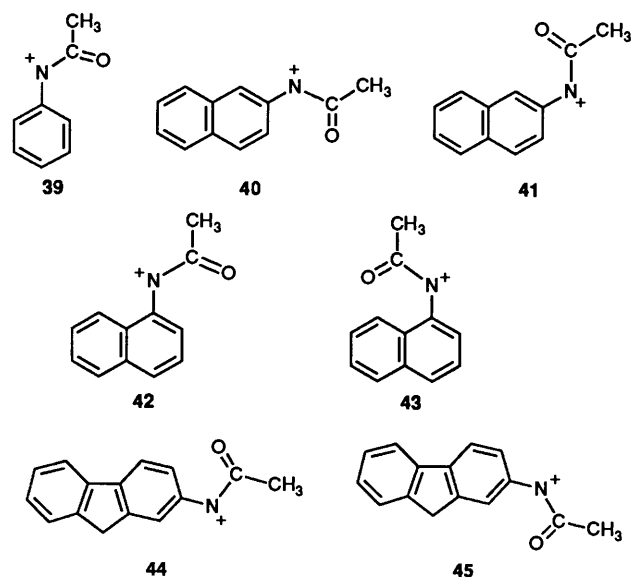
although again energetic differences are very small. A comprehensive survey of the conformational space for the naphthalene and fluorene derivatives was not carried out. However, a selective sampling of several alternative conformations revealed a situation closely analogous to their monocyclic analogues.

***N*-Methyl- and *N*-Acetyl-*N*-arylnitrenium Ions.**—Geometrical and other data for the *N*-methyl-*N*-arylnitrenium ions **32**–**38** are summarized in Table 8. The predicted geometries are qualitatively as expected.<sup>25,26</sup> The elongation of the N-C<sub>Ar</sub> bonds and distortion of the ring C-C bonds of the aromatic rings are consistent with the resonance formulation in which the formal charge on nitrogen is significantly delocalized. All but **36** are predicted to be C<sub>s</sub> structures. The N<sup>+</sup>CH<sub>3</sub> group is predicted



to be coplanar with the remainder of the molecule. In **36** the N<sup>+</sup>CH<sub>3</sub> group is slightly out of plane due to steric interference with the *peri*-hydrogen and is predicted to be 2.3 kcal mol<sup>-1</sup> less stable than its rotamer **35**.

In contrast, none of the *N*-acetyl-*N*-arylnitrenium ions **39**–**45** are predicted to be C<sub>s</sub> structures. Here the acetyl groups were inclined to the planes of the aromatic moieties. This is most



marked in **43** where the acetyl function is rotated out of the molecular plane by 74.9° ( $\tau$  in Table 9). In other cases this angle lies in the range  $42.7 \pm 6.6^{\circ}$ . This lack of planarity may be an artifact of the AM1 procedure. Our *ab initio* HF/3-21G calculations suggest that **39**, at least, has a plane of symmetry.<sup>25</sup> Unlike acetanilide itself the conformers analogous to **10** were not found to be stationary points owing presumably to the unfavourable orientation of the C=O dipole in this conformation.<sup>25</sup>

**Substituent Effects on the Energetics of Nitrenium Ion Formation.**—The effects of varying the substituents attached to nitrogen on both the stabilities of the nitrenium ions themselves, and on the energetics of their formation are conveniently discussed with reference to the energetics of the isodesmic processes described by eqns. (2)–(5). By definition<sup>27</sup> the number of bonds of each formal type in reactions of this kind is conserved. Their energetics therefore provide a convenient

**Table 6** Calculated (AM1) data for *N*-acetoxy-*N*-acetyl aminonaphthalenes<sup>a</sup>

	<i>N</i> -Acetoxy- <i>N</i> -acetyl-2-naphthylamine				<i>N</i> -Acetoxy- <i>N</i> -acetyl-1-naphthylamine			
	26a	26b	29a	29b	27a	27b	30a	30b
$\alpha$	83.2	-93.4	30.9	-143.9	104.5	-93.7	63.0	-105.4
$\beta$	-55.9	127.6	-98.5	86.8	-44.6	126.9	-65.6	125.3
$\theta$	61.6	61.8	-106.7	-107.9	63.6	62.2	-114.9	-110.1
$\phi$	6.5	6.7	13.9	14.1	-0.2	6.0	11.3	14.0
$\psi$	6.6	5.9	-3.9	-4.2	5.2	6.6	-3.3	-4.4
$\Sigma q$	93	93	84	85	110	96	95	100
$\Sigma q^\pi$	5	5	-21	-17	4	5	5	6
$\Delta H_f$	-25.4	-25.5	-24.4	-24.3	-22.3	-24.1	-23.0	-23.4
$\Delta\Delta H$	0.1	0.0	1.0	1.2	1.8	0.0	1.1	0.7

<sup>a</sup> Units: bond angles/°; energies/kcal mol<sup>-1</sup>. See Fig. 2 for definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$ ,  $\phi$  and  $\psi$ . Unsubstituted ring is fused at the 3-4 bond in **26** and **29** and at the 2-3 bond in **27** and **30** (Fig. 2 numbering).  $\Sigma q$  and  $\Sigma q^\pi$  are the total and  $\pi$ -charges associated with the naphthalene nuclei ( $\times 10^3$ ).

**Table 7** Calculated (AM1) data for *N*-acetoxy-*N*-acetyl-2-aminofluorene<sup>a</sup>

	28a	28b	31a	31b
$\alpha$	85.8	-94.8	32.4	-145.2
$\beta$	-53.3	126.1	-96.8	85.5
$\theta$	61.7	61.6	-108.1	-107.9
$\phi$	6.4	6.6	13.4	13.7
$\psi$	6.5	6.5	-1.8	1.9
$\Sigma q$	95	95	85	86
$\Sigma q^\pi$	-13	1	-20	-53
$\Delta H_f$	-11.8	-11.7	-10.6	-10.7
$\Delta\Delta H$	0.0	0.1	1.2	1.1

<sup>a</sup> Units: bond angles/°; energies/kcal mol<sup>-1</sup>. See Fig. 2 for definition of dihedral angles  $\alpha$ ,  $\beta$ ,  $\theta$ ,  $\phi$  and  $\psi$ . The indene ring is fused at the 3-4 bond (Fig. 2 numbering) with the methylene attached at C(3).  $\Sigma q$  and  $\Sigma q^\pi$  are the total and  $\pi$ -charges associated with the fluorene nucleus ( $\times 10^3$ ).

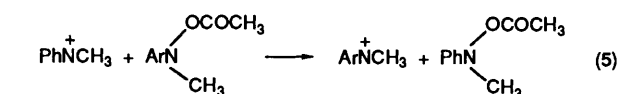
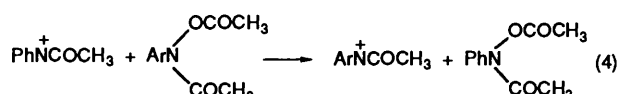
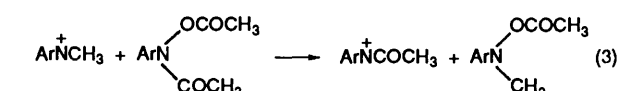
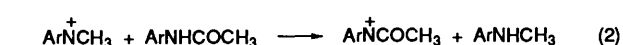
framework for discussion of the more subtle electronic interactions that are manifest as deviations from simple additivity of bond energies. These were based on the most stable nitrenium ion isomer in each case and are collected in Table 10.\*

The effect of the *N*-acetyl group on nitrenium ion formation (relative to methyl) is conveniently quantified using eqn. (2). On this basis the energetic penalty associated with the presence of the *N*-acetyl group is greatest for phenyl (17.3 kcal mol<sup>-1</sup>) and decreases in the order 2-naphthyl > 2-fluorenyl > 1-naphthyl. The presence of the acetyl group also disfavors nitrenium ion formation from the *N*-acetoxy precursors [eqn. (3)] in a similar manner although the effect is some 7 kcal mol<sup>-1</sup> less in this series.

The relative energetics of nitrenium ion formation from the *N*-acetoxy precursors as a function of the aryl group are conveniently quantified using eqns. (4) and (5). In both series the formation of the nitrenium ion is least favourable for phenyl, and increases in the order 2-naphthyl < 1-naphthyl < 2-fluorenyl.

## Discussion

According to a suggestion by Haberfield and DeRosa,<sup>8</sup> the presence of an *N*-acetyl group should facilitate NO heterolysis in compounds analogous to **2-6** by preferentially stabilizing the 'perpendicular' conformation [Fig. 1(b)]. Compounds lacking the *N*-acetyl group, they reasoned, should adopt a 'planar' conformation [Fig. 1(a)] from which NO heterolysis would be



less favourable as a result of the need to surmount an orbital symmetry-induced barrier.

From the variable-temperature NMR spectra of *N*-acetoxy-*N*-acetyl-2-aminofluorene (**6**) Evans and Miller<sup>28</sup> concluded that the acetamido substituent did indeed adopt an approximately orthogonal conformation. A similar situation was predicted by the present calculations for *N*-acetoxyacetanilide (**21**). While exhaustive surveys of the hypersurfaces were not carried out, the lowest energy conformations of **26-28** optimized here were also those in which the acetamido substituents were approximately perpendicular to the aryl rings.

As far as we are aware there is no experimental information on the preferred conformations of *N*-acetoxy amines. For *N*-hydroxyaniline the present calculations, at both the *ab initio* and semiempirical levels, predict a conformation in which the N-O bond lies close to the plane of the aryl ring (**7**). However, rotation about the C<sub>Ar</sub>-N bond *via* the orthogonal geometry is hindered by a barrier of <3 kcal mol<sup>-1</sup>. The energetics of rotation about the C<sub>Ar</sub>-N bond are further reduced on *O*-acylation. In fact the orthogonal conformation of *N*-acetoxy-*N*-methylaniline, **25**, is predicted to be marginally (0.7 kcal mol<sup>-1</sup>) more stable than the planar form **25**.

The present calculations therefore do not support the idea that N-O heterolysis in aryl hydroxylamines and their esters should be retarded by the need to overcome an unfavourable conformational barrier. In fact the recent kinetics studies by Novak and co-workers<sup>5</sup> on the rates of NO heterolysis in 4-chloro-*N*-(pivaloyloxy)aniline and 4-chloro-*N*-(pivaloyloxy)acetanilide indicate that the reaction is retarded, rather than accelerated, by the presence of the *N*-acetyl group as would have been expected simply on the basis of its electron-withdrawing effect. Whether an orbital symmetry-induced barrier could be observed in a system in which geometrical constraints require

\* Computed from the data in Tables 1 and 4-9 and  $\Delta H_f[\text{ArN}(\text{CH}_3)\text{OCOCH}_3]$  for Ar = Ph, 2-naphthyl, 1-naphthyl and 2-fluorenyl = -11.8, 6.9, 8.3 and 20.6 kcal mol<sup>-1</sup>.

**Table 8** Calculated (AM1) data for *N*-methyl-*N*-aryl nitrenium ions<sup>a</sup>

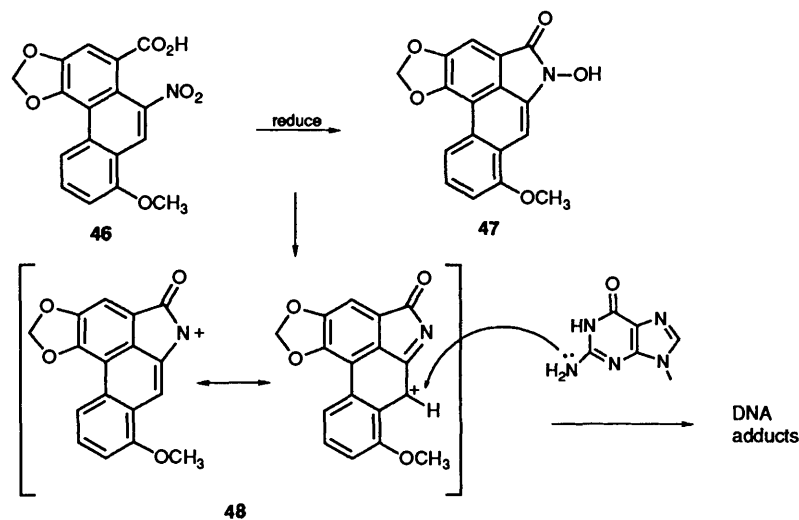
	Phenyl 32	2-Naphthyl		1-Naphthyl		2-Fluorenyl	
		33	34	35	36	37	38
$r[\text{C}(1)\text{-N}]$	1.316	1.310	1.309	1.305	1.303	1.305	1.305
$r[\text{C}(8)\text{-N}]$	1.402	1.407	1.407	1.410	1.410	1.410	1.410
$\beta$	179.9	180.0	0.1	179.9	3.8	179.9	0.0
$\Sigma q(\text{Ar})$	673	757	750	803	809	792	792
$\Sigma q(\text{N})$	61	6	22	-23	-28	-9	-9
$\Sigma q(\text{Me})$	263	238	227	220	220	217	218
$\Sigma q^{\pi}(\text{Ar})$	764	764	759	817	(824)	805	804
$\Delta H_f$	238.4	248.4	250.4	246.5	248.8	257.7	257.6

<sup>a</sup> Units: bond lengths ( $r$ )/Å; bond angles/ $^{\circ}$ ; energies/kcal mol<sup>-1</sup>. See Fig. 2 for definition of dihedral angle  $\beta$ . See footnotes to Tables 6 and 7 for the orientations of the aromatic residues.  $\Sigma q$  and  $\Sigma q^{\pi}$  are the total and  $\pi$ -charges associated with the aryl groups ( $\times 10^3$ ).

**Table 9** Calculated (AM1) data for *N*-acetyl-*N*-aryl nitrenium ions<sup>a</sup>

	Phenyl 39	2-Naphthyl		1-Naphthyl		2-Fluorenyl	
		40	41	42	43	44	45
$r[\text{C}(1)\text{-N}]$	1.299	1.297	1.296	1.296	1.287	1.294	1.295
$r[\text{C}(8)\text{-N}]$	1.445	1.440	1.440	1.437	1.421	1.437	1.438
$r[\text{C}(8)\text{-O}]$	1.235	1.235	1.239	1.238	1.236	1.238	1.238
$\beta$	180.0	-179.7	-1.0	-179.3	-0.7	-179.6	-0.6
$\tau$	45.3	49.3	36.1	42.1	74.9	42.6	42.3
$\Sigma q(\text{Ar})$	843	919	933	961	965	958	959
$\Sigma q(\text{N})$	-43	-96	-91	-128	-136	-113	-113
$\Sigma q(\text{OAc})$	199	177	159	159	172	155	154
$\Sigma q^{\pi}(\text{Ar})$	850	926	947	982	958	978	977
$\Delta H_f$	216.2	224.6	224.9	220.6	222.7	232.0	231.8

<sup>a</sup> Units: bond lengths ( $r$ )/Å; bond angles/ $^{\circ}$ ; energies/kcal mol<sup>-1</sup>. See Fig. 2 for definition of dihedral angle  $\beta$ , and  $\tau$ . See footnotes to Tables 6 and 7 for the orientations of the aromatic residues.  $\Sigma q$  and  $\Sigma q^{\pi}$  are the total and  $\pi$ -charges associated with the aryl groups ( $\times 10^3$ ).



Scheme 5

**Table 10** Calculated (AM1) heats of reaction [eqns. (2)–(5)]<sup>a</sup>

Aryl group	Eqn.			
	(2)	(3)	(4)	(5)
2-Fluorenyl	13.7	6.6	-16.7	-13.2
1-Naphthyl	13.2	6.5	-15.6	-12.0
2-Naphthyl	15.6	8.6	-10.2	-8.7
Phenyl	17.3	10.1	0.0	0.0

<sup>a</sup> Energies/kcal mol<sup>-1</sup>.

NO fission to take place in the aryl plane remains an interesting question. Pfau *et al.*<sup>29</sup> have proposed a mechanism for the

activation of aristolochic acid (46) via the planar lactam 47 and corresponding nitrenium ion 48 (Scheme 5). If this mechanism is correct it would imply that the symmetry-imposed barrier to NO heterolysis leading to 48 is not insurmountable.

According to the present calculations the anticipated destabilization of the *N*-acetyl nitrenium ions relative to the *N*-methyl analogues amounts to some 12–17 kcal mol<sup>-1</sup> depending on the nature of the aryl group. These values are probably somewhat too small. Our previous *ab initio* calculations at levels up to MP2/6-31G(d)//HF/3-21G suggest<sup>25</sup> a value closer to 22 kcal mol<sup>-1</sup> for the phenyl case. In that work we concluded that most of the apparent destabilization of the *N*-acetyl nitrenium ions was due to loss of amide resonance in the precursors,<sup>25</sup>



rather than to the expected destabilization of the ion itself.\* On this basis the energetic penalties associated with the presence of the *N*-acetyl groups in the analogous *N*-acetoxy precursors should be rather smaller since the electron-withdrawing acetoxy group would be expected to reduce the importance of amide resonance. According to AM1 this reduction amounts to *ca.* 7 kcal mol<sup>-1</sup>, although again, this may be too small.

The hydrolyses of compounds 2–6 were studied in detail by Underwood and Kirsch.<sup>10</sup> They identified two kinetically distinct processes. One was first order in hydroxide concentration. This was assumed to correspond to simple ester hydrolysis *via* attack at the carbonyl function of the acetoxy substituent. The second was independent of pH and assumed to correspond to uncatalysed loss of the acetoxy group to a nitrenium ion *via* N–O cleavage. The ester hydrolyses proceeded at essentially the same rates regardless of the nature of the aryl group while the rates of NO cleavage increased in the order: 2 < 4 < 5 < 6. Making the reasonable assumption that the rates of NO heterolysis will parallel the stabilities of the nitrenium ions themselves, these results are entirely consistent with those of the present calculations [heat of reaction for eqn. (4), Table 10].

There is an obvious analogy between the nitrenium ions and the corresponding arylmethyl carbenium ions.<sup>10,26</sup> Indeed, the relative abilities of alternative aryl groups to stabilize the nitrenium ions studied here are qualitatively identical to their abilities to accelerate the S<sub>N</sub>1 solvolysis of 1-aryl-1-chloroethanes.<sup>30,31</sup> The latter have been very satisfactorily rationalized using elementary perturbational molecular orbital theory.<sup>31,32</sup> We have carried out a detailed study of the quantitative relationship between the nitrenium and carbenium ions and established a similar device for predicting the stabilities of the former, again based on elementary molecular orbital procedures.<sup>33</sup>

Whether or not the predicted stabilities of the nitrenium ions will be useful in the interpretation of the genotoxicities of their precursors remains to be seen. Such procedures have met with some success in the polycyclic aromatic hydrocarbon series.<sup>34</sup> However, the situation for the arylamines and amides is clearly more complex. Unlike the aromatic hydrocarbons, which predominantly react at the guanine 2-amino group, a far greater variety of arylamine and arylamide adducts are formed.<sup>2</sup> The 1- and 2-aminonaphthalenes, for example, bind to guanine in quite different ways,<sup>35</sup> and ways expected to have different genetic consequences.<sup>36</sup>

Silverman and Lowe concluded that there was no relationship between the carcinogenic and/or mutagenic potentials of various polycyclic arylamines and the stabilities of the corresponding nitrenium ions predicted from INDO molecular orbital calculations.<sup>37</sup> However, their computed energetics compare poorly with those obtained in the present work and *ab initio* calculations to be presented elsewhere,<sup>33</sup> and are surely incorrect.† Hartman and Schlegel were able to broadly classify a group of polycyclic arylamines and substituted anilines as either carcinogenic/mutagenic or noncarcinogenic/nonmutagenic on the basis of the calculated differences in the energies of the

singlet and triplet states of the nitrenium ions.<sup>38</sup> In fact the methods they used are now known to grossly exaggerate the stabilities of the triplets<sup>39</sup> which are most unlikely to be directly involved.<sup>26,39</sup> The correlation discovered by these authors is therefore more likely to be related to the differing abilities of the substituted aryl groups to stabilize the nitrenium ions themselves (an effect which is expected to parallel singlet–triplet energy differences<sup>26</sup>) rather than to the factors relating to their ground-state multiplicities. On this basis the paper by Hartman and Schlegel appears to provide an encouragingly simple relationship between the genotoxicities of a homogeneous group of compounds and their stabilities.

## Conclusions

In the lowest energy conformations of both *N*-hydroxyaniline and *N*-hydroxyacetanilide the NO bonds lie in the approximate planes of the aryl rings. However, the barriers to rotation about the C<sub>Ar</sub>–N bonds are quite small. *Ab initio* MP2/6-31G(d)//HF/3-21G calculations suggest  $\Delta H^\ddagger < 3$  kcal mol<sup>-1</sup> in the former. *Ab initio* calculations were not carried out beyond the HF/3-21G level for the latter. However, comparison of the semiempirical and *ab initio* results in the two series suggests that the barrier in the *N*-hydroxyacetanilide is not significantly larger.

The slight preference for the planar arrangement of the NO bond in the hydroxy amines and amides is more than offset by alternative conformational requirements in the acetoxy derivatives. The lowest energy conformations in both the *N*-acetoxy-*N*-acetylaminoarenes and the *N*-acetoxy-*N*-methylaminoarenes include those in which the NO bonds are approximately parallel and those in which they are approximately orthogonal to the aryl rings. According to arguments put forward by Haberfield and DeRosa<sup>8</sup> NO heterolysis to the corresponding nitrenium ions should proceed more favourably from the latter conformations since the orbital occupancies correlate directly with the nitrenium ions in their ground states. They further suggested that NO heterolysis should be less favourable in the absence of the *N*-acetyl group because of the unfavourable energetics associated with achieving the orthogonal conformation. This suggestion is not supported by the present calculations which suggest that such conformations are readily accessible in both series.

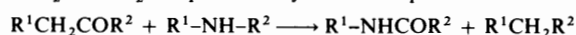
AM1 calculations indicate that NO heterolysis is in fact energetically less favourable in *N*-acetyl derivatives owing, as suggested before,<sup>25</sup> to the loss of amide resonance in the precursors. The stabilities of the aryl nitrenium ions vary with changes in the nature of the aryl moiety in a manner that exactly parallels the stabilities of the isoelectronic arylmethyl cations: Ph < 2-naphthyl < 1-naphthyl ≤ 2-fluorenyl.

Significantly more calculations of the present type will have to be carried out before the possibility of any relationship between the nitrenium ion stabilities and the biological activities of their carcinogenic precursors can be assessed.

## Acknowledgements

This work was supported by the Robert A. Welch Foundation (Grant N-1080). Many of the larger calculations were carried out on the IBM 3090 at the IBM Los Angeles Scientific Center. We thank the IBM Corporation for access to these facilities

\* On this basis the underestimation of the enthalpy of eqn. (2) (R = Ph) at the AM1 level is readily attributable to the tendency of AM1 to underestimate resonance energies. While the magnitude of the amide 'resonance energy' defies precise description it can be conveniently associated with the special stability of the NHCO grouping relative to –NHCH<sub>2</sub>– or CH<sub>2</sub>CO quantified by  $\Delta H$  for the process:



For R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub> this is known experimentally to be –20.4 kcal mol<sup>-1</sup> and for R<sup>1</sup> = Ph; R<sup>2</sup> = CH<sub>3</sub>, –20.9 kcal mol<sup>-1</sup>.<sup>25</sup> The corresponding values computed from the AM1 heats of formation are –10.9 and –10.4 kcal mol<sup>-1</sup>, respectively.

† These calculations predict the 2-fluorenylnitrenium ion to be less stable than the 1- and 2-naphthyl analogues, whereas our previous<sup>26</sup> and present semiempirical calculations, our *ab initio* calculations<sup>33</sup> and our interpretation of the chemical data, as well as the analogy with the 1-aryl-1-chloroethyl solvolysis data,<sup>30</sup> all suggest the reverse.

through Grant RSP 1044. We are grateful to SMU for a generous allocation of computer time on the IBM 3081 at the Bradfield Computer Center where most of the remainder of the calculations were performed. The Harris Corporation H800 minicomputer used in this work was a gift from the Harris Corporation.

## References

- 1 R. C. Garner and D. B. Clayson, in *Chemical Carcinogens*, ed. C. E. Searle, ACS Monogr. Series 182, American Chemical Society, Washington D.C., 1984, p. 175.
- 2 A. M. Jeffery, in *Mechanisms of Cell Transformation by Carcinogenic Agents*, ed. D. Grunberger and S. Goff, Pergamon, New York, 1987, p. 33.
- 3 F. F. Kadlubar and F. A. Beland, in *Polycyclic Hydrocarbons and Carcinogenesis*, ed. R. G. Harvey, ACS Monogr. Series 283, American Chemical Society, Washington D.C., 1985, p. 341.
- 4 M. Novak, M. Pelecanou, A. K. Roy, A. F. Andronico, F. M. Plourde, T. M. Olefirowicz and T. J. Curtin, *J. Am. Chem. Soc.*, 1984, **106**, 5623.
- 5 M. Novak, K. A. Martin and J. L. Heinrich, *J. Org. Chem.*, 1989, **54**, 5430; M. Novak and R. K. Lagerman, *J. Org. Chem.*, 1988, **53**, 4762; M. Novak, M. Pelecanou and L. Pollack, *J. Am. Chem. Soc.*, 1986, **108**, 112; M. Novak and A. K. Roy, *J. Org. Chem.*, 1985, **50**, 4884.
- 6 *Third Annual Report on Carcinogens*, National Technical Information Service, Research Triangle Park, North Carolina, U.S.A., 1983.
- 7 J. A. Miller and E. C. Miller, *Environ. Health Perspect.*, 1983, **49**, 3.
- 8 P. Haberfield and M. DeRosa, *J. Chem. Soc., Chem Commun.*, 1985, 1716.
- 9 J. D. Scribner, J. A. Miller and E. C. Miller, *Cancer Res.*, 1970, **30**, 1570.
- 10 C. M. Scott, G. R. Underwood and R. B. Kirsch, *Tetrahedron Lett.*, 1984, **25**, 499; G. R. Underwood and R. B. Kirsch, *J. Chem. Soc., Chem. Commun.*, 1985, 136.
- 11 R. B. Woodward and R. Hoffman, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1971.
- 12 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899, 4907.
- 13 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
- 14 J. J. P. Stewart, *QCPE Bull.*, 1983, **3**, 43.
- 15 G. P. Ford, *QCPE Bull.*, 1989, **9**, 53.
- 16 S. Olivella, *QCPE Bull.*, 1984, **4**, 109.
- 17 GAUSSIAN 82 program package: J. S. Binkley, M. Frisch, K. Raghavachari, E. Fluder, R. Seeger and J. A. Pople, Carnegie-Mellon University, 1984; GAUSSIAN 86: M. J. Frisch, J. S. Binkley, H. B. Schlegel, K. Raghavachari, C. F. Melius, R. L. Martin, J. J. P. Stewart, F. W. Bobrowoc, C. M. Rohlfing, L. R. Kahn, D. J. DeFrees, R. Seeger, R. A. Whiteside, D. J. Fox, E. M. Fluder and J. A. Pople, Carnegie-Mellon Quantum Chemistry Publishing Unit, Carnegie-Mellon University, Pittsburgh, PA, 1984.
- 18 J. S. Binkley, J. A. Pople and W. J. Hehre, *J. Am. Chem. Soc.*, 1980, **102**, 939.
- 19 P. C. Harihan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213.
- 20 J. S. Binkley and J. A. Pople, *Int. J. Quantum Chem.*, 1975, **9**, 229.
- 21 D. G. Lister, J. K. Tyler, J. H. Høg and W. Larsen, *J. Mol. Struct.*, 1974, **23**, 253.
- 22 M. E. Coles, A. J. Merer and R. F. Curl, *J. Mol. Spectrosc.*, 1984, **103**, 300.
- 23 A. E. Reed and P. v. R. Schleyer, *Inorg. Chem.*, 1988, **27**, 3969.
- 24 O. Exner, in *Correlation Analysis in Chemistry*, eds. N. B. Chapman and J. Shorter, Plenum, New York, 1978, p. 439.
- 25 G. P. Ford and P. S. Herman, *J. Mol. Struct. (THEOCHEM)*, 1990, **204**, 121.
- 26 G. P. Ford and J. D. Scribner, *J. Am. Chem. Soc.*, 1981, **103**, 4281.
- 27 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986, p. 298.
- 28 F. E. Evans and D. W. Miller, *J. Am. Chem. Soc.*, 1983, **105**, 4863.
- 29 W. Pfau, H. H. Schmeisser and M. Wiessler, *Carcinogenesis*, 1980, **11**, 313.
- 30 E. Berliner and N. Shieh, *J. Am. Chem. Soc.*, 1957, **79**, 3849.
- 31 M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 1956, 2789; *J. Chem. Soc.*, 1957, 2946.
- 32 M. J. S. Dewar and R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum, New York, 1975, p. 254.
- 33 G. P. Ford and P. S. Herman, submitted to *J. Mol. Struct. (THEOCHEM)*.
- 34 I. A. Smith, G. D. Berger, P. G. Seybold and M. P. Serve, *Cancer Res.*, 1978, **38**, 2968.
- 35 F. F. Kadlubar, J. A. Miller and E. C. Miller, *Cancer Res.*, 1978, **38**, 3628; F. F. Kadlubar, L. E. Unruh, F. A. Beland, K. M. Straub and F. E. Evans, *Carcinogenesis*, 1980, **1**, 139.
- 36 F. F. Kadlubar, *Chem.-Biol. Interact.*, 1980, **31**, 255.
- 37 D. B. Silverman and J. P. Lowe, in *Polynuclear Aromatic Hydrocarbons: Chemistry, Characterization and Carcinogenesis*, eds. M. Cooke and A. J. Dennis, Battelle, Columbus, 1986, p. 855.
- 38 G. D. Hartman and H. B. Schlegel, *Chem.-Biol. Interact.*, 1981, **36**, 319.
- 39 G. P. Ford and P. S. Herman, *J. Am. Chem. Soc.*, 1989, **111**, 3987.

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