Origins of Regioselectivity in Radical Reactions of Axially Twisted Anilides

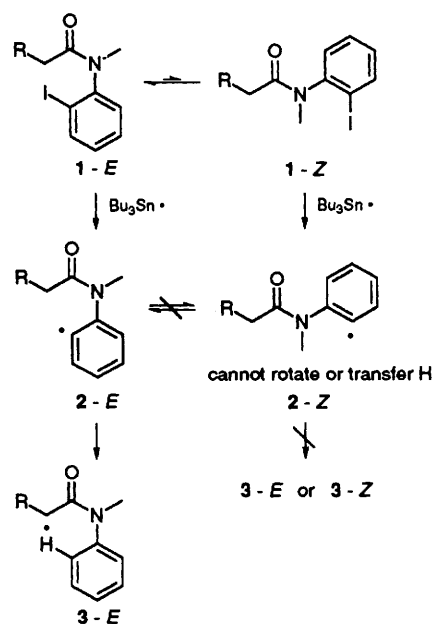**Dennis P. Curran* and Nicholas C. DeMello**

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A new model for the origins or regioselectivity in radical reactions of axially twisted anilides is proposed and supported by crystallographic and computational data.

In aryl amides, the selectivity of short-lived aryl radicals is dominated by the relatively high rotational barriers of the C–N bonds.[1] For example, o-iodoacetanilide **1** is an efficient precursor of radical **3** through the sequence of radical translocation shown in Scheme 1 (**1-E** → **2-E** → **3-E**).[2] This efficiency is a direct consequence of the well known[3] preference of N-aryl amides to exist in an E (Ar and O anti) geometry. The small amount of aryl radicals generated in the Z conformation (**2-Z**) cannot suffer 1,5 hydrogen transfer reactions because they do not live long enough for C–N bond rotation to occur. As far as an aryl radical is concerned, the amide C–N bond geometry is fixed. Similar observations have been made in radical cyclization reactions of unsaturated o-halogenoanilides[4] and in cyclization[5] and hydrogen transfer[6] reactions of o-halogenobenzamides.

Jones and coworkers[4] have conducted seminal studies on the cyclization reactions of unsaturated o-halogenoanilides. In explaining selectivities of competing cyclization and hydrogen transfer reactions of anilide radicals, Jones and Storey have recently suggested that the rotational features of the N–Ar bond play a key role.[7] Fig. 1 shows a sampling of competing reactions of anilide radicals that the Jones–Storey model attempts to rationalize. These are taken from the work of Jones,[4] Dittami,[8] Togo[5] and ourselves.[2] In each example, the radical has a choice of reacting either with a functional group (C–H bond, vinyl or aryl group) in the carbon substituent of the amide or in the other nitrogen substituent, and an arrow indicates the observed direction of reactivity. In this communication, we suggest that the intriguing Jones–Storey model for site selectivity of these reactions is not valid, and support our suggestion with X-ray and computational evidence. We also provide a more traditional rationale for the selectivities in Fig. 1 based on standard rate trends in radical reactions.

The Jones–Storey model as applied to N-allyl-N-(2-bromophenyl)acrylamide **6** is illustrated in Fig. 2. Because the amide C–N bond is mainly E, cyclizations to both the acryloyl and allyl groups are possible, but cyclization to the acryloyl group is the only pathway observed. The new feature of the Jones–Storey model is the attribution of this regioselectivity (N-allyl vs. acryloyl) to the rotamer preference of the N–Ar
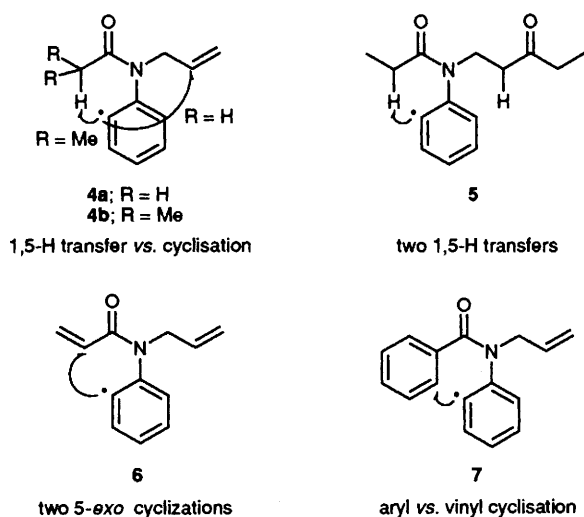

Scheme 1

4a; R = H
4b; R = Me

1,5-H transfer *vs.* cyclisation

5

two 1,5-H transfers

6

two 5-*exo* cyclizations

7

aryl *vs.* vinyl cyclisation

Fig. 1 Selective reactions of acetanilide radicals. Arrows indicate exclusive direction of reaction.

6a   6b

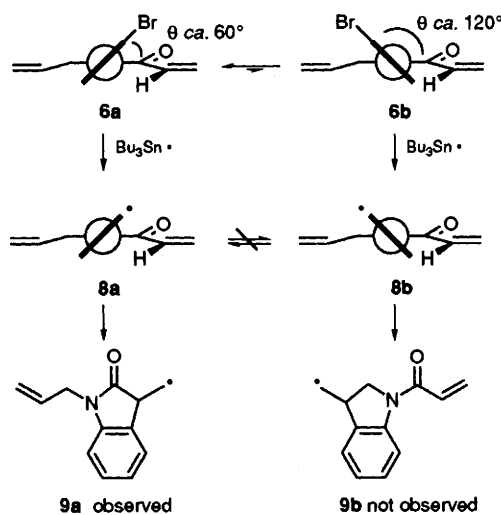8a   8b

9a observed   9b not observed

Fig. 2 The Jones–Storey transition state model

6   ent-6

Scheme 2

10; R = H
11; R = Br

bond of the starting *o*-bromoacrylamide. There are three key postulates that underlie the Jones–Storey model: (*i*) *o*-bromoacrylamides have two distinct minima **6a** and **6b** with the plane of the amide twisted by about 60 and 120° relative to the aryl ring, (*ii*) tin radicals react with these two bromides at roughly equal rates to generate **8a** and **8b**, and (*iii*) the rate of interconversion† of these radicals **8a** and **8b** is slower than the subsequent rates of reaction.

The relationship of this N–Ar model with the well established C–N models is apparent; product ratios are determined by the rotamer preference of the starting *o*-bromophenyl amide **6a** (Scheme 1). A radical generated in conformation **8a** reacts with the neighbouring substituent to give **9a** without ever sampling conformation **8b**, and *vice versa*. Molecular mechanics calculations conducted by Jones and Storey suggested that **6a** is more favoured than **6b** by 1.7–2.5 kcal mol⁻¹ (1 cal = 4.184 J). This explains the observed regioselectivity. By inference, rotamer preferences of all the halide precursors
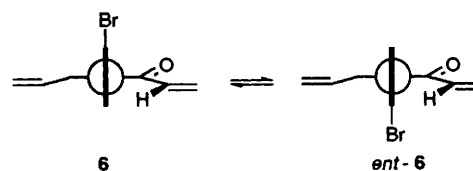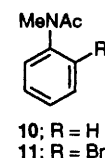
of the radicals shown in Fig. 1 can be deduced from the results of the competing reactions.

Chemical intuition, X-ray crystal structures, and calculations all lead us to question the first and third postulates of the Jones–Storey model. It has long been known that *ortho*-substituted acetanilides are chiral by virtue of N–aryl twisting and have significant rotational barriers.[3c,d] Depending on substituents, these barriers can approach and even exceed those of the amide C–N bond.[9] Such barriers are widespread in highly substituted compounds that contain two adjacent sp² atoms; biaryls are the most widely recognised examples of this large class.[10] However, the simple existence of this barrier and the fact that it could be higher than barrier of an aryl radical cyclization or 1,5-hydrogen transfer reaction are of no consequence in the selective reactions of Fig. 1. This is because the large barrier is not between **6a** and **6b**, but instead between **6** and *ent*-**6** (Scheme 2). In the Jones–Storey model, the key barrier is not the (known) barrier to racemization but instead the (postulated) barrier for the *ca.* 60° twist needed to go between **6a** and **6b**.

Are **6a** and **6b** local minima? For *o*-bromoacetanilides, intuition suggests that they are not. The twist angle of these molecules will be determined by an interplay of two competing effects: resonance delocalization of the nitrogen lone pair into the aromatic ring favours planar conformers, θ = *ca.* 0°, while steric interactions between the *ortho*-bromine atom and the amide substituents favour perpendicular conformations, θ = *ca.* 90°. By analogy with biaryls,[10] *o*-bromoanilides must twist significantly to avoid severe steric interactions that are experienced in the planar conformations favoured by resonance. By the time that the twist angle reaches 60° (the proposed minimum in the Jones–Storey model), nearly all conjugation is lost, and there should be little or no barrier to further rotation through 90°. Inspection of several X-ray crystal structures of *o*-halogenoanilides suggests that intuition is correct:[11] twist angles of *o*-halogenoanilides range from 75 to 105°. Related *ortho*-carbon-, nitrogen- and oxygen-substituted anilides show a similar range of angles in their crystal structures, and angles close to 90° are common. The structures suggest that conformers with θ = *ca.* 90° are not local maxima, but instead are global minima.

To support this idea, we have modelled the rotational profile of *N*-methylacetanilide **10** and *N*-methyl-*o*-bromoacetanilide **11** by using readily available computational packages.‡ Some MM2 force fields reproduce X-ray structure geometries very poorly. For example, the standard parameters of the MM2 provided with the CAChe workstation

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† Jones and Storey seem to suggest that the barrier to rotation in the starting bromide (not the radical) is crucial. This is clearly incorrect. Once the radical is generated, subsequent chemistry will depend on the rate of rotation of the radical (not the bromide) *versus* its rate of reaction.

‡ Calculations with the actual Jones system (**6**) were similar to those with **10** and **11**. This system is complicated by the presence of a number of local minima caused by rotamers about the *N*-allyl group; however, N–Ar twist angles of all the local minima are about 90°.

suggest that **10** is nearly planar (θ = 10°). Numerous X-ray structures show that this is clearly incorrect;[11] even simple acetanilides (including **10**[11c]) are twisted, and twist angles θ are in the range of 70–90°. The CAChe MM2 force field suggests that **11** is twisted, but the twist angle of **11** is reproduced very poorly; calculated minima are at 43 and 150° rather than the expected 75–105°. We believe that these poor calculations are because the force field parameterization overcompensates for the desire of anilides to be planar. Such overcompensation could easily generate twisted minima with barriers between them where none exist.

More reasonable results are given by a modified MM2 force field with parameters provided by Dr S.-Y. Liu.§ This force field calculates two minima for **10** at about 72 and 108° (which are identical owing to symmetry), and a single minimum for **11** at 90°. Similar results were obtained with the MacroModel implementation of the MM2, Amber and MM3 parameter sets; the calculated minima are listed in Table 1. We also conducted a series of semiempirical calculations with AM1 parameters (MOPAC version 6.10). Once again, we locate two (identical) mimina for **10** (76, 104°), and a single minimum for **11** (91°). Semiempirical calculations with PM3 (generally superior to AM1[12]) were not useful; PM3 pyramidizes the nitrogen atoms of all *ortho*-bromo-substituted *N*-aryl amides. Finally, *ab initio* calculations with the STO-321G* basis set indicated angles θ of 91 and 87° for **10** and **11**.

In addition to energy-minimization calculations, we conducted several optimized rotamer searches of the aryl amide bonds in **10** and **11**. The angle θ was locked at 15° increments and the resulting conformers were minimized by various computational packages. The locking constraints were removed, and single point energies were calculated for each conformer. The saddle points were not further optimized with gradient minimization calculations, so these calculations are not intended to offer a value for the barrier of rotation through planarity. These calculations indicated no local maximum between 120 and 60°. Fig. 3 shows the AM1 rotational profile of **10**; MM2 profiles were similar, as were profiles of **11**. In the AM1 profile of **11** (not shown), interactions are so severe when θ approaches 0° that the amide C–N bond is forced to rotate. This suggests the interesting possibility that amide N–Ar and C–N bond rotations may be coupled for some substrates.

A consistent picture of the N–Ar rotational profile of anilides now emerges. In all cases, energetic maxima are expected at planar conformations where steric interactions are maximized. This is the barrier to enantiomerization that has been measured for many differentially *ortho*-substituted systems.[9] Aryl groups with two *ortho*-hydrogen atoms are significantly twisted, indicating that steric effects already dominate over resonance. The potential surface in the vicinity of 90 ± 30° is very flat. There is probably not a barrier at 90°, but if there is, it is very small. In *ortho*-substituted anilides, steric factors now overwhelm resonance, and twist angles approach 90°. The potential surface in the range of 90 ± 20° is

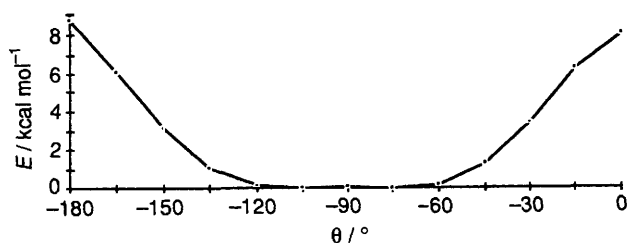again relatively flat because resonance is essentially lost and steric interactions are also as low as possible.

All this suggests that the first postulate of Jones and Storey is certainly wrong, and the third postulate is probably wrong as well. The most likely scenario is that there is only one local minimum for typical *ortho*-bromoanilides with a twist angle near 90°. Because of the flat potentials around 90°, it is possible that two local minima exist, but their angles would be much closer to 90° than Jones and Storey suggest, and the barrier between them (and hence their maximum possible energy difference) would be insignificant. Regarding the third postulate, the rotational profiles of the aryl radical are probably best modelled by the unsubstituted acetanilide **10**. Despite the short lifetime of aryl radicals, we suggest that the radical can sample minima related to **8a** and **8b**.

Our view of these reactions is shown in Fig. 4. Radical **6** is generated with a twist angle of near 90° and this angle can easily increase or decrease at least 30°. A standard Curtin–Hammet[13] picture emerges where twisting of the N–Ar bond (but not enantiomerization) is fast relative to subsequent reactions. Selectivities are then due to the relative energies of the two competing transition states.

The results in Fig. 1 suggest that, all other things being equal, there is an overwhelming preference for the radical to react with the functional group in the carbon side chain of the amide. Indeed, several of the reactions in Fig. 1 are exceptionally fast. We have suggested[2] that this is due to the rigidity of the amide group, which links the radical and the reacting functional group in a highly favourable orientation. Consider the two competing modes of cyclization of Jones's radical **8** (Fig. 4). Cyclization to the acryloyl group requires only very minor changes in the geometry of **6**. Slight further reduction of the N–Ar twist angle and a small twisting of the acryloyl bond away from the ideal s-*cis* orientation leads to a perfect transition state (TS) geometry **12a** for an aryl radical cyclization. Cyclization to the allyl group requires a slight opening of the N–Ar twist angle and rotations of the C–N and C–C bonds of the *N*-allyl group into favourable orientations for cyclization TS **12b**. Though the enthalpy and entropy costs of these rotations are not unusually high, paying even a small price to go to TS **12b** is significant compared to the tiny price paid to go to TS **12a**.

The exception to the generalization is the reaction of radical **4a**, where cyclizaion to the *N*-allyl group is preferred to hydrogen transfer from the methyl group. In comparison, radical **4b** eschews cyclization in favour of 1,5-hydrogen transfer. We suggest that this reversal is due to standard radical substituent effects. Tertiary hydrogen atoms are much
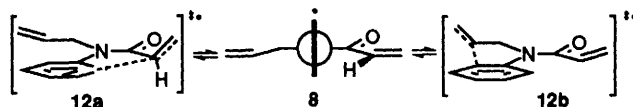

Fig. 4 Traditional transition state model

Fig. 3 AM1 rotational profile of **10**

Table 1 Calculated twist angles (θ) of *N*-arylanilides **10** and **11**

Method	Parameters	θ/° **10**	θ/° **11**
CAChe 3.0	MM2 (standard)	10	43, 150
	MM2 (modified)	72	90
Macromodel 5.1a	MM2	75	93
	Amber	91	90
	MM3	66	90
MOPAC 6.10	AM1	89	102
Spartan 2.1	AM1	68	91
	STO 321G*	91	87

more readily abstracted than methyl hydrogens,[14a] and the rate differences are especially large in 1,5-hydrogen transfer reactions of sp^2 carbon-centred radicals.[14b] For substrate **4a**, the favourable geometry provided by the amide linker is not sufficient to overcome the lack of reactivity of a methyl hydrogen.

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