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Selectivity in the Addition of Electron Deficient Radicals to the C2 Position of Indoles.

Yi Li^a, Roy J. Vaz^b, Steven H. Olson^b, Mark Munson^a, Nick A. Paras^b, Jay Conrad^b

^aIntegrated Drug Discovery, Sanofi US, 153-2nd Ave., Waltham, MA 02451, United States

^bInstitute for Neurodegenerative Diseases (IND), UCSF Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, California, 94158, United States

Abstract

The addition of electron deficient radicals to the C2 position of indoles has been described in the literature as opposed to electrophilic addition at the C3 position. Density functional theory calculations were used to understand the switch in regioselectivity from C3 to C2 for indole to undergo radical additions. Electron deficient radicals have a lower barrier for reaction at C2 and a lower energy radical intermediate that benefits from benzylic radical stabilization. Trifluoromethyl radical addition has a lower energy barrier than acetonitrile radical, and the C3 addition transition state is just 0.8 kcal/mol higher than C2. This is supported by experimental observations.

Graphical Abstract

Computational methods are used to model the addition of electron deficient radicals ($\cdot\text{CH}_2\text{CN}$ or $\cdot\text{CF}_3$) at 2 or 3-position of indoles. Lower reaction barriers are found for reaction at C2 rather than C3. The resulting C2 substituted indole radical intermediate is also lower in energy leading to the experimentally observed C2 selectivity. This is in contrast to long established C3 selectivity for indole reactions with electrophiles.

Keywords

radical reactions; photocatalysis; density functional calculations

jay.conrad@ucsf.edu.

Supporting information for this article is given via a link at the end of the document.

Supporting information (see footnote on the first page of this article): Optimized structures in SDF format (2 files) are provided in the supporting information.

Introduction

Indole is one of the most common heterocycles found in nature. A review article has estimated that over 80,000 papers have been published describing the synthesis or modification of indole, a structural element in tryptophan, serotonin and many alkaloids.^[1] Indoles are well-described carbon nucleophiles participating in polar $2 e^-$ additions by electrophiles at the *C3*-position.^[2] While there is HOMO character at *C3* and *C2* (Figure 1A), there is a higher natural charge from natural population analysis at *C3* (Figure 1B: *C3*, -0.32 vs *C2*, -0.04). When both *C2* and *C3* are unsubstituted, reaction proceeds at *C3* and as early as 1952 has been exploited by organic chemists.^[3] This reactivity has led to the invention of widely used transformations including Friedel-Crafts,^[4] conjugate addition, Mannich,^[5] Tsuji-Trost allylation^[6] or direct arylation^[7] reactions. Enantioselective alkylations are known using Cu-H,^[8] iminium^[9] or thiourea catalysts^[10] (Figure 1C). Alternatively, direct reaction with electrophiles at *C2* in preference to *C3* can be accomplished with an *N*-protecting group metallation via deprotonation^[11] or copper catalysis.^[12]

In contrast, electron deficient radicals are reported to react directly and selectively at the *C2* position of unprotected or unsubstituted indoles (Figure 1D). Bromoacetonitrile^[13] or bromomalonates^[14] activated with Ir or Ru based photocatalysts provide the *C2* addition products in high yield (Figure 2). Trifluoromethylation has been accomplished using CF_3SO_2Cl photoredox catalysis,^[15] CF_3I with $Pt(ppy)(acac)$ as photocatalyst,^[16] CF_3I with Fe(II) peroxide,^[17] photoactivation of a Co- CF_3 reagent,^[18] $TMSCF_3$ with copper catalyst (with *N*-methylindole),^[19] or bistrifluoroacetyl peroxide.^[20] To understand this switch in regioselectivity, we carried out quantum mechanical calculations to describe the factors that determine the *C2* selectivity in radical addition reactions to indoles.

Results and Discussion

For both bromoacetonitrile^[13] and trifluoromethylation^[15], the mechanism has been described to first involve photocatalyst quenching to reduce the precursor (bromoacetonitrile or CF_3SO_2Cl) to generate radical. The electron deficient radical then adds to indole, and the indole is subsequently oxidized by single electron transfer back to the photocatalyst. The resulting cation is deprotonated to return aromaticity to afford the substituted product. This mechanism is supported experimentally by Stern-Volmer quenching studies where either CF_3SO_2Cl or bromoacetonitrile quench photocatalyst emission while indole does not. To understand the *C2* selectivity of these reactions, we performed calculations^[21] on the radical addition to either the indole 2 or 3 position using M06-2X density functionals^[22] with the CC-PVQZ(-g) basis set.^[23] The M06-2X method with large basis set has been shown to perform well on prediction of transition state geometries and the energetics of radicals.^[24] Since secondary derivatives cannot be calculated with an f-basis function, the changes of free energies G_f° at the M06-2X/CC-PVQZ(-g) level were estimated by frequency calculations using CC-PVTZ(-f) basis function on the M06-2X/CC-PVQZ(-g) optimized structures. For comparison we also provide calculations using B3LPY//6-311G**^[25] in Table 1.

The transition state for addition of $\bullet\text{CH}_2\text{CN}$ to *C2* was lower by 2.9 kcal/mol via **2a** with an energy barrier G_f° of 11.1 kcal/mol (**2a**) compared to G_f° 14.1 kcal/mol for *C3* addition (**3a**, Figure 3). The resulting radical addition intermediate was significantly lower in energy for addition to *C2* (**2b**, -7.4 kcal/mol) vs *C3* (**3b**, -1.9 kcal/mol, Figure 3). For comparison, the Hansen group has computed the energy barrier for the addition of malonate radical to *N*-methyl indole *C2* to be 4.5 kcal/mol lower than for addition at *C3*.^[26]

Shown in Table 1, the energetics of the indole addition transition states for positions 4 through 7 were also computed. The resulting dienyl radicals **4b** and **7b** were lower in energy than for addition at *C3*. Addition to the 5- and 6-positions was found to be slightly endothermic. The transition state energies follow the trend for radical intermediates **2a** < **7a** < **3a**, **4a** < **6a** < **5a**. The lower energy found for reaction at the 2-position correlates with the experimentally observed selectivity for *C2* functionalization.

Trifluoromethylation of indoles at the 2-position has been well described using many different sources of $\bullet\text{CF}_3$ in the literature^[15–20], and in most cases, *C3* alkylation is observed as a minor product. Calculations at the M06-2X/CC-PVQZ(-g) level of theory reveal a small difference in energy barrier between addition at the 2-position (**2e**) compared with the 3-position (**3e**) (G_f° 4.2 kcal/mol vs 5.0 kcal/mol for reaction, respectively). Of note is the reduced energy barrier as compared to $\bullet\text{CH}_2\text{CN}$ (11.2–14.1 kcal/mol). Shown in Figure 4, the transition state is earlier with a C...C bond length of 2.26 Å ($\bullet\text{CF}_3$ addition, **2e**) vs 2.16 Å ($\bullet\text{CH}_2\text{CN}$ addition, **2a**). The resulting *C2* adduct is lowest in energy (**2f**, -26.1 kcal/mol) compared to *C3* (**3f**, -22.2 kcal/mol). Exergonic trifluoromethyl radical addition to *C3* of 2-phenyl-*N*-methyl-indole has also been described (-8.9 kcal/mol).^[27] Houk and co-workers have also computationally studied the $\bullet\text{CF}_3$ addition to enolates. They concluded that addition is near barrierless, as transition states could not be optimized and the product formation is exergonic (-24.9 kcal/mol).^[28] Addition of $\bullet\text{CF}_3$ to other indole positions was found to have a slightly higher energy barrier (4.8–6.5 kcal/mol) (Table 1, **4e–7e**). The lower barriers and small difference (0.8 kcal/mol) in transition state energies for **2e** and **3e** explain the formation of the experimentally observed *C3* regioisomer (*C2*: *C3*, 4:1).^{[15],[20]} The radical intermediate **2f** (-26.1 kcal/mol) is lowest in energy followed by **4f** (-24.5 kcal/mol), **7f** (-23.1 kcal/mol) and then **3f** (-22.2 kcal/mol).

The next step in the reaction involves oxidation of the radical intermediate to cation Figure 5. This process is more endothermic for *C2* adduct **2b** to **2c** compared to **3b** to **3c**. Deprotonation then returns aromaticity and reaction products **2d** and **3d**. Loss of proton to return aromaticity in an analogous malonate system has been calculated to be exothermic.^[26]

We also calculated the spin density and relative energies in solution for intermediates **2** and **3** (Figure 6). In structures **3b** and **3f** radical character is mostly localized on *C2* (**3b**, 0.71; **3f**, 0.71). In structures **2b** and **2f** the radical is conjugated to the aromatic system and the radical spin density is delocalized from *C3* (**2b**, 0.56; **2f**, 0.57). Radicals **2b** and **2f** were found to be lower in energy than **3b,f** in either gas, or using Poisson Boltzmann Finite element method (PBF)^[29] with water or DMSO as solvent. Delocalization of the radical spin density correlates with the benzylic stabilization^[30] of intermediates **2** vs **3**.

For comparison trifluoromethyl cations are lower in energy when substituted at the 3-position. Shown in Figure 7 benzylic cation **2g** is 7.0 kcal/mol higher in energy than aromatic iminium **3g**. It requires breaking aromaticity for the amine lone pair electrons in **2g** to stabilize the cation resulting from electrophilic addition at the 2-position. This is in contrast to the radicals **2b/2f** which are lower in energy than **3b/3f**. Further the C2 product **2h** is higher in energy than the C3 product **3h** by 3.6 kcal/mol. For comparison indole protonation with addition of H⁺ to C3 (Figure 7B, **9**) is 7.1 kcal/mol lower in energy than the corresponding H⁺ addition to C2 (**8**). Placing the cation in the benzylic position is less advantageous than the cation stabilized by the nitrogen lone pair (iminium **9**).

Conclusions

In conclusion, we have performed density functional theory calculations that explain the regioselectivity in the addition of electron deficient radicals to indoles. Despite greater nucleophilicity at the 3-position of indoles, the barrier is lower for radical additions at the 2-position. This is in part due to the increased stability of the radical addition products for 2 versus 3. The very low reaction barriers for •CF₃ additions also explain why, depending on the synthetic method, regio-isomers are reported, whereas for •CH₂CN, the higher reaction barrier and greater separation in transition state energies imparts greater selectivity.

Experimental Section

Optimized structures in SDF format are provided in the supporting information. Jaguar (<https://www.schrodinger.com/jaguar>) was used for all calculations^[21] using M06-2X or B3LYP/6–311G** density functionals with the CC-PVQZ(-g) basis set.^[22] Solvation Model using Poisson-Boltzmann Finite element method (PBF) in Jaguar was applied to model the solvent effect in water or DMSO.^[29] Free energies G_f° at the M06-2X/CC-PVQZ(-g) level were estimated by frequency calculations using CC-PVTZ(-f) basis function on the M06-2X/CC-PVQZ(-g) optimized structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A) Indole HOMO **B) Natural charges of C,N atoms from Natural Population Analysis** **C) C3 Addition of Electrophiles (refs 3-9)** **D) C2 Addition of electron deficient radicals (refs 12-19)** **Figure 1.**

A) Diagram of indole HOMO. B) Natural population analysis charges for indole. C) Divergent addition regiochemistry for electrophiles (C3) and D) electron deficient radicals (C2).

Photoredox addition of acetonitrile (13)

Photoredox addition of malonates (14)

Photoredox addition of trifluoromethyl (15)

Photoredox addition of trifluoromethyl (20)

Figure 2.

Examples of photoredox-mediated radical addition to the 2-position of indoles.

Figure 3. Transition state and intermediate energies (estimated G_f°) for the addition of acetonitrile radical to indole at either the C2 (2) or C3 (3) position using the M06-2X/CC-PVQZ(-g) method.

Figure 4. Transition state and estimated intermediate energies (estimated G_f°) for the addition of trifluoromethyl radical to indole at either the C2 (2) or C3 (3) position using the M06-2X/CC-PVQZ(-g) method.

Figure 5. Oxidation of radical intermediates to M06-2X/CC-PVQZ(-g) fully optimized cations followed by deprotonation and rearomatization to provide indole addition products **2d,h** or **3d,h**.

2b

E_{rel} (gas)	0.0
E_{rel} (PBF, water)	0.0
E_{rel} (PBF, DMSO)	0.0

3b

5.8 kcal/mol
5.5 kcal/mol
5.6 kcal/mol

2f

E_{rel} (gas)	0.0
E_{rel} (PBF, water)	0.0
E_{rel} (PBF, DMSO)	0.0

3f

4.4 kcal/mol
3.8 kcal/mol
3.9 kcal/mol

Figure 6.
Spin density and relative energies in solution for **2b,f** and **3b,f** using the M06-2X/CC-PVQZ(-g) method.

Figure 7.

A) Comparison of *C2* or *C3* trifluoromethyl substituted cations. B) Comparison of *C2* or *C3* protonation using the M06-2X/CC-PVQZ(-g) method.

Table 1. Geometries and energetics of calculated structures at B3LPY/6-311G** or [M06-2X/CC-PVQZ(-G)].

Transition State	C...C distance (Å)	E [‡] (kcal/mol)	G _f [‡] (kcal/mol)	Radical Intermediate	CC bond length (Å)	E (kcal/mol)	G _f [‡] (kcal/mol)
2.179 [2.162]	10.8 [11.1]	11.7 [11.2]		1.556 [1.539]	-5.8 [-8.9]	-2.9 [-7.4]
2.098 [2.106]	14.7 [13.8]	16.5 [14.1]		1.560 [1.542]	1.6 [-3.0]	4.1 [-1.9]
2.140 [2.149]	14.7 [3.8]	15.5 [14.2]		1.570 [1.553]	-0.9 [-6.4]	2.0 [-4.3]
2.063 [2.070]	17.3 [15.9]	18.4 [16.4]		1.576 [1.558]	6.5 [1.7]	89 [3.5]
2.099 [2.105]	15.7 [14.5]	16.6 [15.0]		1.572 [1.556]	2.8 [-2.0]	5.4 [-0.1]

Transition State	C ... C distance (Å)	E [‡] (kcal/mol)	G [‡] (kcal/mol)	Radical Intermediate	CC bond length (Å)	E (kcal/mol)	G [°] (kcal/mol)
	2.115 [2.124]	12.7 [11.2]	14.3 [11.8]		1.574 [1.555]	-0.6 [-6.7]	2.7 [-4.5]
	2.339 [2.262]	2.3 [4.5]	3.5 [4.2]		1.533 [1.524]	-26.1 [-26.0]	-22.0 [-26.1]
	2.246 [2.203]	3.5 [5.3]	5.2 [5.0]		1.528 [1.520]	-20.8 [-22.1]	-16.7 [-22.2]
	2.285 [2.239]	3.8 [5.0]	5.6 [4.8]		1.534 [1.526]	-23.3 [-25.2]	-19.0 [-24.5]
	2.194 [2.159]	5.6 [6.8]	7.5 [6.5]		1.537 [1.528]	-15.6 [-17.2]	-11.9 [-16.7]

Transition State	6e	C ... C distance (Å)	E [‡] (kcal/mol)	G _f [‡] (kcal/mol)	Radical Intermediate	6f	CC bond length (Å)	E (kcal/mol)	G _f [‡] (kcal/mol)
2.238 [2.194]	4.6 [5.8]	6.3 [5.8]			1.535 [1.526]	-19.3 [-20.7]	-15.4 [-20.1]
7e	2.266 [2.217]	3.9 [5.6]	5.7 [5.1]		7f	1.533 [1.523]	-21.8 [-23.7]	-17.3 [-23.1]