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Why Do Some Fischer Indolizations Fail?

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Abstract

The mechanisms of the Fischer indole synthesis and competing cleavage pathways were explored with SCS-MP2/6-31G(d) and aqueous solvation calculations. Electron-donating substituents divert the reaction pathway to heterolytic *N-N* bond cleavage and preclude the acid-promoted [3,3]-sigmatropic rearrangement.

Keywords

[3,3]-sigmatropic rearrangements; acid-promoted; mechanism; substituent effects; 3-aminoindoles; 3-amidoindoles; 3-substituted indoles; computational; DFT; MP2; ab-initio calculations

Indole derivatives continue to receive substantial interest due to their wide range of biological activity.^{1–5} The Fischer indole synthesis⁶ remains among the most widely used approaches to indoles, with more than 700 reports over the last 15 years.⁵ Despite the extensive application of the Fischer indole sequence, certain substitution patterns cause the reaction to fail.

A notable challenge for the Fischer indolization reaction is the synthesis of C3 *N*-substituted indoles (**1**→**3**, Scheme 1). Various 3-aminoindole derivatives display antimalarial, anti-muscarinic, anti-bacterial, anti-viral, anti-plasmodial, and anti-hyperglycemic activities and are attractive pharmacological targets.^{7,8} However, to date, there are no examples of 3-aminoindole synthesis by the Fischer method, and the corresponding preparation of *N*-(indol-3-yl)amides^{9–12} and 3-pyrazolylindoles^{13,14} proceeds poorly in the presence of protic acids. While the use of Lewis-acids (e.g., ZnCl₂ or ZnBr₂) improves the efficiency of cyclizations,⁹ the question remains: Why do these Fischer indolizations fail?

We have encountered similar difficulties in efforts to synthesize complex indoline-containing natural products using the interrupted Fischer indolization cascade¹⁵ (**4**+**5**→**6**, Scheme 1). Reactions between aryl hydrazines **4** and latent aldehydes **5** delivered 3-alkyl and 3-aryl substituted pyrrolidindolines, **6a** and **6b**, in good yields,¹⁵ but the transformation failed en route to 3-indolyl pyrrolidindoline, **6c**, intended to be a model study for the synthesis of psychotrimine^{16,17} (**7**) and related alkaloids.

Table 1 shows a sampling of our unsuccessful interrupted Fischer indolization attempts of substrate **5c**. Phenylhydrazine was employed in initial experiments. Acetic acid-based

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Supporting Information Available: Benchmarking results, Cartesian coordinates, electronic and zero-point vibrational energies, enthalpy and free energy corrections of all reported structures, experimental procedures and complete reference ²⁰. This material is available free of charge via the Internet at <http://pubs.acs.org>.

conditions, commonly used for the interrupted Fischer indolization reaction, gave none of the desired indoline product (entries 1–2). Similarly, the use of stronger acids typically used to promote Fischer indole synthesis was also unsuccessful (entries 3–6).¹⁸ All of these experiments gave rise to two significant byproducts: 3-methylindole and aniline. Comparable results were obtained when treating arylhydrazone derivatives of **5c** under acidic conditions.

Despite being a widely utilized process, many essential mechanistic details underlying the acid-promoted Fischer indolization remain unclear. Previous computational investigations on the mechanism of the Fischer indole reaction are limited to semiempirical methods,¹⁹ and the effect of substituents on the possible competing pathways has not yet been addressed. Here, we report the first computational study on the mechanism of the Fischer indole reaction using accurate quantum mechanical methods, and demonstrate that substituents on the starting carbonyl compound play a pivotal role in the success or failure of the Fischer indole synthesis. We also show that the commonly used B3LYP method fails to reproduce the concerted nature of the acid-promoted 3,4-diaza-Cope rearrangement.

We first studied the parent unsubstituted rearrangement using different levels of theory, including CBS-QB3, B3LYP, SCS-MP2, MP2 and M06-2X with Gaussian 09.²⁰ Solvation effects were taken into account in geometry optimizations and in energy calculations using the SMD model.²¹ B3LYP favors *N*–*N* bond cleavage, without *C*–*C* bond formation, for the protonated species and failed to predict the concerted nature of the sigmatropic rearrangement transition states upon substitution. These results and a detailed comparison of all methods are given in the Supporting Information. In the text, we discuss results obtained at the SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water) level of theory, which provide the best results in test calculations.

Figure 1 shows the free energies of the ene-hydrazine intermediates and [3,3]-sigmatropic rearrangement transition states relative to the phenylhydrazone for both the thermal and acid-catalyzed (*N*α-protonated and *N*β-protonated) pathways. In the thermal reaction, ene-hydrazine intermediate **9** lies 17.5 kcal/mol higher in energy than phenylhydrazone **8**. The rearrangement transition state (**t**–**TS**) is concerted, but asynchronous with a very high activation barrier of 43.7 kcal/mol. Protonation of either nitrogen gives earlier transition states, increased asynchronicity, and a substantial decrease in the activation energy by 11–13 kcal/mol. Stabilization of the ene-hydrazine intermediates due to protonation (**9a** and **9b**) is less significant ($\Delta\Delta G = 3.1$ kcal/mol). Overall, the *N*β-protonated pathway is favored by 1.5 kcal/mol and yields the rearranged product **10b** in a concerted fashion. M06-2X significantly overestimated the barrier of the [3,3]-sigmatropic rearrangement by ~6–10 kcal/mol (see SI).

The influence of various substituents was evaluated computationally (Table 2). A single methyl substituent (entry 2) led to additional stabilization of both ene-hydrazine intermediates ($\Delta\Delta G \approx 4$ kcal/mol) and [3,3]-sigmatropic rearrangement transition states ($\Delta\Delta G \approx 6$ kcal/mol) compared to the parent reaction (entry 1). The energies of protonated ene-hydrazines are essentially identical, and the **β**–**TS** is still favored over the **α**–**TS**. The favorable [3,3]-sigmatropic rearrangement of the monomethylated substrate (entry 2) is consistent with experimental data on Fischer indole synthesis.⁵

Condensation of phenylhydrazines with 3-substituted hemiaminals or lactols, the so-called interrupted Fischer indolization strategy,¹⁵ involves disubstituted phenylhydrazone intermediates. We find that the second substituent further stabilizes the intermediates and transition states by 1–3 kcal/mol (entry 3) compared to the monomethyl substituted reaction. The *N*α- and *N*β-protonated pathways have comparable energies (Figure 2).

The reaction profile obtained with the indolyl-substituent, on the other hand, is completely different (entry 4, and Figure 3). The **α -TS-indolyl** ($\Delta G = 18.0$ kcal/mol) is noticeably lower in energy than **β -TS-indolyl** ($\Delta G = 21.2$ kcal/mol), but the favored transition state is not that of a [3,3]-sigmatropic rearrangement (Figure 3). Instead, the intrinsic reaction coordinate (IRC) gives the stable π -complex, **11**. In solution, this complex will dissociate, forming aniline and iminylcarbocation **12**. Therefore, for the indolyl substituted reaction, the $N\alpha$ -protonated pathway leads to dissociation rather than rearrangement in solution. This suggests that the iminylcarbocation, formed by the heterolytic $N-N$ bond cleavage, is stabilized by the electron-donating indolyl substituent, and this is responsible for the failure of the Fischer indolization for this substitution pattern. In place of an indolyl substituent, an acylated amine was evaluated (entry 5). Similarly, heterolytic $N-N$ bond cleavage was favored over [3,3]-sigmatropic rearrangement. This result explains why the acid-catalyzed Fischer indolization of amide-containing substrates has proved challenging.^{9–14}

To better understand this behavior, we calculated the heterolytic bond dissociation enthalpies of $N\alpha$ - and $N\beta$ -protonated ene-hydrazine intermediates (Table 3). As highlighted by entries 1–5, substantial weakening of the $N-N$ bond occurs in **9a** with more electron-donating substituents on the terminal alkene. The activation barriers of the $N\alpha$ -protonated species are lowered, and the transition states became more dissociative. The dissociative character of the weak $N-N$ bond eventually precludes the [3,3]-sigmatropic rearrangement, and the ene-hydrazine intermediate collapses to aniline and a stabilized iminylcarbocation. The heterolytic $N-N$ bond cleavage leads to side reactions rather than the Fischer indolization. These results are in accord with our experimental observations, and experimental findings by Mann and Cook.²² Previous studies of substituent effects on the Cope rearrangement and related 3,3-sigmatropic shifts indicate that substituents that stabilize either associative or dissociative transition states accelerate the concerted rearrangement.²³ Extreme stabilization of the dissociative transition state can eventually lead to dissociation, as was noted previously for amido-Cope rearrangements.²⁴

In contrast to electron-donating substituents, electron-withdrawing groups weaken the $N-N$ bond in **9b**, and stabilize the $N-N$ bond in **9a** (Table 3, entry 8 vs. 6). This suggests that changing the amino substituent to amido would somewhat disfavor the competing dissociative pathway. Indeed, the N -acyl group notably increases the strength of the $N-N$ bond in the $N\alpha$ -protonated ene-hydrazines compared to indolyl (Table 3, entries 4 and 7). However, the bond dissociation enthalpy is still low (8.9 kcal/mol) compared to the case with only alkyl substituents (31.0 kcal/mol). These results explain in part the relatively poor yields obtained in the acid-catalyzed Fischer indole synthesis of 3-amido indoles.¹⁰ Disubstitution with an amido and alkyl group is predicted to be detrimental for the $N\alpha$ -protonated rearrangement (Table 3, entry 6).

Electron-donating substituents weaken the $N-N$ bond in the $N\alpha$ -protonated ene-hydrazine and lower the activation energy for the rearrangement step. However, excessive stabilization of heterolytic $N-N$ bond cleavage precludes the products of the [3,3]-sigmatropic rearrangement, leading to the dissociation of the ene-hydrazine intermediate. This eventually translates to lower yields, or even to the failure of cyclization. Bond dissociation enthalpies are excellent guides to determine the feasibility of the cleavage process. Beyond providing an explanation for the failure of certain Fischer indolization reactions, we expect these findings will enable the judicious design of synthetic routes that employ aza-[3,3]-sigmatropic rearrangements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Thermal reaction

Acid-promoted reaction

Figure 1.

Free energies (ΔG , in kcal/mol) for the transformation of hydrazone to imine for the thermal and acid-promoted reaction [SCS-MP2/ 6-31G(d)(water)//MP2-6-31G(d)(water)].

Figure 2. Energy profile ($\Delta G[\Delta H]$, in kcal/mol) for the acid-promoted transformation of dimethyl substituted hydrazone.

Figure 3. Energy profile ($\Delta G[\Delta H]$, in kcal/mol) for the acid-promoted transformation of indolyl substituted hydrazone.

Scheme 1.
Classical and Interrupted Fischer Indolization Sequences

Table 1

Interrupted Fischer Indolization Attempts with 5c

entry	conditions
1	1:1 AcOH/H ₂ O, 25 °C to 110 °C
2	AcOH, 25 °C to 110 °C
3	TFA, C ₂ H ₄ Cl ₂ , 25 °C to 80 °C
4	HCl _(aq) , CH ₃ CN, 25 °C to 120 °C
5	H ₂ SO _{4(aq)} , CH ₃ CN, 25 °C to 120 °C
6	TsOH, <i>t</i> -BuOH, 25 °C to 80 °C

Table 2
Substituent Effects on the Free Energy (Enthalpy)^a Profile [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

Entry	Substituents
1	R ₁ : H, R ₂ : H	0.0 (0.0)	14.3 (14.1)	32.6 (30.3)	0.6 (0.6)	14.4 (14.3)
2	R ₁ : CH ₃ , R ₂ : H	0.0 (0.0)	10.6 (10.3)	26.1 (23.9)	0.5 (0.4)	10.7 (10.7)
3	R ₁ : CH ₃ , R ₂ : CH ₃	0.2 (0.0)	9.3 (8.7)	22.9 (20.3)^b	0.0 (0.0)	8.7 (7.7)
4	R ₁ : Indolyl, R ₂ : CH ₃	0.0 (0.0)	9.2 (8.8)	18.0 (16.5)^c	2.2 (2.7)	9.0 (9.3)
5	R ₁ : CH ₃ , R ₂ : N(H)acetyl	0.0 (0.0)	7.3 (7.6)	18.5 (17.7)^c	1.1 (1.5)	7.4 (8.5)
						31.1 (28.7)^b
						24.7 (22.8)^b
						22.3 (20.0)^b
						21.2 (19.3)
						19.6 (17.9)

^aFree energies (enthalpies in parenthesis) are given relative to phenylhydrazine in kcal/mol.

^bFavored transition state involves [3,3]-sigmatropic rearrangement.

^cFavored transition state leads to *N-N'* bond cleavage products.

Table 3

Bond Dissociation Enthalpies (BDE) of Protonated Ene-hydrazines [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

Entry	Substituents	BDE-9a ^a	BDE-9b ^a
1	R ₁ : H, R ₂ : H	47.1 (36.3)	34.2 (23.6)
2	R ₁ : CH ₃ , R ₂ : H	31.0 (19.8)	35.9 (25.1)
3	R ₁ : CH ₃ , R ₂ : CH ₃	20.7 (9.7)	38.1 (26.0)
4	R ₁ : Indolyl, R ₂ : H	0.0 (−10.1)	32.3 (21.2)
5	R ₁ : Indolyl, R ₂ : CH ₃	−1.8 (−13.2)	33.2 (21.5)
6	R ₁ : CH ₃ , R ₂ : N(H)acetyl	1.0 (−10.7)	36.4 (25.8)
7	R ₁ : H, R ₂ : N(H)acetyl	8.9 (−2.6)	34.9 (23.7)
8	R ₁ :N(H)acetyl,R ₂ :acetyl	10.7 (0.4)	22.4 (10.9)

^aRelative enthalpies of *N*–*N* bond cleavage of the corresponding ene-hydrazine intermediate (ΔH , kcal/mol). Relative free energies (ΔG , kcal/mol) are given in parenthesis.