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Why Do Some Fischer Indolizations Fail?

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Supporting Information

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.

Indole derivatives continue to receive substantial interest because of their wide range of biological activity.[1−5] The Fischer indole synthesis[6] 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, antimuscarinic, antibacterial, antiviral, antiplasmoidal, and antihyperglycemic activities and are attractive pharmacological targets.[7,8] However, to date there have been no examples of 3-aminoindole synthesis by the Fischer method, and the corresponding preparations of *N*-(indol-3-yl)amides[9−12] and 3-pyrazolylindoles[13,14] proceed poorly in the presence of protic acids. While the use of Lewis acids (e.g., $ZnCl_2$, $ZnBr_2$) improves the efficiency of these 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 cascade[15] (**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**, respectively, in good yields,[15] but the transformation failed en route to 3-indolylpyrrolidindoline **6c**, which was 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 attempts at interrupted Fischer indolization of substrate **5c**. Phenylhydrazine was employed in initial experiments. Acetic acid-based conditions, commonly used for the interrupted Fischer indolization reaction, gave none of the desired indoline product (entries 1 and 2). Similarly, the use of stronger acids typically employed to promote the 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 arylhydrazone derivatives of **5c** were treated under acidic conditions.

Even though it is 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 have been limited to semiempirical methods,[19] and the effect of substituents on the possible competing pathways has not been addressed to date. Here we report the first computational study of the mechanism of the Fischer indole reaction using accurate quantum-mechanical methods. We 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, as implemented in Gaussian 09.[20] Solvation effects were taken into account in geometry optimizations and 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 of the methods are given in the Supporting Information (SI). In the text, we discuss results obtained at the SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water) level of theory, which provided 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 (Nα-protonated and Nβ-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 Nβ-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 the SI).

The influence of various substituents was evaluated computationally (Table 2). A single methyl substituent (entry 2) leads to additional stabilization of both the ene−hydrazine intermediates ($\Delta\Delta G \approx 4$ kcal/mol) and [3,3]-sigmatropic rearrangement

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Scheme 1. Classical and Interrupted Fischer Indolization Sequences

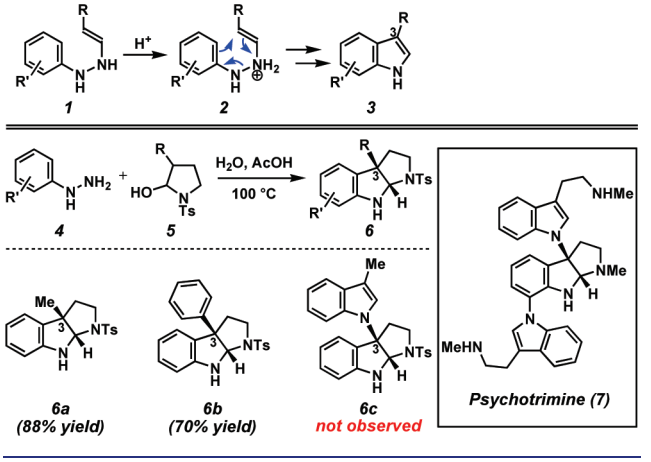
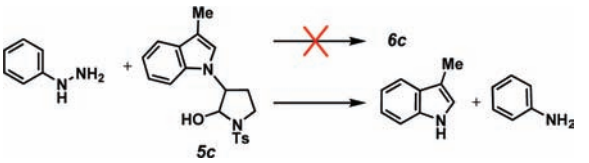


Table 1. Interrupted Fischer Indolization Attempts with 5c



entry	conditions
1	1:1 AcOH/H_2O, 25 to 110 °C
2	AcOH, 25 to 110 °C
3	TFA, $C_2H_4Cl_2$, 25 to 80 °C
4	HCl(aq), CH_3CN, 25 to 120 °C
5	H_2SO_4(aq), CH_3CN, 25 to 120 °C
6	TsOH, *t*-BuOH, 25 to 80 °C

transition states ($\Delta\Delta G \approx 6$ kcal/mol) relative to the parent reaction (entry 1). The energies of the protonated ene−hydrazines are essentially identical, and **β−TS** is still favored over **α−TS**. The favorable [3,3]-sigmatropic rearrangement of the monomethylated substrate (entry 2) is consistent with experimental data for the 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 found that the second substituent further stabilizes the intermediates and transition states by 1−3 kcal/mol (entry 3) relative to the monomethyl-substituted reaction. The Nα- and Nβ-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). **α−TS-indolyl** (ΔG = 18.0 kcal/mol) is noticeably lower in energy than **β−TS-indolyl** (ΔG = 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 dissociates to form aniline and iminyl carbocation **12**. Therefore, for the indolyl-substituted reaction, the Nα-protonated pathway leads to dissociation rather than rearrangement in

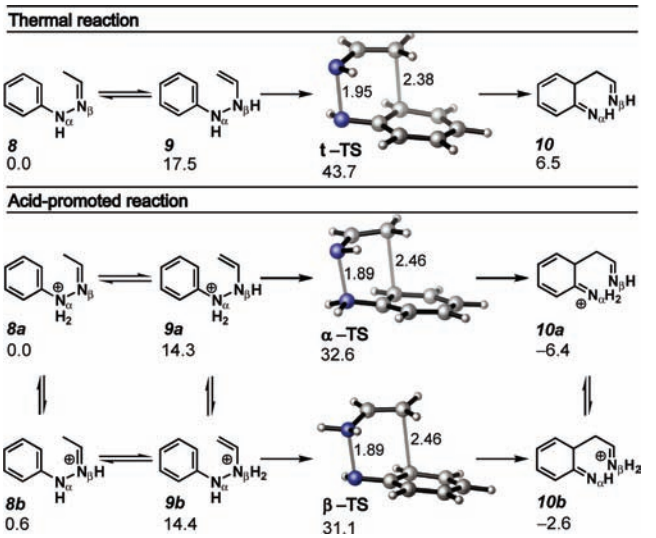


Figure 1. Free energies (ΔG, in kcal/mol) for the transformation of hydrazone to imine for the (top) thermal and (bottom) acid-promoted reactions [SCS-MP2/6-31G(d)(water)//MP2−6-31G(d)(water)].

solution. This suggests that the iminyl carbocation formed by the heterolytic N−N bond cleavage is stabilized by the electron-donating indolyl substituent and that 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 the [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 (BDEs) of Nα- and Nβ-protonated ene−hydrazine intermediates (Table 3). As highlighted by entries 1−5, substantial weakening of the N−N bond occurs in **9a** having more electron-donating substituents on the terminal alkene. The activation barriers of the Nα-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 iminyl carbocation. 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 the experimental findings by Mann and Cook.[22] Previous studies of substituent effects on the Cope rearrangement and related 3,3-sigmatropic shifts indicated 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 Nα-protonated ene−hydrazines relative to indolyl (Table 3, entries 4 and 7). However, the BDE is still low (8.9 kcal/mol) in comparison with the case having only alkyl substituents

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

Entry	Substituents	8a	9a	α-TS	8b	9b	β-TS
1	R_1: H, R_2: H	0.0 (0.0)	14.3 (14.1)	32.6 (30.3)	0.6 (0.3)	14.4 (14.3)	**31.1 (28.7)**[b]
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)	**24.7 (22.8)**[b]
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)	**22.3 (20.0)**[b]
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)	21.2 (19.3)
5	R_1: CH_3, R_2: N(H)acetyl	0.0 (0.0)	7.5 (7.4)	**18.5 (17.7)**[c]	1.1 (1.5)	7.4 (8.5)	19.6 (17.9)

[a] Free energies (enthalpies in parentheses) in kcal/mol relative to the phenylhydrazone are given. [b] Favored transition state involves [3,3]-sigmatropic rearrangement. [c] Favored transition state leads to N−N bond cleavage products.

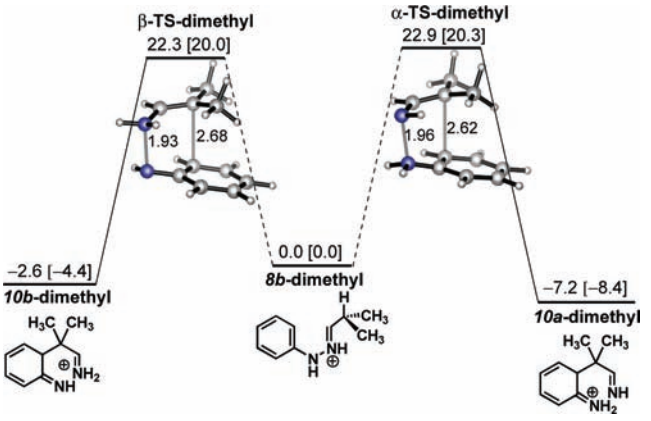

Figure 2. Energy profile (ΔG [ΔH], in kcal/mol) for the acid-promoted transformation of dimethyl-substituted hydrazone.

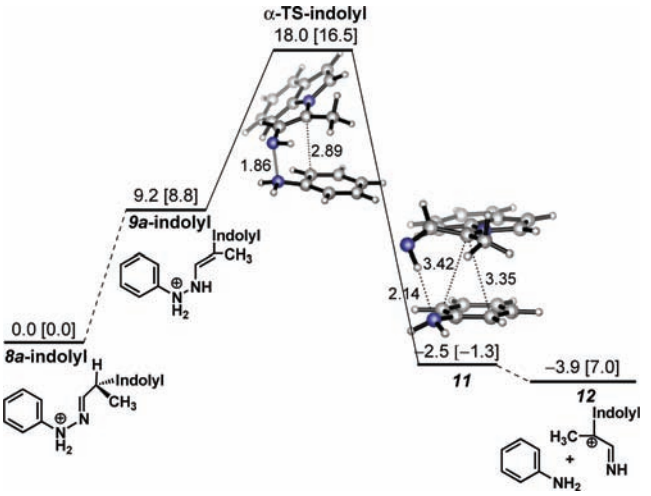

Figure 3. Energy profile (ΔG [ΔH], in kcal/mol) for the acid-promoted transformation of indolyl-substituted hydrazone.

(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 group and an alkyl group is predicted to be detrimental for the Nα-protonated rearrangement (Table 3, entry 6).

Table 3. Bond Dissociation Enthalpies (BDEs) of Protonated Ene−Hydrazines [SCS-MP2/6-31G(d)(water)//MP2/6-31G(d)(water)]

		BDE[a]	
entry	substituents	9a	9b
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 (−13.1)	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)

[a] Relative enthalpies of N−N bond cleavage of the corresponding ene−hydrazine intermediate (ΔH, kcal/mol). Relative free energies (ΔG, kcal/mol) are given in parentheses.

Electron-donating substituents weaken the N−N bond in the Nα-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 instead to the dissociation of the ene−hydrazine intermediate. This eventually translates to lower yields or even failure to cyclize. BDEs are excellent guides to determine the feasibility of the cleavage process. We expect that beyond providing an explanation for the failure of certain Fischer indolization reactions, these findings will enable the judicious design of synthetic routes that employ aza-[3,3]-sigmatropic rearrangements.

■ ASSOCIATED CONTENT

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

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