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Unusual Aryl Migration in a Mesomeric Betaine in the Solid and Liquid State: Mechanistic Insights into the S_NAr Reaction[†]

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An intramolecular S_NAr mechanism has been identified in the unexpected aryl migration observed in a mesomeric betaine. The process changes drastically the optical and spectroscopic properties and should be a valuable model for related heteroaromatic systems.

Mesomeric betaines along with the inherently aromatic mesoionic rings, by virtue of their electronic delocalization and luminescent properties, represent rising candidates for optoelectronic applications which include nonlinear effects¹ or the design of near-IR dyes.²

Among mesoionics, our group has extensively studied the synthetic versatility of 1,3-thiazolium-4-olates,³ turning recently to their 4-thiolate cousins as the presence of a bulkier and polarizable exocyclic sulfur atom was predicted to cause larger nonlinearities.⁴ We recently reported the synthesis of imidazo[2,1-*b*]thiazolium-3-thiolate systems (1) from the corresponding imidazo[2,1-*b*]thiazolium-3-olates (2) by reaction with aryl isothiocyanates, proving unequivocally

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that this thionation does actually proceed via a domino mechanism.⁵



In this conversion, mesomeric betaines 3 could also be isolated when either an electron-donating isothiocyanate was employed as dipolarophile ($R^2 = OCH_3$) or an electron-withdrawing group was linked to the imidazolinic nitrogen of 2 (Ar = 4-NO₂C₆H₄).

Here, we present the first aryl rearrangement occurring in mesomeric betaines such as $3a (R^1 = R^2 = NO_2)$ to give 2-(4-nitrophenylthio)imidazo[2,1-*a*]pyrimidin-4-one system (4a) (Scheme 1). The process took place spontaneously in both the solid state and CHCl₃ solution. In the absence of solvent, this rearrangement was clearly visible to the naked eye as orange crystals of 3a placed in a vacuum desiccator converted gradually into colorless crystals of 4a. Complete decoloration was observed after 2 weeks.

Figure 1 shows the gradual process in CDCl₃ monitored by ¹H NMR (400 MHz). The protons of the sugar moiety in compounds **3a** and **4a** showed similar chemical shifts and identical coupling constants, thus demonstrating that both the structure and conformation of the sugar fragment remained unaffected during the rearrangement. However, dispersion of signals corresponding to the 4-nitrophenyl groups of **3a**, caused by the hindered rotation of these aromatic rings, disappeared in the ¹H NMR spectrum of **4a** showing the typical coupling pattern of two AA'XX' systems. Also, as a result of this transposition, the carbon resonances for C-2 and C-6a underwent significant upfield shifts ($\Delta \delta = 14.7$ and 5.6 ppm, respectively), while C-3 and C-4 carbon atoms were deshielded to a lesser extent ($\Delta \delta =$ 1.8 and 4.3 ppm, respectively).

The solid-state structure of **4a** could be unambiguously elucidated by single-crystal X-ray diffraction (Figure 2). Crystal data⁶ revealed the favorable T-shaped arrangement adopted by the two 4-nitrophenyl groups in agreement with previous literature.⁷

This rearrangement can be interpreted as an intramolecular aromatic nucleophilic substitution (S_NAr) in which the thiolate group displaces the pyrimidinium ion of the nearest 4-nitrophenyl ring. Several factors appear to promote this intramolecular process such as the activation exerted by the nitro group, the good ability of the pyrimidinium ion as leaving group, and the offset stacking disposition of both

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 π -deficient *N*-aryl groups, the latter favoring the frontal approach of the 4-nitrophenyl group to the neighboring sulfur atom. In order to understand the way in which **3a** is transformed into **4a**, we have carried out a computational study on the relative migratory aptitude of the *N*-aryl group in compounds **3a** and **3b** (R¹ = NO₂; R² = OCH₃) in the gas phase at the B3LYP/6-31G(d)⁸ level using the Gaussian03 package.⁹ Figure 3 collects the relative electronic energies of all optimized stationary states involved in both the experimental **3a**—**4a** and the hypothetical **3b**—**4b** rearrangements.

During the search of the stationary states involved in these processes, concerted transition structures $TS_{3a \rightarrow 4a}$ and $TS_{3b \rightarrow 4b}$ could be located, and their relative energies $(\Delta \Delta E^{\pm} = 9.0 \text{ kcal/mol})$ account for the evolution of 3a into 4a and why, under the same reaction conditions, the transformation of 3b into 4b does not occur. Moreover, when 3b was heated at reflux in toluene for 6 h or in CHCl₃ at 100 °C (sealed vessel) for 2 h, aryl migration could not be observed either.

However, there was still a missing link between structure and migratory ability in those betaines. To shed light into steric and electronic factors and looking for a predictive picture as well, a comparative study on a series of structural parameters (bond lengths and angles, and bond orders) in nine betaines resulting from the different R¹ and R² combinations (R¹ and R² = H, OCH₃, NO₂) (see the Supporting Information) as well as the energy of the corresponding frontier orbitals was undertaken (Table 1).

An analysis of these data rules out geometry parameters as responsible of the different behavior. In stark contrast, inspection of the frontier orbitals reveals that the nature of R^2 profoundly affects both the energy and symmetry of the virtual orbitals. Thus, the UMOs for betaines **3a**, **3d**, and **3g**, possessing the appropriate symmetry to interact with the OMO located at the sulfur atom, have a gap of ~2.7 eV.



FIGURE 1. Transformation of betaine 3a into its isomer 4a in CDCl₃. Compound 3a (a) just dissolved, (b) after 2 h, (c) after 24 h.



FIGURE 2. ORTEP drawing of the crystal structure of 4a.



FIGURE 3. Energetics of the 3a-4a and 3b-4b rearrangements.

 $TABLE \ 1. \qquad Energy \ Differences \ (in \ eV) \ of \ the \ Orbitals \ Involved \ in \ Rearrangement \ at \ the \ B3LYP/6-31G(d) \ Level$

compd	\mathbb{R}^1	\mathbb{R}^2	$\Delta E (OMO - UMO)^a$	exptl result (yield, %) ^{b}
3a	NO_2	NO ₂	2.79	reaction (78)
3b	NO_2	OCH ₃	4.82	no reaction
3c	NO_2	Н	4.82	no reaction
3d	Н	NO_2	2.74	not tested
3e	Н	OCH ₃	5.04	no reaction
3f	Н	Н	4.80	not tested
3g	OCH_3	NO_2	2.74	not tested
3h	OCH ₃	OCH ₃	4.87	no reaction
3i	OCH ₃	Н	4.78	not tested
^a [a] H0	OMO-1 and	[b] LUMO f	or 3d and 3g; LU	JMO+1 for 3a;
LUMO+	6 for 3i ; LU	MO+7 for 3	b, 3c, and 3f; LU	JMO+8 for 3h;
LUMO+	9 for 3e . ^b See	ref 5.		

Compounds 3d and 3g could not be obtained experimentally. In the remaining derivatives, the UMOs with adequate symmetry for overlapping differ by at least 4.8 eV. In fact, compounds 3b, 3c, 3e, and $3h^5$ did not undergo aryl migration.

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FIGURE 4. (a) HOMO-1 of 3a, (b) LUMO+1 of 3a (B3LYP/6-31G(d) level).

 TABLE 2.
 Significant Geometry Parameters for the Stationary Points

 Involved in the Rearrangements of 3a and 3b (B3LYP/6-31G(d) Level)

\mathbb{R}^2	structure	C-N (Å)	C-S (Å)	N-C-S	exptl result (yield, %)
NO ₂	3a	1.45	3.01	63.4	reaction (78)
	TS _{3a→4a}	1.76	2.14	77.1	
	4a	2.88	1.79	65.8	
OMe	3b	1.45	3.04	62.4	no reaction
	TS _{3b→4b}	1.87	2.29	72.9	
	4b	2.85	1.79	66.4	

Figure 4 shows the orbitals involved in the rearrangement of **3a** (Table 2) and Figure 5 the most significant bond lengths and bond orders for $TS_{3a \rightarrow 4a}$.

As a final and intriguing mechanistic question, assuming a formal nucleophilic displacement, we also wondered whether an alternative stepwise mechanism through a Meisenheimertype intermediate did exist. To provide a clear-cut response, we decided to construct the potential energy surface (PES) for this reaction. Since the calculation is now computationally expensive, this was carried out using the hybrid ONIOM-[B3LYP/6-31G(d):PM3] method.^{10,11} A total of 176 (16 × 11) optimized structures were required to create the PES stemming from the sequential lengthening (0.1 Å) of both the N–C (a) and S–C (b) bonds (Figure 6a). Following the procedure previously described for us,¹² we have created a new hyper surface with a three-dimensional representation essentially identical (r > 0.9999) where we have superimposed the contour maps of isovalue lines (Figure 6b) to establish the real location of each stationary point on the PES.

Calculations of first derivatives with respect to either X or Y coordinates and their graphical plots gave rise to isovalue lines. Incorporation of these lines into the PES defined a single saddle point coincident with $TS_{3a \rightarrow 4a}$ (Figure 7) and discarded an alternative stepwise mechanism through a Meisenheimer-type intermediate. These results have further been confirmed by the IRC calculation for this transition structure at the B3LYP/6-31G(d) level (see the Supporting Information).

That this aryl migration proceeds via a rather concerted pathway may add further understanding to mechanism of



FIGURE 5. Significant bond lengths and bond orders (in brackets) for $TS_{3a \rightarrow 4a}$ (B3LYP/6-31G(d) level).



FIGURE 6. (a) PES corresponding to the transformation of **3a** into **4a**, calculated at the ONIOM[B3LYP/6-31G(d):PM3] level with full optimization of each structure. (b) Three-dimensional representation of the Chebyshev polynomial that fits to the PES data with superposition of its first derivative plots. Red and blue lines correspond to zones where the derivative values with respect to X (C-N bond) and Y (C-S bond), respectively, are close to zero.



FIGURE 7. ONIOM[B3LYP/6-31G(d):PM3]-optimized structure for $TS_{3a \rightarrow 4a}$ (C---N bond length, 1.78 Å; C---S bond length, 2.14 Å). Ball and sticks represent the partial system treated at the B3LYP/6-31G(d) level, whereas the wire-shaped structure corresponds to the molecular fragment assessed at the PM3 level.

nucleophilic aromatic substitution in a wide range of aromatic substrates. The transformation described here is consistent with the ab initio study of reactions of benzenediazonium ion with water.¹³ Thus, our results agree with a direct S_NAr reaction with a rather loose transition state analogous to the saddle structures of front-side nucleophilic replacement at saturated centers.

In conclusion, this note discusses an unexpected aryl migration occurring through a concerted mechanism and may

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stimulate the search for this short of pathways in aromatic and heteroaromatic systems.

Experimental Section

Synthetic procedure and spectroscopic data for 1,6-bis(4nitrophenyl)-4-oxo-3-phenyl- $(3',5',6'-tri-O-acetyl-1,2-dideoxy-\alpha-$ D-glucofurano)[1',2':4,5]-5aH,5bH-imidazo[2,1-*a*]pyrimidin-5ilium-2-thiolate (**3a**) are given in the Supporting Information of ref 5a.

6-(**4**-Nitrophenyl)-2-(**4**-nitrophenylthio)-3-phenyl-(3',5',6'-tri-*O*-acetyl-1,2-dideoxy- α -D-glucofurano)[1',2':4,5]-5aH,5bH-imidazo-[1,2-*a*]pyrimidin-4-one (4a). A solution of 3a (200 mg) in chloroform (10 mL) was kept at room temperature and monitored by TLC (benzene-acetonitrile 3:1; $R_{/3a}$, 0.3; $R_{/4a}$, 0.55) until the disappearance of 3a was observed (~24 h). The solution was evaporated, and the residue was crystallized from ethanol (143 mg, 72%): colorless crystals; mp 231–232 °C; $[\alpha]_D$ +7, $[\alpha]_{578}$ +8, $[\alpha]_{546}$ +15, $[\alpha]_{436}$ +122 (*c* 0.5, chloroform); ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, 2H, J 8.8 Hz), 7.91 (d, 2H, J 9.2 Hz), 7.73 (d, 2H, J 8.8 Hz), 7.53 (d, 2H, J 9.2 Hz), 7.49–7.41 (m, 5H), 6.35 (d, 1H, J 6.4 Hz, H-1'), 6.14 (d, 1H, J 2.8 Hz, H-3'), 5.30–5.26 (m, 1H, H-5'), 4.95 (d, *J* 6.4 Hz, 1H, H-2'), 4.49 (dd, 1H, *J* 2.0 Hz, *J* 12.0 Hz, H-6'), 4.21 (dd, 1H, *J* 2.8 Hz, *J* 9.6 Hz, H-4'), 4.10 (dd, 1H, *J* 12.0 Hz, *J* 5.6 Hz, H-6''), 2.11 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 169.7, 168.1, 163.3, 157.7, 149.5, 148.3, 143.9, 142.0, 138.5, 136.6, 131.4, 130.5, 128.8, 128.5, 124.3, 123.7, 118.8, 116.5, 90.1, 77.6, 71.6, 66.6, 63.4, 63.0, 20.7, 20.6, 20.5; IR (KBr, cm⁻¹) 1743, 1675, 1579, 1526, 1502, 1423, 1347, 1225, 1109, 1046. Anal. Calcd for C₃₄H₂₉N₅O₁₂S: C, 55.81; H, 3.99; N, 9.57; S, 4.38. Found: C, 55.67; H, 4.13; N, 9.52, S, 4.31.

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Supporting Information Available: Copies of NMR spectra, molecular-modeling coordinates, X-ray data (CIF), and additional tables and graphs. This material is available free of charge via the Internet at http://pubs.acs.org.