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Arylazo-3,5-dimethylisoxazoles – Azoheteroarene photoswitches exhibiting high *Z*-isomer stability, solid state photochromism and reversible light-induced phase transition

Pravesh Kumar, Anjali Srivastava[‡], Chitranjan Sah[‡], Sudha Devi and Sugumar Venkataramani^{*}

Dedicated to Prof. K. S. Viswanathan on the occasion of his retirement

Abstract: Reversibly photoswitchable phenylazo-3.5dimethylisoxazole and 37 aryl substituted derivatives have been synthesized. Excellent photoswitching ability of these molecules in solution and solid phase has been demonstrated. Through kinetics studies using NMR spectroscopy, a long Z-isomer stability has also been perceived. Interestingly, majority of the derivatives showed the light-induced contrasting colour changes in solution as well as the solid phase. Apart from that, many derivatives exhibit partial phase transition upon UV light irradiation. The highlight of this class of photoswitches is the reversible light-induced phase transition between solid and liquid phases in the parent compound that can be used in patterned crystallization. All these results on this new class of azoheteroarene based photoswitches provide opportunities to be useful in various domains.

Introduction

Azoheteroarenes are one of the increasingly popular classes of photoswitches that acquired importance in various applications such as spin-crossover, NIR dyes, catalysis, medicinal chemistry, etc.^[1-3] The replacement of aryl groups with heterocycles in the azoarenes provides the possibility of coordination and the hydrogen bonding networks.^[4-5] Particularly, the presence of the heterocyclic moiety closer to azo group significantly increases the photoswitching properties and amplifies the application potential. In this regard, azoimidazole^[6], azopyrazoles^[7] and azoindoles^[8] have been reported as the improved photoswitches with excellent features such as increased Z-isomer stability, quantitative isomerization for forward and reverse photoisomerization steps, tunability, etc. Following this, many other azoheteroarene classes and derivatives have also been unraveled with interesting photophysical properties.^[9] Among the recently reported azoheteroarenes, Fuchter's phenylazo-Nmethylpyrazole showed excellent photoswitching ability and Zisomer stability that enabled these systems to be utilized in several applications.^[10] A T-type geometry with C-H.. π interactions was found to be a necessary condition in enhancing the stability of the Z-isomer.

Interestingly, if methyl groups are introduced at the *ortho* position to the azo group in the pyrazole moiety, the half-life of

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azopyrazole was lowered by an order of two owing to steric factors.^[7b] Equally, the removal of *N*-methyl group of pyrazole resulted in lowering of the half-life. Moreover, such systems with 3,5-dimethyl-NH-pyrazole derivatives were strongly susceptible to substituent as well as hydrogen bonding effects. Substantial influences of substituents have been predicted majorly through the steric and electronic effects. However, the impact of hydrogen-bonded dimerization at higher concentration, and solvent-assisted tautomerism at lower concentration have also been envisaged. This results in a complex interplay of all these factors that influences the photoswitching and thermal reverse isomerization steps. Either functionalization at pyrazole nitrogen, or replacing N-H with a group or an atom that can disable the hydrogen bond donating ability and tautomerism prospects could be the viable strategies to overcome this situation. Since Fuchter and coworkers already reported the benefits and improvement in the half-life using N-Me group, the alternative strategy is still unattempted. Accordingly, a simple replacement of N-H with O to generate 3,5-dimethylisoxazole derivatives can open up yet another class of photoswitches. Despite the fact that such compounds have already been reported for their therapeutic effects in medicinal chemistry, the photoswitching aspects have been seldom studied.[11,12]

The impact of the isoxazole moiety in photoswitching behavior and thermal stability aspects of Z-isomers is the focus of this contribution. Besides understanding those, the aryl substituent effects and the added benefits of utilizing such photoswitches were also considered. The advantage of isoxazole unit is that hydrogen bonding and tautomeric channels are cut off, and so steric and electronic influences of the substituents can be realized. In this regard, we have synthesized arylazo-3,5dimethylisoxazole derivatives with different ortho, meta and para substituents. A few selected di-substituted derivatives have also been synthesized. Photoswitching studies have been carried out for all the azo derivatives, and the analysis has been carried out using UV-vis spectroscopy. The stability of the Z-isomer has been estimated by following the first order thermal reverse isomerization kinetics through NMR spectroscopy. In order to determine the effects of substituents in electronic structural aspects of both *E*- and *Z*-isomers, and also the stability aspects undermining the reverse thermal isomerization, computations have been extensively performed.

During our investigations, apart from the photoswitching, we have also observed photochromic behavior accompanied by the light-induced phase transition in majority of the derivatives. The native solid state of the molecules upon exposure to UV light underwent partial to complete melting. Such room temperature phase transitions provide a variety of applications such as photolithography, reversible adhesives, photoresists, etc.^[13] Indeed, the parent phenylazo-3,5-dimethylisoxazole **1d** is found to be one of the simplest azo derivatives exhibiting such reversible light-induced phase transition. For understanding this phenomenon, differential scanning calorimetric (DSC), polarized optical microscopic (POM) imaging, IR spectroscopic studies

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along with computations have also been carried out. Overall, the investigations on arylazo-3,5-dimethylisoxazoles clearly reveal that they are indeed a very interesting class of photoswitches with several salient features. Herein, we report the details of the synthesis, photoswitching, kinetics studies, and reversible lightinduced phase transition through spectroscopic and computational studies arylazo-3,5-dimethylisoxazole on photoswitches.

Results and Discussion

Synthesis: A common diazonium salt strategy has been adopted in synthesizing the parent phenylazo-3,5dimethylisoxazole and majority of their 36 substituted derivatives (Scheme 1 and Supporting Section S2). In this regard, commercially available aniline derivatives have been used as the starting materials. Both the generation of hydrazone derivatives 1-37c, and the consecutive cyclization step with hydroxylamine hydrochloride to access the target isoxazole based derivatives 1-37d have been adopted using the literature procedure.^[7c] However, the presence of a base provided good to excellent yields in the cyclization step. The 2-amino derivative 32d was synthesized by reduction of the corresponding nitro derivative 20d.^[14] On the other hand, 3- and 4-amino derivatives 33d and 34d were obtained through the hydrolysis of 23d and 24d, respectively.



| Entry | R = | Yield ^d | Entry | R = | Yield ^d |
|-------|---------------------|--------------------|------------------|---------------------------|--------------------|
| 1d | Nil | 85 | 20d | 2-NO ₂ | 60 |
| 2d | 2-F | 96 | 21d | 4-NO ₂ | 97 |
| 3d | 3-F | 89 | 22d | 4-CH ₃ | 87 |
| 4d | 4-F | 50 | 23d | 3-NHCOCH ₃ | 82 |
| 5d | 2-Cl | 54 | 24d | 4-NHCOCH ₃ | 80 |
| 6d | 3-Cl | 84 | 25d | R-Ph = α -Naphthyl | 78 |
| 7d | 4-Cl | 85 | 26d | 2,5, di-Cl | 54 |
| 8d | 2-Br | 67 | 27d | 2,6-di-Cl | 71 |
| 9d | 3-Br | 72 | 28d | 2,4-di-F | 78 |
| 10d | 4-Br | 75 | 29d | 2,5-di-F | 54 |
| 11d | 4-I | 94 | 30d | 2,6-di-F | 53 |
| 12d | 2-OH | 93 | 31d | 3,5-di-F | 87 |
| 13d | 3-OH | 71 | 32d ^e | 2-NH ₂ | 78 |
| 14d | 4-OH | 79 | 33d ^f | 3-NH ₂ | 82 |
| 15d | 3-CF ₃ | 89 | 34d ^f | 4-NH ₂ | 73 |
| 16d | 4-CF ₃ | 62 | 35d | 2-CN | 51 |
| 17d | 2-OCH ₃ | 78 | 36d | R-Ph = 3-Pyridyl | 78 |
| 18d | 3-0 CH₃ | 75 | 37d | R-Ph = 4-(Ph-N=N-Ph) | 69 |
| 19d | 4-0 CH ₃ | 80 | | | |

Scheme 1. Synthesis of substituted phenylazoisoxazole derivatives 1-37d. Conditions: (a) NaNO₂, HCl, H₂O, 0-5 °C; (b) acac, NaOAc; (c) NH₂OH.HCl, Na₂CO₃, EtOH, reflux; (d) isolated yields of the final step; (e) Condition: 20d, Na₂S.9H₂O, 1,4-dioxane, EtOH, H₂O, reflux; (f) Condition: 23d/24d, conc. HCl, EtOH, reflux.

Absorption properties and photoswitching in solution phase and solid-state: In order to understand the effects of substituents and also to evaluate their impact on photoswitching characteristics, we have compared the electronic spectral properties of the native *E*- and *Z*-isomers of all the 37 arylazoisoxazole derivatives 1-37d (Figure 1, Table 1 and Supporting Section S3). In this regard, the electronic spectral analysis in a common solvent (acetonitrile) has been carried out for all the derivatives. All the derivatives were subjected to 365 nm UV light irradiation in the same solvent to induce the E-Z photoisomerization. In spite of the observation of changes in the spectral features, the relative isomerization conversion was found to vary from one derivative to the other. For few derivatives such as 14d, 15d, 16d, 20d, 27d, 30d, 36d, and 37d, exhibited poor isomerization conversion, inferred from the subtle lowering of intensity without a significant blue shift, a key signature for the π - π * transition corresponding to E-Z isomerization process. However, we observed an enhancement in the $n-\pi^*$ feature indicating the isomerization. Apart from that, the presence of isosbestic points confirmed the interconversion between the two isomers without any intermediate. On the other hand, excellent photoswitching has been observed in many derivatives based on both the variation in the intensity as well as the blue shifts at the π - π * band.

For a better understanding of the substituent effects on the Eand Z-isomers, the electronic spectral characteristics have been utilized in the form of λ_{max} vs ϵ plots (Figure 2). At the outset, both the π - π ^{*} and n- π ^{*} absorption features in *E*- and *Z*-isomers of all the compounds have been modeled around the parent 1d using this ε vs λ_{max} plot. The plots have been split into four quadrants by keeping the corresponding λ_{max} and ϵ values of the parent compound 1d as the origin. The results revealed that both the π - π ^{*} and n- π ^{*} absorption maxima were more sensitive to the substituents in the Z- than in the E-isomers. In general, the para-substitution influences the λ_{max} , whereas the meta- and ortho-substituents affects the molar absorptivity of the $\pi-\pi^*$ absorptions in both E- and Z-isomers. This observation can be due to the interplay of electronic effects through inductive and mesomeric effects. Indeed, the role of steric effect can clearly be understood from the shifts in 2-substituted analogs, where $n-\pi^*$ bands were found to be more susceptible.



Figure 1. Photoisomerization in phenylazo-3,5-dimethylisoxazole 1d. Analysis
of reversible *E-Z* photoisomerization in 1d using UV-Vis spectroscopy in (a)
solution phase (Solvent: CH₃CN, 35.8 μ M); (b) in solid phase (Medium: KBr);
Analysis of photoswitching using ¹H-NMR spectroscopy (Solvent: CDCl₃, 9.9
mM); (c) Before irradiation; (d) After 365 nm irradiation; (e) After 505 nm
irradiation; (f) Reversible photoisomerization in 1d.

| Table 1. UV-Vis spectroscopic and photoswitching data of (E) - and (Z) |)- isomers of phenylazo-3,5- |
|---|------------------------------|
| dimethylisoxazole derivatives 1-37d . | |

| | σ | | E-isomer ^a | | | | Z-isomer ^a | | | | | ion | |
|-------|---------|-------------------|-----------------------------|------------------------------|---------------------|-------------------------------------|--------------------------------------|------------------------------|-------|---------------------|---------------|---------------------|--------------|
| S. No | Compoun | | ππ* λ _{max} , ε | n–π* λ _{max} , ε | Δλ _{trans} | <i>E-Z</i> PSS⁵ (% <i>Z</i>) | π–π ∗ λ _{max} , ε | n–π* λ _{max} , ε | Δλcis | Z-E PSS° (%E) | Δλ.conjugatio | Concentrati [µM] | |
| 1 | 1d | н | 315 (18162±117) | 422 (481±17) | 107 | 46 59 | 302 (15100) | 428 (1428) | 126 | 78 76 | 13 | 36 | _ |
| 2 | 2d | 2-F | 321 (14301±183) | 416 (609±7) | 95 | 47 | 313 (16782) | 422 (1345) | 109 | 76 | 8 | 42 | |
| 3 | 3d | 3-F | 315 (8340±753) | 421 (336±36) | 106 | 34 | 309 (7741) | 428 (916) | 119 | 93 | 6 | 56 | |
| 4 | 4d | 4-F | 318 (16360±153) | 421 (481±8) | 103 | 93 80 | 296 (6857) | 428 (1378) | 132 | 80 82 | 22 | 37 | + |
| 5 | 5d | 2-Cl | 321 (12124±220) | 424 (383±40) | 103 | 58 | 304 (8889) | 426 (1186) | 122 | 75 | 17 | 51 | \bigcirc |
| 6 | 6d | 3-CI | 315 (17731±71) | 425 (425±15) | 110 | 66 | 294 (6181) | 429 (1605) | 135 | 81 | 21 | 39 | - |
| 7 | 7d | 4-Cl | 323 (22789±269) | 423 (670±16) | 100 | 92 94 | 294 (7780) | 429 (2301) | 135 | 78 62 | 29 | 28 | |
| 8 | 8d | 2-Br | 321 (9830±688) | 428 (418±7) | 107 | 42 | 310 (15503) | 428 (1112) | 118 | 81 | 11 | 56 | U |
| 9 | 9d | 3-Br | 315 (7822+744) | 423 (388+35) | 108 | 91 89 | 306 (11094) | 429 | 123 | 84 76 | 9 | 41 | S |
| 10 | 10d | 4-Br | 325 (21083±89) | (679±14) | 96 | 49 | 295 (13767) | 432 (1976) | 137 | 84 | 30 | 32 | |
| 11 | 11d | 4-I | 330 (23665+614) | 424 (830+35) | 94 | 67 | 295 (11728) | 432 (4530) | 137 | 73 | 35 | 28 | |
| 12 | 12d | 2-OH | 316 (17128+549) | - | | 46 | 316 | - | 316 | 73 | - | 39 | |
| 13 | 13d | 3-OH | 313 (16908+46) | 418 (596+15) | 105 | 67 87 | 288 (8317) | 432 (1948) | 144 | 76 80 | 25 | 36 | σ |
| 14 | 14d | 4-OH | 340 | - | - | - | - | - | - | - | - | 48 | |
| 15 | 15d | 3-CF₃ | 314 (19730±419) | 418 (569±54) | 104 | 38 | 308 (32445) | 426 (1081) | 118 | 77 | 6 | 34 | 2 |
| 16 | 16d | 4-CF₃ | 312 (8744±757) | 425 (384±8) | 113 | 35 | 309 (20332) | 429 (817) | 120 | 83 | 3 | 62 | |
| 17 | 17d | 2-OMe | 311 (10598±419) | 414 (1036±36) | 103 | 62 | 285 (6732) | 426 (2296) | 141 | 69 | 26 | 64 | \mathbf{O} |
| 18 | 18d | 3-OMe | 312 (14802±133) | 423 (604±16) | 111 | 68 | 289 | 430 (1813) | 141 | 75 | 23 | 46 | (I) |
| 19 | 19d | 4-OMe | 337 (21570±319) | 403 (1314±138) | 66 | 65 98 | 309 (20332) | 434 (3187) | 125 | 82 92 | 28 | 28 | L L |
| 20 | 20d | 2-NO ₂ | 318 (17241±110) | 421 (640±19) | 103 | 16 | 318 (91429) | 415 (1037) | 97 | 92 | - | 35 | 5 |
| 21 | 21d | 4-NO ₂ | 332 (22095+113) | 431 (905+30) | 99 | 55 | 295 (18140) | 436 (2393) | 141 | 86 | 37 | 28 | |
| 22 | 22d | 4-CH₃ | 323 (12333±1450) | 420 (973±34) | 97 | 42 | 308 (23450) | 430 (2220) | 122 | 93 | 15 | 41 | U |
| 23 | 23d | 3-NHAc | 315 (18797±1328) | 429 (573±48) | 114 | 69 | 295 | 429 (2171) | 134 | 69 | 20 | 33 | \mathbf{O} |
| 24 | 24d | 4-NHAc | 342 (25152±129) | 416 (1336±28) | 74 | 65 | 315 (14035) | 437 (8817) | 122 | 35 | 27 | 27 | 5 |
| 25 | 25d | R-Ph = α- Np | 362 (6789±354) | 439 (881±10) | 77 | 59 | 342 (4876) | 440 (1970) | 98 | 79 | 20 | 70 | |
| 26 | 26d | 2,5-diCl | 320 (10850±556) | 430 (452±16) | 110 | 53 | 298 (10045) | 427 (1267) | 129 | 85 | 22 | 50 | |
| 27 | 27d | 2,6-diCl | 297 (10893±31) | 429 (409±8) | 132 | 23 | 292 (36409) | 421 (809) | 129 | 82 | 5 | 60 | |
| 28 | 28d | 2,4-diF | 324 (20900+443) | 420 (766+53) | 96 | 44 | 323 (27197) | 420 (1818) | 97 | 72 | 1 | 36 | |
| 29 | 29d | 2,5-diF | 328 | 417 | 89 | 68 | 287 | 422 | 135 | 70 | 41 | 38 | |
| 30 | 30d | 2,6-diF | (1602/±//) 309 | (503±12) 419 | 110 | 30 | (8405) 305 (26.476) | (2222) 419 (1646) | 114 | 73 | 4 | 38 | |
| | | · | (10809±155) | (882 ± 28) | - | - | (26476) | (1646) | | | | | |

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| 31 | 31d | 3,5-diF | 315 (16104±19) | 417 (427±10) | 102 | 60 | 297 (10953) | 429 (1324) | 132 | 82 | 18 | 36 |
|----|-----|------------------------------|---------------------|------------------|-----|-----------------|----------------|---------------|-----|-----------------|----|----|
| 32 | 32d | 2-NH ₂ | 310 (11667±1227) | - | - | 54 61 | 304 (14387) | 438 (7566) | 134 | 60 92 | 6 | 34 |
| 33 | 33d | 3-NH ₂ | 315 (18293±113) | 373 (3212±14) | 58 | 65 | 290 (9804) | 428 (2590) | 138 | 73 | 25 | 36 |
| 34 | 34d | 4-NH ₂ | 371 (17176±378) | - | - | 53 | 348 (15207) | 439 (4988) | 91 | 70 | 23 | 38 |
| 35 | 35d | 2-CN | 325 (16353±1035) | 431 (499±39) | 106 | 65 90 | 304 (8317) | 434 (1501) | 130 | 78 83 | 21 | 52 |
| 36 | 36d | R-Ph = 3- Pyridine | 316 (7810±1340) | 421 (376±7) | 105 | 18 | 311 (40431) | 429 (741) | 118 | 98 | 5 | 83 |
| 37 | 37d | R-Ph = 4- (Ph-N=N- Ph) | 358 (37483±309) | 428 (3041±60) | 70 | 37 | 348 (65006) | 434 (4051) | 86 | 87 | 10 | 17 |

^aThe values of λ_{max} are given in nm and ε in L.mol⁻¹.cm⁻¹; ^bPSS for *E-Z* isomerization has been estimated at 365 nm (normal: UV-Vis (CH₃CN); bold: ¹H-NMR (italics: CDCl₃ (**1d** & **32d**); normal: DMSO-*d_e*); ^cPSS for *Z-E* isomerization has been estimated at appropriate wavelengths of light as indicated in the supporting Table S2 with 2-5% uncertainity^{7a} (normal: UV-Vis (CH₃CN); bold: ¹H-NMR (italics: CDCl₃ (**1d** & **32d**); normal: DMSO-*d_e*); ^dThe difference in the π - π * absorptions for *E*- and *Z*-isomers has been estimated in understanding the degree of conjugation breaking upon isomerization. (The ε values for *Z*-isomers have been estimated based on the PSS composition at *E-Z* isomerization step; α -Np = α -naphthyl.)



Figure 2. Effect of substituents in the absorption properties of *E*- and *Z*-isomers of the substituted phenylazo-3,5-dimethylisoxazoles: (a) and (b) corresponding to π - π^* and n- π^* absorptions for *E*-isomers, respectively; (c) and (d) corresponding to π - π^* and n- π^* absorptions for *Z*-isomers, respectively. (The variation in the absorption in terms of ε and λ_{max} shifts are separated into four quadrants with respect to that of the parent **1d**, which was considered as the origin.)

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The solution phase photoswitching showed only a minimal concentration dependency in the forward isomerization step. Even at a very high concentration (1.6 mM), the E-Z isomerization was found to be as good as at µM concentration (supporting Figure S1). This clearly supported our understanding (based on the earlier studies on azopyrazoles) that the photoisomerization step can be limited by the hydrogen bonding.7c Surprisingly, the 2-hydroxy 12d and 2-amino 32d substituted derivatives were also found to undergo photoswitching. This is in contrary to many azoarenes and azoheteroarenes with such functional groups at ortho position, which has been attributed to the intramolecular hydrogen bonding and the resulting tautomeric equilibrium.^[15] However, at higher concentration, 12d did not show any photoswitching indicating that either the reverse isomerization step is faster or intermolecular hydrogen bonding dominates. Compared to the hydroxy, the amino derivative indeed showed a better photoswitching. Indeed, 32d exhibited visible liaht photoswitching as well. For obtaining better prospects, both the molecules were subjected to photoswitching and were followed by NMR spectroscopy as well. The ¹H-NMR of the hydroxy protons in 12d was found to appear at 11.94 ppm, clearly indicating the possibility of an intramolecular hydrogen bonding with the azo nitrogen. On the other hand, the amine protons in 32d were not strongly influenced by the hydrogen bonding inferred from the appearance of a single broad signal around 5.35 ppm. In yet another case of bis(azo) derivative 37d, we observed photoswitching, in which four different species were observed, due to the unsymmetrical environment about the two azo groups. Since the photoisomerization happens only to a limited extent, both forward and the reverse isomerization steps led to a mixture of photoproducts. For the best photoswitching derivatives, PSS compositions have been estimated using ¹H-NMR that revealed good to excellent photoswitching for both forward and reverse isomerization steps (Supporting Section S6). Furthermore, the studies on selected derivatives by repeating the forward and reverse photoswitching over five cycles using UV-vis spectroscopy revealed the photoswitching stability without any fatigue (Supporting Section S7).

Apart from the solution phase photoisomerization, all the 37 arylazoisoxazole derivatives have been subjected to solid-state photoswitching. In this regard, we have studied the reversible photoisomerization of them in KBr medium. Despite showing excellent *E-Z* photoisomerization, the reverse step was found to be partial in the majority of the derivatives. In order to understand the efficiency of the photoisomerization, the isomerization conversion has been estimated at their respective photostationary states (PSS) for the forward *E-Z* and reverse *Z-E* step in the solid-state, as well as in the solution phase. The PSS compositions have been estimated based on the literature methods^[4a,7a,7c,10c] and the results are tabulated (Table 1 and Supporting Table S2 for solid-state PSS data).

Computational studies^[16]: For understanding the effects of the substituents in the electronic structure of the E- and Z-isomers of the arylazo-3,5-dimethylisoxazoles, selected meta-substituted derivatives have been chosen.[17] In order to envisage the effects of substituents on structural characteristics, various properties such as geometries, MOs, and the isomerization mechanisms have been considered and computed at B3LYP/6-311G(d,p) and M06-2X/6-311G(d,p) levels of theory. Primarily, we optimized of the Eand Z-isomers the selected arylazo-3,5-dimethylisoxazoles derivatives to their minima and their thermochemistry data has been obtained (supporting Tables SC1-16). Essentially, the geometrical features (dihedral angles, charges at the azo nitrogens) with respect to their parent E- and Z-isomers have been closely inspected. In spite of significant changes in those parameters, the computed structural data did not show any trend that can be accountable for the electronic effects of the substituents. In fact, this observation was also seen in the case of arylazopyrazoles with metasubstitution.^[7c] Likewise, in our earlier studies on arylazopyrazoles, the inspection of molecular orbitals corresponds to HOMO-1, HOMO and LUMO of the E-isomer of phenylazoisoxazole revealed the n-, π - and π *-orbitals, respectively. On the other hand, the Z-isomer showed a mix of n and π character in the HOMO-1 and HOMO orbitals, whereas, the LUMO was found to be π^* -orbital (Supporting Figure SC1). The energy gaps corresponding to $n-\pi^*$ and $\pi-\pi^*$ MOs exhibited minimal changes with respect to substituents. These computed results have already been observed experimentally, where the meta-substituted derivatives showed only perturbation in the ε values rather than λ_{max} . The only exception was the meta substitution with methoxy group, where the energy gap was found to be marginally higher. Interestingly, for the corresponding *Z*-isomers, more variation in the n- π^* energy gap was observed, whereas only subtle changes were observed in the case of $\pi - \pi^*$ energy gaps. These changes in the n- π^* energy gap can be attributed to the mixing of n and π character in HOMO-1, and subsequent accumulation of substantial π character leading to the electronic effects.



Figure 3. (a) First order reverse thermal (*Z*-*E*) isomerization kinetics of phenylazo-3,5-dimethylisoxazole at 80 \pm 2 °C. (Solvent: DMSO-d₆; 9.9 mM) (b) Thermal *Z*-*E* isomerization channels in phenylazo-3,5-dimethylisoxazole **1d** for two different conformations. (The energies are given in kcal/mol; Normal – B3LYP/6-311G(d,p) and *Italics* – M06-2X/6-311G(d,p)) The TS1 and TS2 correspond to the inversion mechanism, whereas the TS3 is maxima in the rotational channel.

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Thermal stability of Z-isomers: Apart from the efficient photoswitching in the forward E-Z and the reverse Z-E isomerization steps, the stability of the Z-isomer is a decisive factor in many practical applications. So often the thermal reverse isomerization is a crucial step in influencing the utility. In this regard, we have utilized the NMR spectroscopy.^[18] The room temperature (25 ± 2 °C) kinetics showed a slow rate of isomerization with a half-life of 45.5 days in DMSO-d₆. On the other hand, the half-lives have been estimated to be 111, 48 and 16 min, if the kinetics have been followed at 70 ± 2, 80 ± 2 and 90 ± 2 °C, respectively (Figure 3a and Supporting Figure S4).[19a] Using these variable temperature kinetics data, the activation parameters for the reverse thermal isomerization step have been estimated (Supporting Figure S6). The activation barrier for the reaction in 1d was found to be 116 \pm 3 kJ.mol⁻¹, which is comparable with few of the thermally long-lived Z-isomers of the azoarene and azoheteroarenes known.[7a,19b,20]

Inversion and rotational transition states were reported to be the major mechanistic channels for the thermal Z-E isomerization in many azoheteroarenes. Depending on the heterocycles, the pathway can vary, which necessitates the investigation on the mechanistic aspects.^[7b,7c,8] In this regard, we have computed both the mechanistic channels in the Z-E isomerization of arylazo-3,5-dimethylisoxazole. pathways Due to substituents about the group unsymmetrical azo in arylazoisoxazoles, there can be two inversion pathways (inversion along isoxazole ring or along phenyl ring). Furthermore, the conformations of the isoxazole ring relative to the azo group (N-O and O-N) can potentially lead to additional inversion channels.^[21a] On the other hand, the rotational barrier can only be influenced by the conformational preference of the isoxazole ring relative to the azo group and so only two different transition states are possible. All the possible channels have been computed at B3LYP/6-311G(d,p) and M06-2X/6-311G(d,p) and are indicated in figure 3b.[21b] During our investigations, the thermal barrier for inversion along phenyl ring was found to be the lowest channel among all possible barriers in both the levels of theory.^[21c] This is consistent with similar systems such as arylazopyrazoles and arylazoimidazoles.[7b,7c,6b] Indeed, the rotational channels were found to have a barrier more than two times of the minimal energy inversion pathway.

Since the arylazoisoxazole derivatives exhibited long half-life for *Z*-isomers, the thermal reverse isomerization rate constants have not been studied experimentally for all the isomers. Instead, the influence of the electronic effect on the thermal barriers has been computationally studied. For consistency with our previous work, we have considered only the derivatives with *meta* substitution. For all these derivatives, we have estimated the inversion barriers. In all the cases, the transition state acquired a twisted geometry for the inversion along the isoxazole ring whereas, it attained T-shaped geometry for the inversion along the phenyl ring. In principle, we considered both the transition states and obtained weighted average barriers in the estimation of rate constants. Hammett relationships for *meta*-substituted phenylazo-3,5-dimethyl isoxazole using rate constants revealed

a trend with a positive slope despite the poor correlation, which showed agreement with our previous studies on arylazopyrazoles and arylazo-*N*-methylpyrazoles (Supporting Figure SC2). Thus, the arylazo-3,5-dimethylisoxazoles exhibit substantial electronic effects in the thermal stability of *Z*-isomers, without the influence of the hydrogen bonding.



Figure 4. Light-induced phase transition in phenylazo-3,5-dimethylisoxazole. POM image of **1d** (a) before UV irradiation (b) after 30 s of irradiation at 365 nm light (rt); DSC curves obtained (c) before irradiation and (d) after irradiation at 365 nm light. (Heating rate: 10 °C/min) (e) diagram showing the application of photomelting in molding a desired crystalline shape; (f) Photographic images depicting the photomelting under UV light, and patterning the molten sample; (g and h) in the mid-way and at the end of the crystallization under white light irradiation (CFL bulb), respectively.

Light-induced phase transition: One of the salient features of the arylazoisoxazole derivatives is the light-induced phase transition. Many of the derivatives exhibited minimal to partial melting upon solid state irradiation at the UV light (365 nm) accompanied by contrasting color changes. Remarkably, the parent compound 1d showed complete melting. For obtaining further insights, we have followed this phenomenon using POM. The phase transition was observed as changes in the birefringence pattern that gradually turned into a dark, as a result of the conversion of crystalline (E)-1d into an isotropic molten phase upon irradiation at 365 nm (Figure 4). As expected, the DSC studies revealed a clear difference in the phase transition behavior for both the *E*-isomer and the molten sample. The native sample of 1d exhibited both solid to liquid phase transition on heating as well as the liquid to solid phase transition upon cooling. Indeed, the molten sample did not

change its phase even after cooling to -60 °C. In order to understand whether the heating effect of the light source induces the melting, aliquot of sample was kept under water and irradiated. Still, we observed the melting phenomenon.^[22]

Furthermore, IR spectroscopic studies and inspection of the ¹H-NMR of the molten sample, and we observed a small amount of Z-isomer (Supporting sections S11 and S12).^[23,24] Presumably, the presence of Z-isomer and long thermal stability of it prevents the freezing of the molten sample. On the other hand, irradiation of the molten sample using white light led to the change in the phase as well as induce crystallization. Interestingly, the color changes were prominent during this reverse step. An initial orange colored crystalline phase started to appear that ultimately led to a yellow colored crystalline phase. Through the white light irradiation, we were able to crystallize the sample in two hours, whereas, the crystallization was found to be at an extremely slower rate if the same sample was kept at RT that took few days. By using this reversible light-induced phase transition, we were able to demonstrate a patterned crystallization of the 1d (Figure 4e-h).

In order to shed light on this phase transition phenomenon, we considered the crystal structure of 1d, and computational data on the possible dimers of 1d, and accompanying changes in the non-covalent interactions upon isomerization (Supporting sections S15 and S16). Based on the XRD data, the packing was mainly held by several cooperative weak contacts such as $\pi-\pi$ interactions, N...H-C, and azo-N with the aryl rings. Presumably, the absence of strong intermolecular interactions, provides the necessary conditions for phase transition upon irradiation in 1d. Computationally, we also attempted at optimizing the possible dimeric structures based on the crystal packing at B3LYP/6-311G(d,p) and M06-2X/6-311G(d,p) levels of theory. Through these, we were able to optimize the dimeric structure relevant to $\pi - \pi$ interactions of the phenyl and isoxazole rings. Whereas, the other possible structure with head to head interactions led to disorientation. On the other hand, we were able to optimize different dimers with head-to-tail interactions, and antiparallel and displaced π - π interactions (supporting Figure SC4). For all such structures, we estimated the interaction energies for the dimers in E-E, E-Z and Z-Z isomeric pairs. Interestingly, the introduction of Z-isomeric component in the dimeric structures (ZE and ZZ) led to progressive destabilization of the dimers. The order of stabilization of dimeric non-covalent complexes in 1d is as follows E-E > E-Z > Z-Z. Based on this, it is apparent that the E-Z photoisomerization can destabilize the intermolecular interactions that in turn cause the phase transition. Again, the presence of Z-isomer in the molten state hinders the freezing. On the other hand, under irradiation conditions, the Z-isomer can be converted back to E-isomer, and influence the crystallization.

Conclusions

In summary, we have demonstrated the utility of arylazo-3,5dimethylisoxazole derivatives as a new class of azoheteroarene based photoswitches. The ease of synthesis, high yields, excellent photoswitching in solution phase and long half-life of Zisomer make them robust photoswitchable systems. Based on the extensive photoswitching studies, we found out that the parent 1d, 4-fluoro 4d, 3-bromo 9d, and 4-methoxy 19d derivatives were found to be the best photoswitches among the 37 derivatives. On the other hand, most of the other derivatives exhibited moderate to good photoswitching. The photoswitching stability studies on the better photoswitching candidates revealed no fatigue over five cycles. The reverse thermal isomerization kinetics revealed a long half-life for Z-isomers. Besides that, these molecules showed photoswitching in solidstate as well. Most importantly, the parent compound 1d was found to exhibit a reversible light-induced phase transition with contrasting colors that can potentially be useful in patterned crystallization. All these salient features make them ideal for many applications.

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Keywords: Azoheteroarenes • Photoswitching • Isomerization • Phase transition • Photochromism

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- [16] Computational studies have been performed using Gaussian 09 suite of program. All the structures have been optimized to minima or first order saddle points, and confirmed using frequency calculations. All the relevant data from the computations and also the appropriate references are provided in the supporting information (Supporting Sections S9, S10 and S16).
- [17] In our earlier work (ref. 7c), the *N*-methyl pyrazole and *N*H-pyrazole based arylazopyrazoles with *meta* substitutions have been studied in detail. For comparison, we have specifically chosen the *meta*-substituted arylazoisoxazoles and their properties have been explored.
- [18] For understanding the thermal stability of the Z-isomer, we followed the Z-E reverse isomerization kinetics of few derivatives using UV-Vis spectroscopy. The preliminary results suggested that the room temperature thermal isomerization is found to be extremely slow. Hence, the experiments were performed at higher temperature (80 ± 2 °C) in DMSO to determine the rate constants for the selected derivatives, and the kinetics data are available in the supporting information (Supporting Figure S7 and Table S8).

- [19] (a) The reverse thermal isomerization has also been followed at room temperature $(25 \pm 2 \,^{\circ}\text{C})$ in CDCl₃ and the rate constant was found to be $2.2 \times 10^{-5} \pm 8.0 \times 10^{-7}$ min⁻¹ and the half-life was estimated to be 30826 min (21.4 days), which is nearly half of the values observed in DMSO-d₆. The corresponding rate constants in DMSO-d₆ at RT ($25 \pm 2 \,^{\circ}\text{C}$) and at $80 \pm 2 \,^{\circ}\text{C}$ are found to be $1.1 \times 10^{-5} \pm 3.0 \times 10^{-7}$ min⁻¹ and $1.4 \times 10^{-2} \pm 4.3 \times 10^{-4}$ min⁻¹, respectively. The relevant kinetics data and the first order kinetics plot of the thermal reverse isomerization for all the three experiments are provided in the Supporting Section S7. (b) The activation parameters ΔH^{\ddagger} and ΔS^{\ddagger} for the *Z*-*E* thermal reverse isomerization reaction were found to be 1.12 ± 4 kJ.mol⁻¹, and 30 ± 12 J.K⁻¹.mol⁻¹, respectively. The reason for the positive entropy factor can be the relief of steric factor due to the 3,5-dimethyl groups (isoxazole unit) in *Z*-isomer upon attaining the transition state.
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- [21] (a) The energy difference between the two orientations of the Z-isomers were found to be 0.2 kcal/mol using B3LYP/6-311G(d,p) level of theory.
 (b) For the estimation of rotational barrier, dihedral angle ∠CNNC at every 10 degrees was optimized for the reactant. The energies of reactant, transition state as well as the product were optimized at B3LYP/6-311G(d,p) level of theory. (c) The experimentally deduced activation barrier was comparable to the computed (in particular M06-2X level) confirming the possible inversion (along the azo nitrogen connected to phenyl) mechanism. (E_a = 27.7 ± 0.8 kcal.mol⁻¹ (experiment) vs 27.2 kcal.mol⁻¹ (computed)).
- [22] The relaxation process following the photoexcitation of the azo compounds may liberate heat through non-radiative decay, which can increase the temperature locally. However, as mentioned by the Norikane et al. (ref 13e) the local heating alone may not be sufficient enough for the phase transition.
- [23] Both the native yellow solid as well as the molten red liquid of 1d have been subjected to infrared spectroscopic studies using ATR method. Minor broadening of few of the signals, and splitting of one of the bands were observed. On comparing with the computed IR spectral data, a possible Z-isomer formation has been envisaged. The spectral data are available in the Supporting Figure S11.
- [24] The ¹H-NMR spectral data of the molten sample (from 4 mg of 1d after irradiation for 30 seconds) obtained after subjecting to 365 nm irradiation showed 16% Z-isomer. The spectral data is available in the Supporting Figure S12.

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