

“The Sulfur Dance” Around Arenes and Heteroarenes - the Reversible Nature of Nucleophilic Aromatic Substitutions

Sapna Gahlot,^[a] Jean-Louis Schmitt,^{*[b]} Aline Chevalier,^[b] Marco Villa,^[a, c] Myriam Roy,^[a, d] Paola Ceroni,^[c] Jean-Marie Lehn,^{*[b]} and Marc Gingras^{*[a]}

We disclose the features of a category of reversible nucleophilic aromatic substitutions in view of their significance and generality in dynamic aromatic chemistry. Exchange of sulfur components surrounding arenes and heteroarenes may occur at 25 °C, in a process that one may call a “sulfur dance”. These S_NAr systems present their own features, apart from common reversible reactions utilized in dynamic covalent chemistry (DCC). By varying conditions, covalent dynamics may operate to provide libraries of thiaarenes with some selectivity, or conversion of a hexa(thio)benzene asterisk into another one. The

reversible nature of S_NAr is confirmed by three methods: a convergence of the products distribution in reversible S_NAr systems, a related product redistribution between two per(thio)benzenes by using a thiolate promoter, and from kinetic/thermodynamic data. A four-component dynamic covalent system further illustrates the thermodynamically-driven formation of a thiacalix[2]arene[2]pyrimidine by sulfur component exchanges. This work stimulates the implementation of reversible S_NAr in aromatic chemistry and in DCC.

Introduction

Nucleophilic aromatic substitutions are among the most frequently used reactions in organic chemistry.^[1] Such exchanges of chemical components may occur by different mechanisms (S_NAr ,^[2] $S_{RN}1$,^[3] cS_NAr ,^[4] S_NArH ^[5]). In the following, we will use the denomination S_NAr for representing these different mechanistic possibilities of nucleophilic aromatic substitutions. Even if their reversibility was shown in rare cases,^[6] it was overlooked in spite of a great number of S_NAr reactions reported since 1854.^[7] It is conceptually of much interest in aromatic chemistry and in Dynamic Covalent Chemistry (DCC),^[8–13] beside a number of reversible reactions studied, with imines,^[14,15] esters,^[16] disulfides,^[17] dithioacetals,^[18]

hemiacetals,^[19] metathesis,^[20] S_N2 ,^[21] and Diels-Alder reactions.^[22] Reversible S_NAr reactions present a wide scope, involving several types of nucleophiles, leaving groups and aromatic or heteroaromatic substrates, without the need for metal catalysis, as schematically depicted in Scheme 1.

In order to explore these reversible reactions, we chose as model substrates, some thiaarenes and thiaheteroarenes^[23] (hereafter named “asterisks”).^[24] A number of years ago, we investigated the REDOX properties of a range of persulfurated aromatic compounds,^[25] and we showed that per(thio)arenes are electron-acceptors in spite of a rich electronic density.^[26–28] Later on, some of us disclosed their potency as all-organic phosphorescent triplet emitters with quantum yields reaching near 100% in the crystalline state.^[29–31] Many are the most phosphorescent solids known to date. They also display “turn-on” phosphorescence upon supramolecular polymerization by metal-ion complexation, which makes them “smart” and sensitive to their environment by rigidification-induced phosphorescence (RIP).^[32,33] In the course of these studies, we have observed sulfur exchange reactions by S_NAr .^[34] Due to the importance of reversibility in S_NAr reactions, we want to focus here on the general ability of thiaarenes and thiaheteroarenes to undergo components exchange. It could lead to a constitutional variation toward adaptative features, as is the case of processes occurring in the generation of macrocyclic compounds.^[35,36] Such features open new avenues in dynamic

[a] S. Gahlot, Dr. M. Villa, Prof. Dr. M. Roy, Prof. Dr. M. Gingras
Aix Marseille Univ, CNRS, CINaM, 13288 Marseille, France
E-mail: marc.gingras@univ-amu.fr

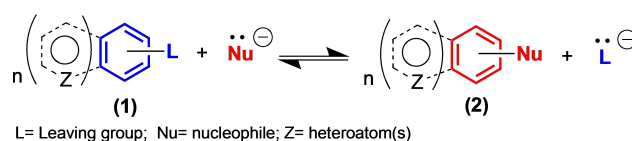
[b] Dr. J.-L. Schmitt, Dr. A. Chevalier, Prof. Dr. J.-M. Lehn
Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006,
Université de Strasbourg,
8 allée Gaspard Monge, BP 70028, 67083 Strasbourg Cedex, France
E-mail: lehn@unistra.fr
jlschmitt@unistra.fr

[c] Dr. M. Villa, Prof. Dr. P. Ceroni
Department of Chemistry (“Giacomo Ciamician”),
University of Bologna,
Via Selmi, 2, 40126 Bologna, Italy

[d] Prof. Dr. M. Roy
Institut Parisien de Chimie Moléculaire,
Sorbonne Université,
75005 Paris, France

Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/chem.202400231>

© 2024 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.



Scheme 1. Schematic representation of the reversibility of nucleophilic aromatic substitutions.

covalent chemistry (DCC). Among a plethora of nucleophiles and arenes, the exchange of sulfurated groups around thiaarene or thiaheteroarene cores (often at room temperature) display a “sulfur dance” behavior, by analogy to the “halogen dance.”^[37] Reversible nucleophilic aromatic substitutions (Scheme 1, Figure 1) on various aromatic or heteroaromatic core components present a manifold of synthetic, structural and physicochemical features. The latter combine luminescence, dyes and redox properties, as additional sensing, monitoring and imaging parameters during dynamic processes. The implementation of S_NAr in DCC opens the door to applications toward dynamic and adaptative assemblies^[38,39] and new materials with relatively non-toxic^[40] and easily available substrates.

Results and Discussion

Reversible nucleophilic aromatic substitutions have rarely been reported and implemented in context of aromatic chemistry and DCC, in spite of their great importance.^[1,2] The classical S_NAr mechanism (i.e. addition-elimination) comprises two steps which were rarely shown to be reversible. It is rather surprising, as reversible exchanges leading to the formation of a σ -complex in the first step have been occasionally reported in arene and heteroarene chemistry with activated electron-poor substrates in S_NAr .^[41] In general, they comprise NO_2 , F, Cl, Br, CN, RS, OR leaving groups, and carbon-, oxygen-, sulfur-, and nitrogen-

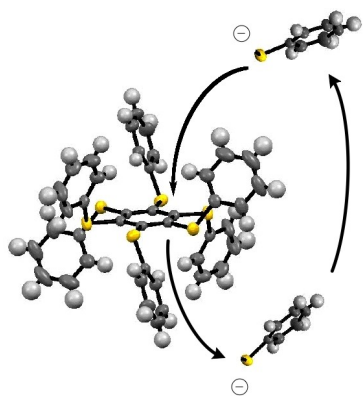
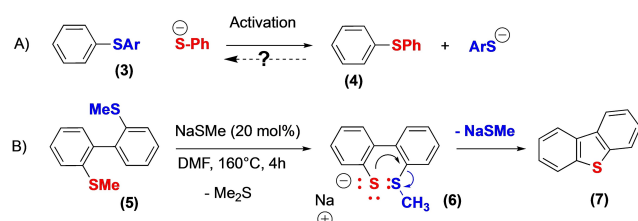


Figure 1. Representation of the “sulfur dance” process. Reversible nucleophilic aromatic substitutions with continuous exchange of sulfur components (thiophenolate anion) around a per(thio)benzene core (DCC template).



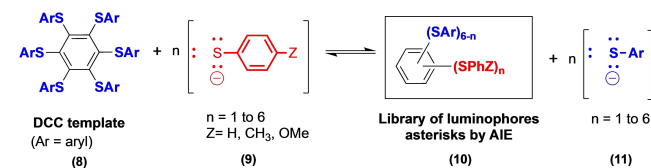
Scheme 2. a) A general scheme of intermolecular, irreversible, sulfur component exchange by S_NAr with an unactivated aryl sulfide (3); b) irreversible sulfur exchange by intramolecular S_NAr at 160 °C.^[42]

centered nucleophiles. However, the elimination step was not shown to be reversible, and thiolate anions were considered as poor leaving groups in S_NAr . As for unactivated thiaarenes (e.g. aryl sulfides), intermolecular sulfur substitutions rarely occurs without strong heating conditions (Scheme 2A). Intramolecular exchange of a sulfur group can proceed irreversibly at high temperatures (Scheme 2B).^[42] In short, exchange of sulfur components by nucleophilic aromatic substitution takes place, but with a proper activation.

We already observed many years ago that sulfur component exchange reactions of some per(thio)arenes and heteroarenes occur with arylthiolate anions (Scheme 3).^[34] Exchange reactions were also reported from 1,2-benzenedithiol derivatives with sulfurated arenes,^[35] and from thiophenols with 3,6-di(thio)tetrazines.^[36] Considering the intense activities in DCC, a general understanding of reversible nucleophilic aromatic substitutions is needed in view of the limited data available.^[34–36] They are promising reactions, distinct from functional groups and reversible reactions most extensively investigated in DCC. Exchanges of chemical components via S_NAr ,^[2] $S_{RN}1$,^[3] cS_NAr ,^[4] S_NArH ^[5] or by other substitution mechanisms are thus of great significance in aromatic chemistry and for DCC. Furthermore, poly- or per(thio)arenes and thiaheteroarenes are particularly attractive because some possess remarkable exalted properties such as phosphorescence by RIP, with a sensitivity and responsiveness to their environment after a molecular rigidification (conformational restriction). Multiple reversible reactions surrounding an aromatic core (Scheme 3) amounts to performing DCC on a template (“the sulfur dance”).

Sulfur component exchanges. We delineate the scope of these reversible S_NAr reactions with poly- and per(thio)arenes and a (thio)heteroarene. In Figure 2, we found that para-substituted asterisks with H, F, CN, Me, CO_2iPr or incorporating benzothiazolyl-2-thio, 1-naphthylthio, 2-naphthylthio and 1,2-dicyano groups are suitable systems for sulfur component exchanges, in the presence of thiophenolates between 25–90 °C. Most importantly, there is no need for metal catalysis^[43,44] nor high temperatures (for instance S_NAr substitutions with thiolates can occur at 180 °C).^[45]

The model substrates in Figure 2 come from hexa- penta- or tetrasulfuration of the central aromatic core. The more electron-poor asterisks provide easier component exchanges at 25 °C, as it is expected in a S_NAr mechanism with a σ -complex. Thus, para-substitution with electron-withdrawing groups on the arms and activating groups directly attached to the aromatic core provide effective sulfur exchange dynamics at 25 °C. Heteroaromatic cores, such as pyridine,^[46] pyrimidine or



Scheme 3. A “DCC template” has been shown to provide a library of mixed substituted luminophores from reversible nucleophilic aromatic substitutions by the “sulfur dance.”^[34]

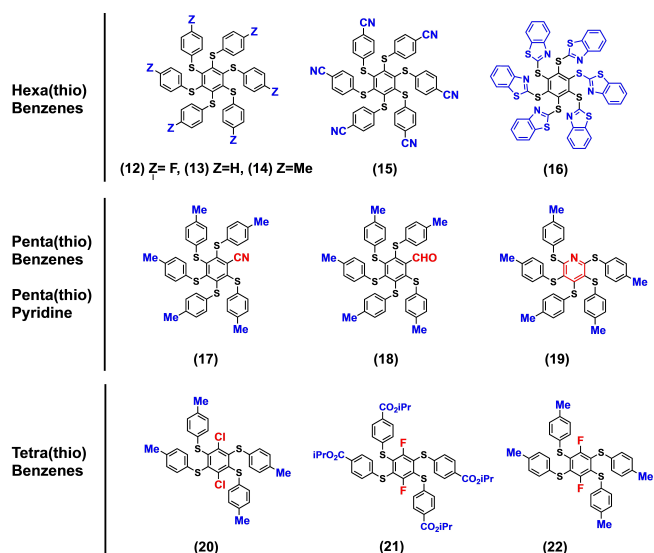


Figure 2. Asterisks undergoing S_NAr with *p*-substituted thiophenolate anions at 25 °C (except for 13 and 14 at 70 °C) for providing a library of asterisks.

pyrazine (Scheme 7), are also effective substrates. This reactivity is in line with the reversibility observed for producing Meisenheimer complexes in S_NAr with activated substrates.^[41a–e] To experimentally quantify and to ascertain these trends, several exchanges by S_NAr were followed by 1H NMR to check kinetics and thermodynamics, notably on some pyrimidine derivatives (see supporting information).

Exchange of sulfur components was tested with the asterisks in Figure 2 at different temperatures and equivalents of thiols (*p*-methoxybenzenethiol or *p*-thiocresol). The reaction progress was monitored by 1H NMR, and the crude mixture was further analyzed by 1H , ^{13}C NMR, HR LC-MS, after a comparison to authentic reference samples (when available). The release of thiolates and their subsequent oxidation to disulfides (mixed or symmetrical ones) further attests to these substitutions. In the next sections, we will detail these sulfur component exchanges, and indicate the generality of the “sulfur dance” process in reversible S_NAr reactions.

Hexasulfurated asterisks. As a typical example, we reacted 15 (1.0 mol-eq.) with *p*-methoxybenzenethiol (6.0 mol-eq.) at 25 °C for two days in the presence of K_2CO_3 in DMF (Figure 3a). The reaction mixture provided a library of at least five asterisks, and traces of unreacted 15. As observed by HR LC-MS, a product selectivity (~70%) was found for the asterisk with three *p*-methoxyphenylthio groups (unoptimized). The regioisomeric structures remain to be determined.

Asterisks with electron-withdrawing fluoro substituents (12) or with benzothiazolyl-2-thio groups (16) provide exchange dynamics at 25 °C, whereas para-substitution with H, Me, OMe, 1-naphthylthio- or 2-naphthylthio- groups requires higher temperature than 25 °C.

Pentasulfurated asterisks. Asterisks (17) and (18) with CN and CHO activating groups directly attached to the benzene core were investigated. After reacting 17 (1.0 mol-eq.) with *p*-methoxybenzenethiol (6.2 mol-eq.) at 25 °C for 38 hours in the

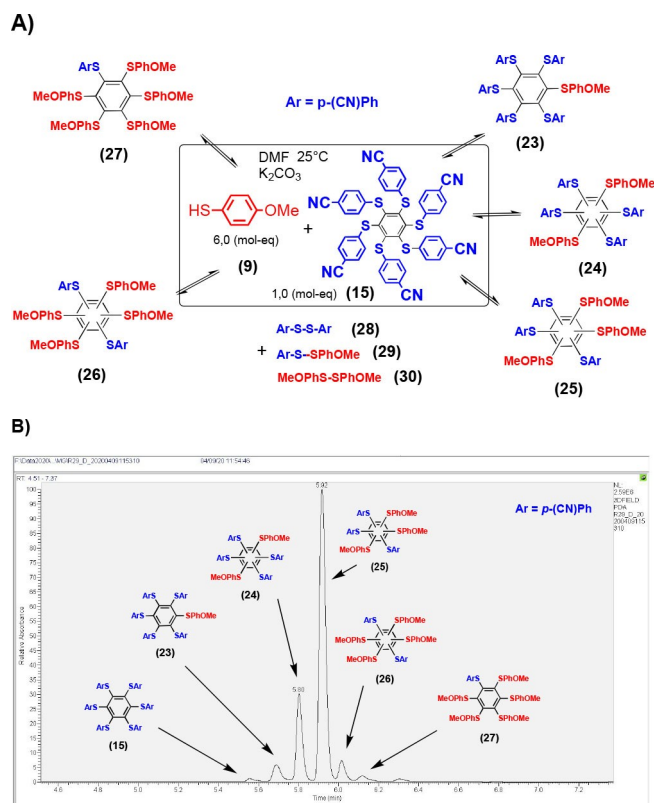
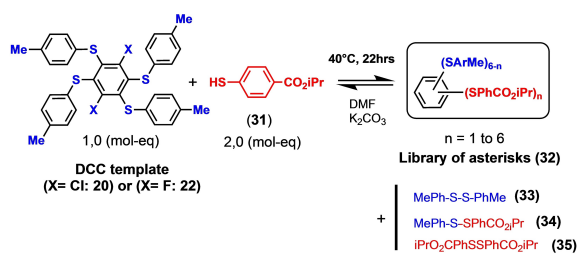


Figure 3. A) A sulfur component exchange system based on the reaction of (15) with *p*-methoxybenzenethiol and K_2CO_3 at 25 °C in DMF; B) A LC chromatogram shows selectivity in the products distribution, as determined by LC-HRMS. The regioisomeric structures remain to be determined.

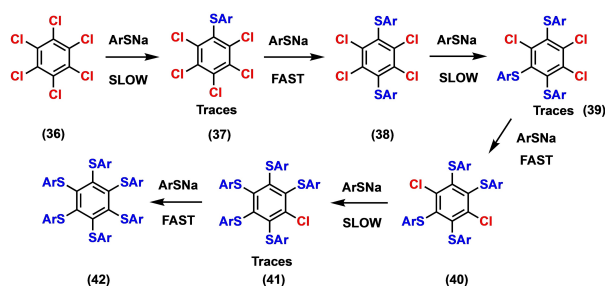
presence of K_2CO_3 in DMF, 1H NMR and LC-HRMS indicated a library of at least five asterisks incorporating one to five *p*-methoxyphenylthio groups and some unreacted 17. The exact regioisomeric structures are unknown at this stage. Under similar conditions, 18 afforded at least five asterisks incorporating one to five *p*-methoxyphenylthio groups after exchanges at 25 °C. The selectivity in the products distribution was favorable to the incorporation of two and three *p*-methoxyphenylthio groups (without optimization). In summary, both 17 and 18 are templates with effective dynamics to afford a non-statistical distribution of products with some selectivity.

Tetrasulfurated asterisks. Asterisk (20) is activated by two Cl substituents toward S_NAr . It allows sulfur exchange components to make a library of asterisks in the presence of isopropyl-4-mercaptobenzoate (31) (2.0 mol-eq.) and K_2CO_3 in DMF at 40 °C for 22 hrs (Scheme 4). The formation of three disulfides (33), (34) and (35) confirmed these exchanges. This sequence is representative of the last two sulfuration steps in scheme 5, starting from 40. Thus, sulfur component exchanges might occur before or after the last hexasulfuration step. Similar results were obtained with 22 (X=F) and with 1,2-dicyano-3,4,5,6-tetra(phenylthio) benzene.^[35]

A LC-MS analysis yields a non-statistical distribution of asterisks with mixed methyl and *p*-isopropoxy carbonyl substituents. Scrambling reactions were observed after only 56% conversion of 20. Thus, isopropyl-4-mercaptobenzoate can



Scheme 4. Exchanges of sulfur components of (20) and (22) with thiol (31) to make a library of asterisks.



Scheme 5. Stepwise formation of a persulfurated benzene asterisk according to literature precedents and the regioselectivity observed. In each step, reversible S_NAr reactions with thiolates cannot be excluded.^[22]

displace a *p*-methylphenylthio group, and a library of asterisks decorated by several combinations of *p*-methyl and *p*-isopropylloxycarbonyl substituents is produced. Both asterisks containing six *p*-methyl or *p*-isopropylloxycarbonyl substituents are also detected. Regioisomeric structures have not been identified at this stage.

Reacting electron-poor **21** with *p*-thiocresol under similar conditions as in Scheme 4 led to the displacement of two F atoms for making about 40% of mixed hexa(thio)benzene asterisks decorated with *p*-methyl and *p*-isopropylloxycarbonyl substituents. Scrambling reactions are clearly evidenced by the hexasulfurated products distribution, where the incorporation of up to four isopropyl-4-mercapto-benzoate groups is observed. Additionally, some mixed disulfides are produced, indicating displacements of *p*-methylphenylthio groups. In summary, the tetrasulfurated asterisks (**20**), (**21**) and (**22**) also display exchange reactions, and are prone to the “sulfur dance” around the benzene core between 25–40 °C.

Pentasulfurated pyridine-cored asterisk. In the thiaheteroaromatic series, we chose the pyridine-cored asterisk (**19**) (1.0 mol-eq.) to react with *p*-methoxybenzenethiol (5.8 mol-eq.) in the presence of K_2CO_3 in DMF at 25 °C for 48 hours. Analysis of the mixture by LC-HRMS indicated the presence of at least five persulfurated asterisks incorporating one to five *p*-methoxyphenylthio groups, thus confirming the displacements of *p*-methylphenylthio groups around a pyridine core. The regioisomeric structures are not identified at this stage. Thus, exchanges of sulfur groups are also appropriate in this heteroaromatic system.

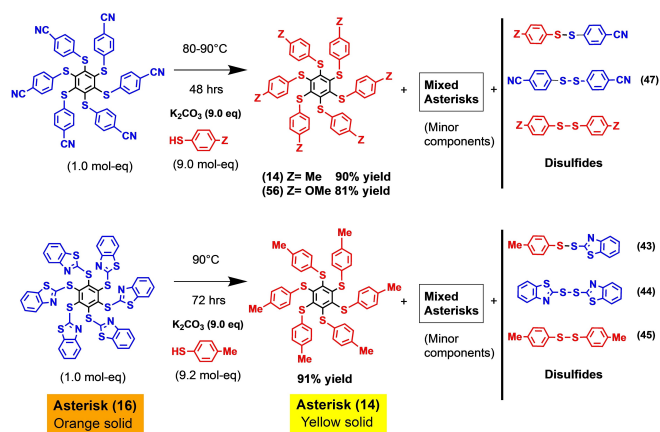
Mechanistic considerations. The “sulfur dance” raise questions about mechanism, reversibility and reactivity. Such

exchanges of components may occur by different mechanisms such as S_NAr , cS_NAr , $S_{RN}1$,^[56] S_NArH and *cine*-substitutions according to the literature data. The denomination S_NAr is broadly used here for these different mechanistic possibilities. Thus, many parameters need to be circumscribed: a) the stepwise formation of the asterisks (scope, kinetics and mechanisms), b) the thiolates exchange processes (scope and mechanism) on the asterisks. Literature precedents are indicative of a stepwise mechanism in the persulfuration.^[23] Six successive steps give only traces of the odd mono-, tri-, and pentasubstituted products. A recent ^{19}F NMR study with C_6F_6 confirmed this trend.^[47] Compounds (**39**) and (**41**) were never isolated. Pentakis(methylthio) chlorobenzene was detected in the methylthio series, but attempts to isolate it failed.^[48]

When reacting perhalogenated benzene with arenethiolates (4 to 5 mol-eq.), di-, tetra-, and hexasulfurated products (**38**), (**40**), and (**42**) are formed in polar aprotic solvents (Scheme 5).^[47] Using an excess of thiolate (9 mol-eq.), the major product is hexasulfurated. In polar protic solvents (e.g. ethylene glycol/pyridine)^[49] and less polar aprotic ones (e.g. diglyme),^[45] sulfuration tends to stop after two or four substitutions under mild conditions.^[50] Polar aprotic solvents such as HMPA (hexamethylphosphoramide),^[51] DMI (1,3-dimethyl-2-imidazolidinone)^[52] and DMF^[53] favor hexasulfuration at 25 °C.^[54] The solvent polarity and its aprotic nature have a strong influence on persulfuration rates. The amount of trisulfurated (**39**) and pentasulfurated products (**41**) remains negligible during the reaction, as they are rapidly converted into tetra- and hexasulfurated products, (**40**) and (**42**) respectively.^[23,47,50b] This behavior is in agreement with fast scrambling hexasulfurations observed for **20**, **21** and **22**, even at 2 mol-eq. Regioselectivity^[55] in each step is summarized in Scheme 5. A divalent sulfur atom is ortho- and para-directing.^[23,47] As for the role of sulfur, it stabilizes a negatively charged σ -complex in S_NAr or presumably in a transition state (cS_NAr). Stabilization of a carbanion by a divalent sulfur atom in σ position is well known.^[57,58] One may see an analogy to the stabilization of a σ -complex intermediate.

Synthetic applications. Typical conversions between two asterisks are shown in Scheme 6. Instead of setting mild conditions at 25 °C for producing a library of asterisks, we tried to overpass the activation energy required to most exchange reactions by heating at 90 °C. As an example, we were successful in converting the hexa(thio)benzene asterisk (**16**) into (**14**) in a 91% isolated yield. Thus, the asterisk (**16**) is transformed into **14**, as the most phosphorescent solid known to date.^[29] Minor components are asterisks with mixed *p*-tolylthio- and benzothiazolyl-2-thio groups. Similarly, the asterisk (**15**) is converted into (**14**) (90% yield) or (**56**) (81% yield). Such nucleophilic aromatic substitutions are unprecedented in aromatic sulfur chemistry because six substitutions occur, even if thiophenolates are rarely used as leaving groups in S_NAr . (note: numérotation compound 15 scheme).

Reversibility in S_NAr . In addition to sulfur exchange components, a demonstration of covalent bonds dynamics was achieved, thus confirming the reversible nature of S_NAr in the “sulfur dance”. We made use of three methods : 1) a



Scheme 6. Conversion of asterisks (15) and (16) (reacting templates) into asterisks (14) and (56) (product templates), with different photophysical properties, through dynamic sulfur exchanges at 80–90 °C.

convergence of the products distribution in reversible S_NAr systems starting from two different asterisks in the presence of thiols (Figure 4); 2) a thiol-promoted exchange of sulfur components between two asterisks (Figure 5); 3) reversible exchanges by S_NAr are ascertained in some pyrimidine systems while using various thiolates, by monitoring over time the evolution of the mixture composition by 1H NMR. Kinetic and thermodynamic data were obtained. Equilibria with quantified products ratios were demonstrated over a prolonged period of time (see supporting information).

As for the first method, it was tested between 70–100 °C. Asterisk (13) reacted with *p*-thiocresol (9 mol-eq) to provide a library of mixed thiaarenes and 14 (Figure 4, reaction from left to right – **blue arrow**). When asterisk (14) reacted with thiophenol (9 mol-eq.), a similar library of mixed asterisks and 13 was produced (Figure 4 reaction from right to left – **red arrow**). The convergence of the product distribution in the two processes points to the reversible nature of the S_NAr process.

As for the second method, we chose a promoter (a thiol) to trigger exchanges of sulfur components between the two asterisks (15) and (16) in the same mixture. In short, we

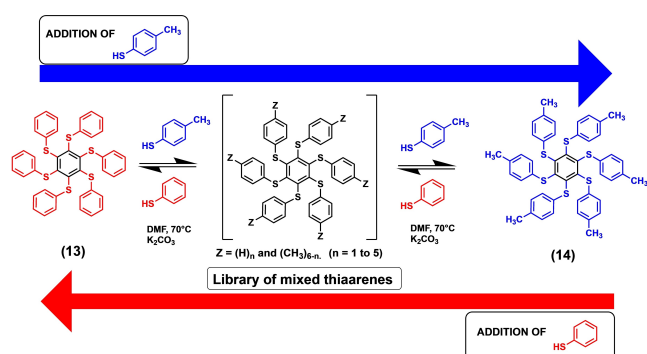


Figure 4. **blue arrow** (from left to right): reaction of asterisk (13) with *p*-thiocresol to provide a library of mixed thiaarenes and asterisk (14). **Red arrow** (from right to left) Reaction of asterisk (14) with thiophenol to provide a related library of mixed thiaarenes and 13. The library of asterisks was analyzed by 1H NMR and HR LC-MS.

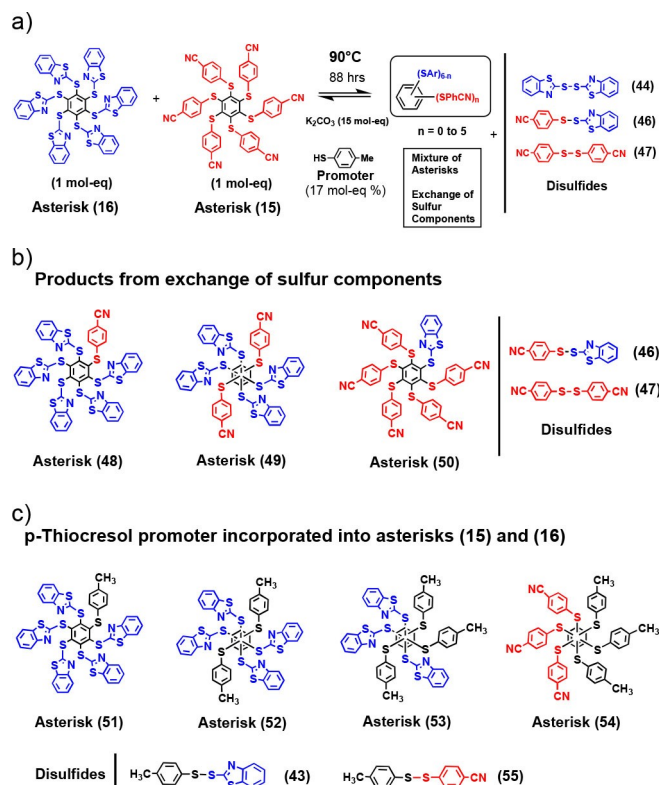


Figure 5. a) Exchange of sulfur components between asterisks (15) and (16) through reversible S_NAr in the "sulfur dance" promoted by *p*-thiocresol; b) Products resulting from reversible exchange of sulfur components from (15) and (16) as determined by LC-HRMS; c) Products resulting from the incorporation of *p*-thiocresol as a promoter into (15) and (16), as determined by LC-HRMS. Compounds (44) to (55) were identified after work-up.

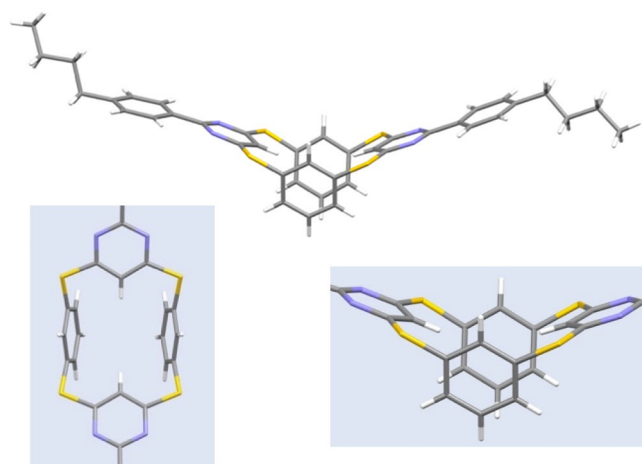
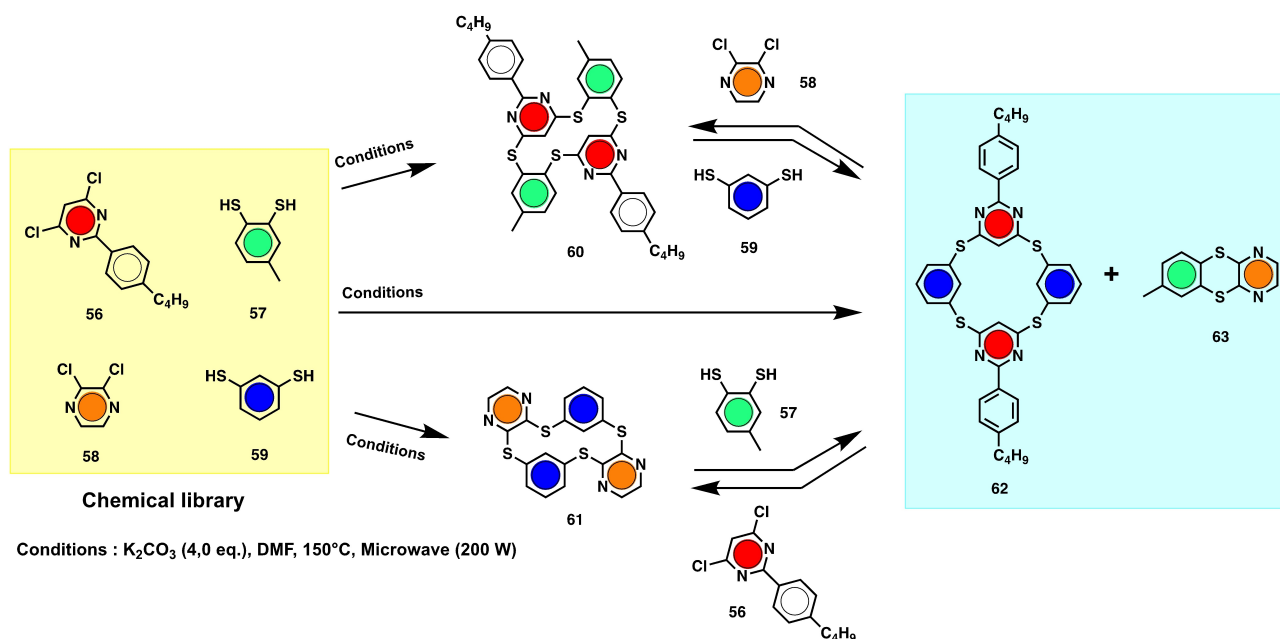


Figure 6. a) Structure determination of (62) by sc-XRD; b) Enlargements (in blue background) showing two inner hydrogen atoms of pyrimidine rings magnetically shielded by the anisotropy of the macrocyclic benzene rings.

investigated the transformation of two different asterisks, toward a library of mixed-substituted asterisks.

As shown in Figure 5a, an equimolar amount of asterisks (15) (1,0 mol-eq) and (16) (1,0 mol-eq) in DMF was treated with *p*-thiocresol as a promoter (17 mol-eq. % relative to each asterisk) in the presence of K_2CO_3 (15 mol-eq.). The mixture was



Scheme 7. Dynamic exchange of sulfur components through reversible $\text{S}_{\text{N}}\text{Ar}$ reactions in the formation of macrocycles (**62**) and (**63**), as monitored by LC-HRMS and NMR data. Initial reaction conditions: (top) (**56**) + (**57**); (middle) (**56**) + (**57**) + (**58**) + (**59**); (bottom) (**58**) + (**59**).

heated at 90°C for 88 hrs. LC-HRMS analysis clearly established a dynamic exchange of sulfur components between the two asterisks in the formation of a library of mixed asterisks incorporating benzothiazolyl-2-thio and *p*-cyanophenylthio arms in a non-statistical distribution (Figure 5b). Most importantly, the initiation of exchange reactions is confirmed by the detection of mixed minor asterisks structures (**51**), (**52**), (**53**) and (**54**) and disulfides (**43**) and (**55**) incorporating *p*-methylphenylthio moieties (Figure 5c). They originate from $\text{S}_{\text{N}}\text{Ar}$ reactions between *p*-thiocresol and the asterisks (**15**) and (**16**). This behavior is coherent with the $\text{S}_{\text{N}}\text{Ar}$ exchange reactions in Figure 5a. The release of *p*-cyanophenylthiolate and benzothiazolyl-2-thiolate anions promoted further scrambling reactions between the asterisks (**15**) and (**16**), as determined by the detection of a series of mixed asterisks (**48**), (**49**), (**50**) and disulfides (**46**) and (**47**) resulting from the exchanges of sulfur components (Figure 5b). Thus, this experiment unambiguously confirmed the dynamic and reversible nature of $\text{S}_{\text{N}}\text{Ar}$.

Dynamic $\text{S}_{\text{N}}\text{Ar}$ with macrocycles. A dynamic system involving reversible $\text{S}_{\text{N}}\text{Ar}$ reactions between four components **56–59** was set up, and investigated in three reaction conditions, as depicted in Scheme 7. It was tested along three different chemical paths, which converged to generate the macrocycle thiocalix[2]arene[2]pyrimidine (**62**) and 7-methylbenzo[5,6][1,4]dithiino[2,3-*b*]pyrazine (**63**). The latter compound was also shown to be ring-opened in the presence of thiolates. This system is thus thermodynamically driven by the formation of stable **62** and **63**, as monitored by ^1H NMR and LC-HRMS. The cyclic compounds **60**, **61**, **62**, **63** were isolated and characterized. A structural analysis of (**62**) by single-crystal X-ray diffraction (sc-XRD) is shown in Figure 6 with enlargements of the macrocyclic core (side and top views).

In the solid state, a 1,3-alternate conformation of (**62**) highlights an anisotropic magnetic effect of the macrocyclic benzene rings with the inner hydrogen atoms of the pyrimidine rings. This is also in agreement with a NMR shielding effect of these hydrogens in solution, with a characteristic shift of this signal to 5,60 ppm (see supporting information).^[59] Three experiments were run : 1) molecules (**56**) and (**57**) produce the macrocycle (**60**). The latter then reacts with (**58**) and (**59**) by exchanging sulfur components to yield the more stable products (**62**) and (**63**); 2) compounds (**58**) and (**59**) generate the macrocycle (**61**). The latter reacts with (**56**) and (**57**) to give (**62**) and (**63**); 3) when the four components (**56–59**) are mixed together, the DCC system is also thermodynamically-driven to (**62**) and (**63**). These experiments confirm the reversible nature of the present $\text{S}_{\text{N}}\text{Ar}$ reactions, leading to the most stable compounds (**62**) and (**63**).

Conclusions

Here, we indicate the generality of reversible nucleophilic aromatic substitutions ($\text{S}_{\text{N}}\text{Ar}$) involving thiaarenes or thiaheteroarenes and thiols, which lead to sulfur exchange components, that one may consider as a sort of “sulfur dance”. In this process, sulfur exchange reactions occur around an aromatic core, where thiolates behave both as nucleophiles and leaving groups in $\text{S}_{\text{N}}\text{Ar}$, without the need for metal catalysis.^[43,44] The exchange of sulfur components between two asterisks, as well as the convergence of product distributions, starting from two different asterisks reacting with appropriate thiolates confirmed the reversible and dynamic nature of the sulfur dance process. The conversion of an asterisk (reacting template) into a library

of asterisks at 25 °C, may change to a selective formation of another asterisk (product template) at 90 °C in high yield. A four-component system illustrates the dynamic formation of cyclic structures thermodynamically-driven by reversible S_NAr reactions to (62) and (63). Overall, we show that reversible S_NAr reactions are of general significance in dynamic aromatic and heteroaromatic chemistry. The “sulfur dance” around aromatic templates opens wider frontiers in view of adaptative and self-correcting features. In the future, it may also be implemented for the discovery of multifunctional, adaptive materials with tunable optical character of potential applications in the fields of imaging, nanoscience, and life sciences.^[60]

Experimental Section

(see supporting information)

Acknowledgements

We are extremely grateful to the Agence Nationale de la Recherche (ANR) in France (program PRC) for the grant ANR-20-CE07-0031 Acronym: “SulfurDance”. We also acknowledge financial support from the Excellence Initiative of Aix-Marseille University – A*Midex, a French “Investissements d’Avenir” programme, and a doctoral contract to S.G.; M.V. acknowledges financial support from the French-Italian University for a doctoral contract (No C2-141 – Vinci program). A CNRS (No. PICS 07573) Program for International Scientific Collaborations with the Univ. of Bologna is thanked, as well as the University of Bologna, Aix-Marseille Université, CINaM and CNRS France. We thank Dr. Raymond Noël for providing us a few samples. This work was also supported by USIAS, the Institute for Advanced Study of the University of Strasbourg (JML) and the CNRS UMR 7006 ISIS (JLS).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Sulfur · S_NAr · ThiaArenes · Reversible reactions · Macrocycles · Dynamic aromatic chemistry

- [1] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443.
 [2] F. Terrier, in *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, Germany **2013**.
 [3] a) R. A. Rossi, A. B. Pierini, A. B. Penenory, *Chem. Rev.* **2003**, *103*, 71; b) J. F. Bunnett, *Acc. Chem. Res.* **1978**, *11*, 413.

- [4] a) S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba, J. A. Murphy, *Angew. Chem. Int. Ed.* **2019**, *58*, 16368; *Angew. Chem.* **2019**, *131*, 16518; b) E. E. Kwan, Y. Zeng, H. A. Besser, E. N. Jacobsen, *Nat. Chem.* **2018**, *10*, 917; c) C. N. Neumann, T. Ritter, *Acc. Chem. Res.* **2017**, *50*, 2822; d) S. D. Schimler, M. A. Cismesia, P. S. Hanley, R. D. J. Froese, M. J. Jansma, D. C. Bland, M. S. Sanford, *J. Am. Chem. Soc.* **2017**, *139*, 1452; e) D. J. Leonard, J. W. Ward, J. Clayden, *Nature* **2018**, *562*, 105.
 [5] a) M. Makosza, *Chem. Soc. Rev.* **2010**, *39*, 2855; b) M. Makosza, *Acc. Chem. Res.* **1987**, *20*, 282.
 [6] For an early discussion on reversible S_NAr : J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, p. 301.
 [7] a) A. Williamson, H. Scrugham, *J. Chem.* **1854**, *7*, 237; b) A. Williamson, H. Scrugham, *Annalen* **1854**, *92*, 316; c) M. F. Pisani, *Compt. Rend.* **1854**, *39*, 852; d) M. F. Pisani, *Annalen* **1854**, *92*, 326.
 [8] J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455.
 [9] J.-M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151.
 [10] F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211.
 [11] Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634.
 [12] M. C. T. Fyfe, J. F. Stoddart, *Acc. Chem. Res.* **1997**, *30*, 393–401.
 [13] P. T. Corbett, J. L. Leclaire, L. Vial, K. R. West, J.-L. Wieter, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652.
 [14] M. E. Belowich, J. F. Stoddart, *Chem. Soc. Rev.* **2012**, *41*, 2003.
 [15] A. Ciesielski, M. El Garah, S. Haar, P. Kovaricek, J.-M. Lehn, P. Samori, *Nat. Chem.* **2014**, *6*, 1017.
 [16] R.-C. Brachvogel, M. von Delius, *Eur. J. Org. Chem.* **2016**, 3662.
 [17] S. P. Black, J. K. M. Sanders, A. R. Stefankiewicz, *Chem. Soc. Rev.* **2014**, *43*, 1861.
 [18] A. G. Orrillo, A. M. Escalante, R. L. E. Furlan, *Chem. Eur. J.* **2016**, *22*, 6746.
 [19] D. Drahonovsky, J.-M. Lehn, *J. Org. Chem.* **2009**, *74*, 8428.
 [20] R. Gu, K. Flidrova, J.-M. Lehn, *J. Am. Chem. Soc.* **2018**, *140*, 5560.
 [21] S. Kulchat, J.-M. Lehn, *Chem. Asian J.* **2015**, *10*, 2484.
 [22] P. J. Boul, P. Reutenauer, J.-M. Lehn, *Org. Lett.* **2005**, *7*, 15.
 [23] M. Gingras, J.-M. Raimundo, Y. M. Chabre, *Angew. Chem. Int. Ed.* **2006**, *45*, 1686; *Angew. Chem.* **2006**, *118*, 1718.
 [24] M. Gingras, A. Pinchart, C. Dallaire, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3149; *Angew. Chem.* **1998**, *110*, 3338.
 [25] J. H. R. Tucker, M. Gingras, H. Brand, J.-M. Lehn, *J. Chem. Soc. Perkin Trans. 2* **1997**, 1303.
 [26] M. Mayor, J.-M. Lehn, *J. Am. Chem. Soc.* **1999**, *121*, 11231.
 [27] M. Mayor, J.-M. Lehn, K. M. Fromm, D. Fenske, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2370; *Angew. Chem.* **1997**, *109*, 2468.
 [28] M. Mayor, J.-M. Lehn, *Helv. Chim. Acta* **1997**, *80*, 2277.
 [29] G. Bergamini, A. Fermi, C. Botta, U. Giovannella, S. Di Motta, F. Negri, R. Peresutti, M. Gingras, P. Ceroni, *J. Mater. Chem. C* **2013**, *1*, 2717.
 [30] A. Fermi, G. Bergamini, R. Peresutti, E. Marchi, M. Roy, P. Ceroni, M. Gingras, *Dyes Pigm.* **2014**, *110*, 113.
 [31] M. Villa, S. D’Agostino, P. Sabatino, R. Noël, J. Busto, M. Roy, M. Gingras, P. Ceroni, *New J. Chem.* **2020**, *44*, 3249.
 [32] A. Fermi, G. Bergamini, M. Roy, M. Gingras, P. Ceroni, *J. Am. Chem. Soc.* **2014**, *136*, 6395.
 [33] M. Villa, M. Roy, G. Bergamini, M. Gingras, P. Ceroni, *Dalton Trans.* **2019**, *48*, 3815.
 [34] a) A. Pinchart, *Synthèses d’architectures moléculaires de sulfure de phénylène et de noyaux aromatiques persulfurés* Ph.D. Thesis, Université Libre de Bruxelles, Belgium and Université de Paris XI Orsay, France, Sept. 26 **2000**, pp. 163–165; <http://www.theses.fr/2000PA112189>; b) R. Noël, *Étude et développement de substrats microporeux pour l’adsorption du radon et son application en physique du neutrino*, doctoral dissertation, Aix-Marseille Université, Marseille, France, Dec. 13, **2015**, <https://tel.archives-ouvertes.fr/tel-01521979>; c) M. Villa, *Smart and Highly Phosphorescent Asterisks for (Bio)Sensors, Antennae, and Molecular Imaging*, doctoral dissertation, Aix-Marseille Université, Marseille, France and University of Bologna, Bologna, Italy, Dec. 14 **2018**, <https://ecole-doctorale-250.univ-amu.fr/fr/soutenance/336>; d) M. Villa, B. Del Secco, L. Ravotto, M. Roy, E. Rampazzo, N. Zaccheroni, L. Prodi, M. Gingras, S. Vinogradov, P. Ceroni, *J. Phys. Chem. C* **2019**, *123*, 29884.
 [35] W. J. Ong, T. M. Swager, *Nat. Chem.* **2018**, *10*, 1023.
 [36] With 3,6-di(thio)tetrazines: a) T. Santos, D. S. Rivero, Y. Pérez-Pérez, E. Martín-Encinas, J. Pasán, A. H. Daranas, R. Carillo, *Angew. Chem. Int. Ed.* **2021**, *60*, 18783; *Angew. Chem.* **2021**, *133*, 18931; b) Z.-C. Wu, Q.-H. Guo, M.-X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 7151; *Angew. Chem.* **2017**, *129*, 7257.
 [37] M. Schnürch, M. Spina, A. F. Khan, M. Mihovilovic, P. Stanetty, *Chem. Soc. Rev.* **2007**, *36*, 1046.
 [38] N. Roy, B. Bruchmann, J.-M. Lehn, *Chem. Soc. Rev.* **2015**, *44*, 3786.

- [39] Y. Liu, J.-M. Lehn, A. K. H. Hirsch, *Acc. Chem. Res.* **2017**, *50*, 376.
- [40] Unpublished preliminary MTT tests.
- [41] a) F. Terrier, *Chem. Rev.* **1982**, *82*, 78; b) S. Kurbatov, S. Lakhdar, R. Goumont, F. Terrier, *Org. Prep. Proced. Int.* **2012**, *44*, 289; c) R. O. Al-Kaysi, I. Gallardo, G. Guirado, *Molecules* **2008**, *13*, 1282; d) E. Buncel, F. Terrier, *Org. Biomol. Chem.* **2010**, *8*, 2285; e) M. Makosza, *Chem. Eur. J.* **2014**, *20*, 5536; f) K. Calfuman, S. Gallardo-Fuentes, R. Contreras, R. A. Tapia, P. R. Campodonico, *New J. Chem.* **2017**, *41*, 12671; g) Y.-F. Kang, L.-Y. Niu, Q.-Z. Yang, *Chin. Chem. Lett.* **2019**, *30*, 1791.
- [42] Y. Masuya, Y. Kawashima, T. Kodama, N. Chatani, M. Tobisu, *Synlett* **2019**, *30*, 1995.
- [43] M. A. Rivero-Crespo, G. Toupalas, B. Morandi, *J. Am. Chem. Soc.* **2021**, *143*, 21331 Doi/org/10.1021/jacs.1c09884.
- [44] Z. Lian, B. N. Bhawal, P. Yu, B. Morandi, *Science* **2017**, *356*, 1059.
- [45] S. D. Pastor, E. T. Hessell, *J. Org. Chem.* **1985**, *50*, 4812.
- [46] L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli, A. Massoli, *Tetrahedron* **1985**, *41*, 1373.
- [47] P. Dognini, P. M. Killoran, G. S. Hanson, L. Lewis Halsall, T. Chaudhry, Z. Islam, F. Giuntini, C. R. Coxon, *Pept. Sci.* **2020**, e24182, Doi/org/10.1002/pep2.24182.
- [48] M. E. Peach, E. S. Rayner, *J. Fluorine Chem.* **1979**, *13*, 447.
- [49] J. J. Jesudason, M. E. Peach, *J. Fluorine Chem.* **1988**, *41*, 357.
- [50] a) M. E. Peach, A. M. Smith, *J. Fluorine Chem.* **1974**, *4*, 399; b) K. R. Langille, M. E. Peach, *J. Fluorine Chem.* **1971/72**, *1*, 407; c) M. Kulka, *J. Org. Chem.* **1959**, *24*, 235.
- [51] P. Cogolli, F. Maiolo, L. Testaferri, M. Tingoli, M. Tiecco, *J. Org. Chem.* **1979**, *44*, 2642.
- [52] D. D. Mac Nicol, P. R. Mallinson, A. Murphy, G. J. Sym, *Tetrahedron Lett.* **1982**, *23*, 4131–4134.
- [53] M. E. Peach, E. S. Rayner, *J. Fluorine Chem.* **1979**, *13*, 447.
- [54] T. R. Crowell, M. E. Peach, *J. Fluorine Chem.* **1982**, *21*, 469.
- [55] E. Buncel, J. M. Dust, F. Terrier, *Chem. Rev.* **1995**, *95*, 2261.
- [56] a) L. Grossi, S. Strazzari, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2141; b) S. Montanari, C. Paradisi, G. Scorrano, *J. Org. Chem.* **1993**, *58*, 5628; c) B. C. Musial, M. E. Peach, *J. Fluorine Chem.* **1976**, *7*, 459; d) S. D. Pastor, *Helv. Chim. Acta* **1988**, *71*, 859.
- [57] D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231.
- [58] C. F. Bernasconi, K. W. Kittredge, *J. Org. Chem.* **1998**, *63*, 1944.
- [59] W. Maes, W. VanRossom, K. Van Hecke, L. Van Meervelt, W. Dehaen, *Org. Lett.* **2006**, *8*, 4161.
- [60] Some applicative areas of hexakis(arylthio)benzenes were disclosed in industry as early as in 1963. Patents on biocidal properties as herbicides, insecticides, anti-oxidant additives to lubricating oils, intermediates in dyestuffs and biologically active materials were reported: a) W. Reifschneider, Aralkyl Poly(thioethers), (Dow Chemicals Co.) US 3 100 802-A, **1963**; b) W. Reifschneider, Thioethers, (Dow Chemicals Co.), US 3 228 989 **1966**; c) W. Reifschneider, Hexakis thioethers (Dow Chemicals Co.), US 3 311 664, **1967** [*Chem. Abstr.* **1967**, *67*, 402893]; d) J. D. Spivack, Compositions Stabilized with Poly(alkylthio)benzenes (Ciba-Geigy AG), DE 2 819 882 **1978** [*Chem. Abstr.* **1978**, *90*, 88309z].

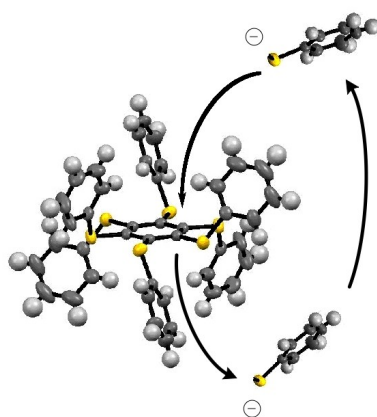
Manuscript received: January 19, 2024

Accepted manuscript online: January 30, 2024

Version of record online: ■■■■■

RESEARCH ARTICLE

The features of a category of reversible nucleophilic aromatic substitution reactions in view of their significance and wide scope in aromatic and heteroaromatic chemistry are presented. Exchange of sulfur components surrounding arenes and heteroarenes may occur at 25 °C, in a process that one may call a “sulfur dance”. A dynamic covalent system involving four components illustrates the thermodynamically-driven formation of a thiacalix[2]arene[2]pyrimidine. This work stimulates the implementation of reversible S_NAr reactions in organic, materials and covalent dynamic chemistry.



S. Gahlot, Dr. J.-L. Schmitt, Dr. A. Chevalier, Dr. M. Villa, Prof. Dr. M. Roy, Prof. Dr. P. Ceroni, Prof. Dr. J.-M. Lehn*, Prof. Dr. M. Gingras**

1 – 9

“The Sulfur Dance” Around Arenes and Heteroarenes - the Reversible Nature of Nucleophilic Aromatic Substitutions

