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ACTIVATION POWER OF VARIOUS ELECTRON WITHDRAWING GROUPS AND AMIDE ACTIVATED NUCLEOPHILIC SUBSTITUTION REACTIONS IN POLYMER SYNTHESIS: A REVIEW

P.Thiruvasagam
Department of Chemistry and Biosciences, Srinivasa Ramanujan Centre, SASTRA Deemed University, Kumbakonam- 612001, India
✉Corresponding author: thiruvasagam@chem.sastra.edu

ABSTRACT
Aromatic nucleophilic substitution reactions are the main tool for synthesizing a variety of organic compounds and polymers. Aromatic nucleophilic substitution reactions are enhanced by the electron-withdrawing groups. The first part of this review article discusses about the activation power of various electron-withdrawing groups. The activation power of electron-withdrawing groups is compared with the keto group of 4,4'-difluoro benzophenone, a standard activated dihalide undergoing facile nucleophilic displacement reactions. The second part of this review article discusses about the activation power of the amide group and its stability at high temperature. The amide-activated displacement reactions for the synthesis of monomers and polymers are discussed. The advantages of nucleophilic displacement reactions in polyamide synthesis, including yields and M.Wt of the polyamides, are analyzed and reported.
Keywords: Nucleophilic Reaction, Electron Withdrawing Group, Activation Power, Amide Group, Bisfluoramide.
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INTRODUCTION

The aromatic nucleophilic displacement reaction was first observed in the year 1854 in the conversion of picryl chlorides into picric acids.[1] In the year 1951, J.F. Bunnet *et al.* predicted the quantitative formation of ether compounds from the reactions of phenolic salts with activated aromatic halides through nucleophilic displacement reactions.[2,3] In this regard, C.N. Merriam *et al*. in the year 1967 reported the synthesis of a series of aromatic polysulfones and polyethers from the reactions of activated dihalo compounds with various bisphenolic salts.[4] A large number of arene compounds and polymers have been synthesised *via* nucleophilic displacement reactions by making use of electron-withdrawing groups. The most common and convenient electron-withdrawing groups are $–SO_2–$ and –CO– that are utilised for the preparation of various organic compounds. Even though the activation power of many groups, such as amides, quinoxalines, benzoxaoles, *etc.,* is comparable with the activation power of $–SO_2–$ and –CO– moieties, the utility of these moieties for the synthesis of organic compounds and polymers is very low. Most importantly, the amide-activated aromatic nucleophilic displacement reactions take place with high selectivity, but the investigations and publications are limited. To date, no broad review is available on the activation power of electron-withdrawing groups and amide-activated nucleophilic displacement reactions. This prompted me to review the activation power of various electron-withdrawing groups, amide-activated aromatic nucleophilic displacement reactions, their significances and applications.

Nucleophilic Substitution Reactions

Aromatic halo compounds that do not have strong electron-withdrawing groups on the ring undergo nucleophilic substitution reactions *(elimination-addition* or *benzyne mechanism)* but require extreme conditions; moreover, the yields of the products will be low. Haloarene that contain strong electron-withdrawing groups undergoes nucleophilic substitution reactions relatively easily and are called the *addition-elimination mechanism* S_NAr. These electron-withdrawing groups stabilise the charged intermediate Meisenheimer complex through resonance charge delocalisation. The rate of the reactions depends on the leaving groups, nucleophiles, solvents and the strength of the electron-withdrawing groups.

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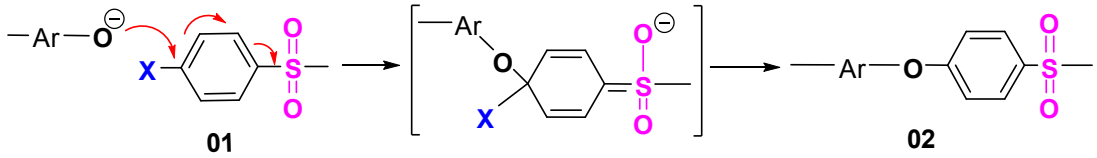
Nucleophilic substitution reactions take place under mild conditions in polar solvents, when the benzene ring carries powerful electron-withdrawing and good leaving groups.[5]

Activation of Nucleophilic Displacement Reactions -Electron-withdrawing Groups (EWG)

The displacement reaction is activated by inductive electron-withdrawing groups or by resonance electron-withdrawing groups. Examples for inductive EWGs are halogens and trifluoromethyl groups, while nitro, sulfonyl, carbonyl, cyano, aldehyde, *etc*., are examples for resonance EWGs. It has been demonstrated that –SO_2– and –CO– are conventional groups which effectively activate the nucleophilic displacement reactions.[6]

Activation by Sulfonyl Groups

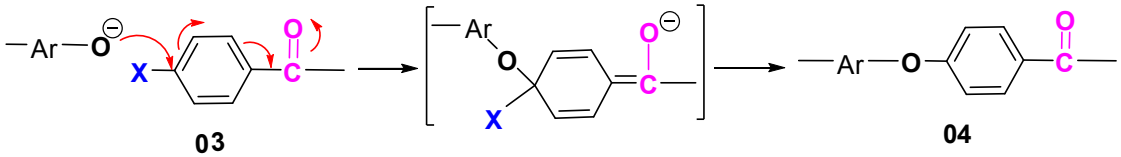
J. B. Rose *et al.* extensively studied the –SO_2– groups activated nucleophilic displacement reactions of halo compounds (01).[7-9] The electron-withdrawing –SO_2– groups stabilise the Meisenheimer complex by accepting the negative charges from the rings (01), and the subsequent loss of the leaving groups results in the formation of the ether sulfones (02) (Scheme–1).



Scheme–1: Resonance Stabilisation of Meisenheimer Intermediate by Sulfonyl Group

Activation by Carbonyl Groups

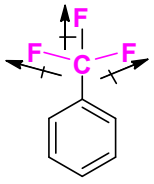
The –CO– group stabilises the Meisenheimer complex and activates the halo or nitro groups (03) towards nucleophilic substitution in the synthesis of ether ketones (04) (Scheme–2).[10]



Scheme–2: Resonance Stabilisation of Meisenheimer Intermediate by –CO– Group

Activation by Trifluoromethyl Groups

The –CF_3 group activates the nucleophilic displacement reactions.[11-13] The strong withdrawing effects of the–CF_3 group (05) was mainly inductive and also due to the hyperconjugation effects. The –CF_3 group effectively activate the –F or –NO_2 groups towards nucleophilic substitution in the facile synthesis of ether compounds under mild conditions.



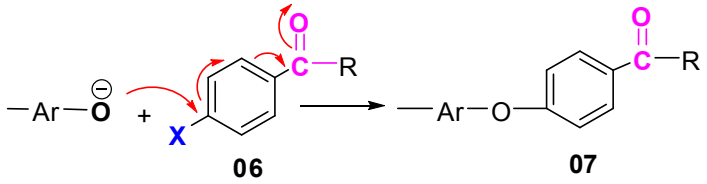
05

Activation by Cyano, Ester, Aldehyde and Azoxy Groups

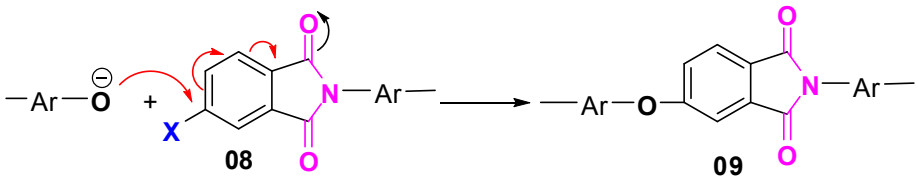
The electron-withdrawing cyano, ester, aldehyde and azoxy groups[14-17] (06) stabilise the Meisenheimer complex similar to –SO_2–, –CO– groups and activate halo or nitro groups for nucleophilic substitution reactions (07) (Scheme–3).

Activation by Imide Rings

Hetero cyclic rings have also been used as activating groups to synthesise various organic compounds. Halo or nitro groups activated by cyclic imides were labile to nucleophilic substitution reactions.[18] The nucleophilic substitution of phenoxide ions on 3 or 4- halo or nitro substitutes of phthalimides (08) results in the formation of ethers (09) in excellent yield (Scheme–4).



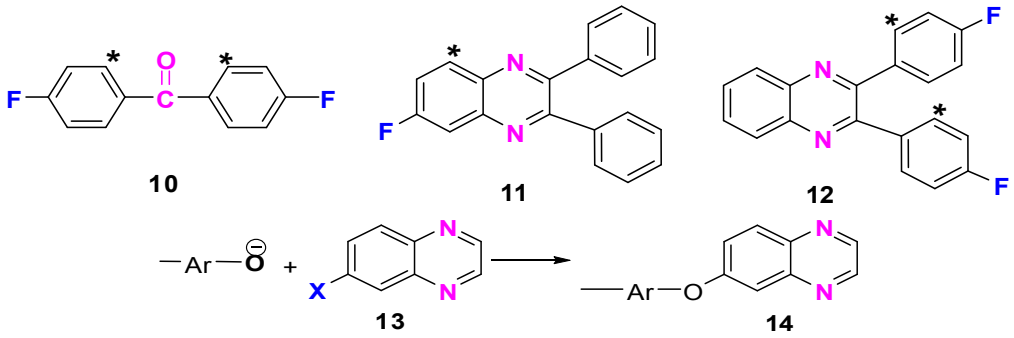
Scheme–3: Resonance Stabilisation of the Meisenheimer Intermediate by the Ester Group



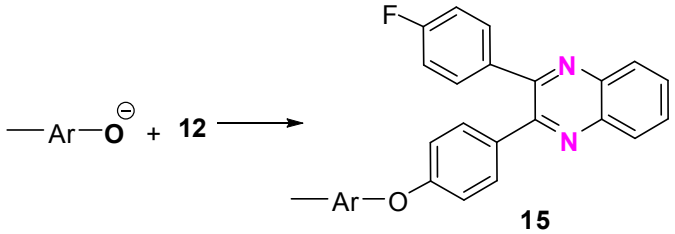
Scheme–04: Resonance Stabilisation of the Meisenheimer Intermediate by the Imide Group

Activation by Quinoxalines (benzopyrazine) Rings

The pyrazine rings in the quinoxaline moieties activate the halogen atoms for the nucleophilic displacement reactions.[19,20] The activation power of pyrazine was studied by ^{1}H-NMR and compared with the –CO– groups of 4, 4'-difluorobenzophenones, a conventional activated dihalide (10). The protons *ortho* to the pyrazine of 2,3-diphenyl-6-fluoroquinoxalines (11) showed a chemical shift at 8.2 ppm. The *ortho* protons in 2-phenyl groups of 2,3-bis(4-fluoro pheny1)quinoxalines (12) showed a chemical shift at 7.55 ppm. Protons present in the *ortho* position to the –CO– group of 4,4'-difluorobenzophenone (10) showed a chemical shift at 7.9 ppm. This data indicated that the pyrazine ring pulls the electron density more effectively away from the benzo ring than on 2-phenyl groups and also higher than the electron-withdrawing effects of the –CO– group of 4,4'-difluoro benzophenone (10). Nucleophilic substitution at the 6-position in the quinoxaline (13) occurred due to the activation of fluoroarene by the pyrazine ring, resulting in the transformation of products 14 (Scheme-05). The chemical shift (δ 7.55 ppm) of *ortho* protons in 2-phenyl groups of 2,3-bis(4-fluoro pheny1)quinoxalines (12) was comparable with the weak electron-withdrawing perfluoroalkyl groups that have chemical shifts at δ 7.6 ppm, which effectively activated the nucleophilic aromatic substitution (Scheme–6).



Scheme–5: Reaction between Phenoxide and 6-fluoroquinoxaline

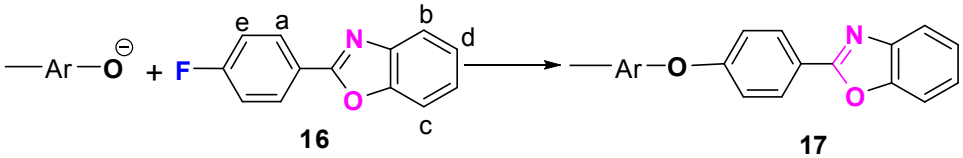


Scheme–6: Reaction between Phenoxide and 2,3-bis (4-fluorophenyl)quinoxaline

Activation by Benzoxazole Rings

J. L. Hedrick *et al.* studied the 2-benzoxazolyl activated nucleophilic aromatic substitution with phenoxide ions.[21] The electron-withdrawing effects of the oxazole ring was evaluated by 1H-NMR of 4-

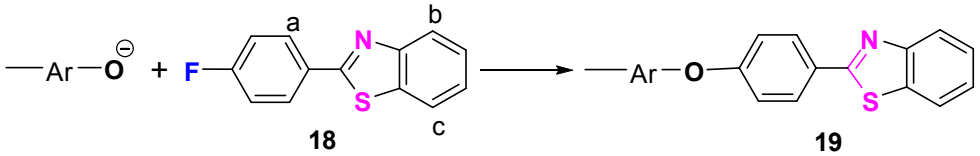
fluorophenyl benzoxazole (16). The chemical shift of the Ha of the 2-phenyl ring, the Hb, and Hc of the benzo ring appeared at 8.3 ppm, 7.8 ppm and 7.6 ppm, respectively. This data indicated that the –F atom present in the 2-phenyl ring was more susceptible to nucleophilic attack. The benzoxazole ring stabilised the intermediate during the transformation into products 17 (Scheme-7).



Scheme–7: Benzoxazoles Activate Nucleophilic Displacement Reactions

Activation by Benzothiazoles Rings

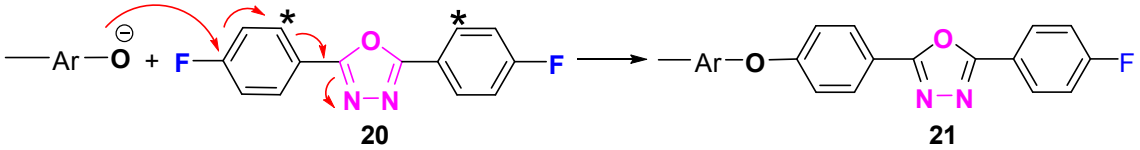
The electron-withdrawing effects of the thiazole ring was studied by 1H-NMR of 4-fluorophenyl benzothiazole (18). The chemical shift of the Ha of the 2-phenyl ring, the Hb, and Hc of the benzo ring appeared at 8.2 ppm, 7.9 ppm and 7.5 ppm, respectively. This data indicated that in the 2-phenyl ring, the 4th-position was susceptible to nucleophilic substitution reactions. The thiazole group stabilised the intermediate formed during the transformation into products 19 (Scheme–8).[22]



Scheme–8: Benzothiazoles Activate Nucleophilic Displacement Reactions

Activation by Oxadiazole Rings

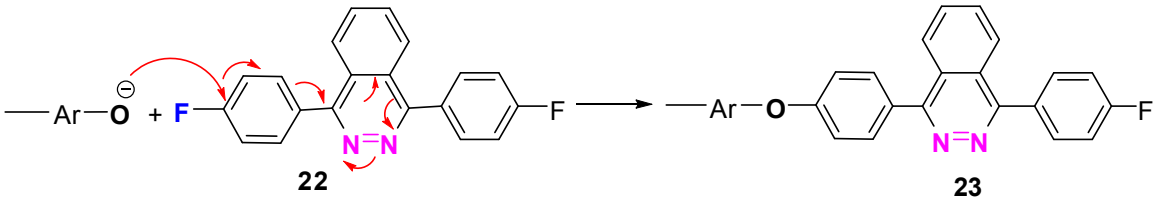
The electron-withdrawing effects of the oxadiazole ring was estimated by 1H-NMR. In oxadiazole (20), the *ortho* protons appeared at δ = 8.0 ppm. The chemical shift value indicated that the oxadiazole has greater electron affinity than the conventional electron-withdrawing –CO– group in 4,4'-difluorobenzophenone (10). The oxadiazole (20) activated the nucleophilic aromatic substitution with phenoxides, resulting in the generation of ether linkages (21).[23,24] The oxadiazole group stabilised the Meisenheimer complex during the transformation into products, Scheme–9.



Scheme–9: Oxadiazole Activated Nucleophilic Displacement Reaction

Activation by Phthalazines Rings

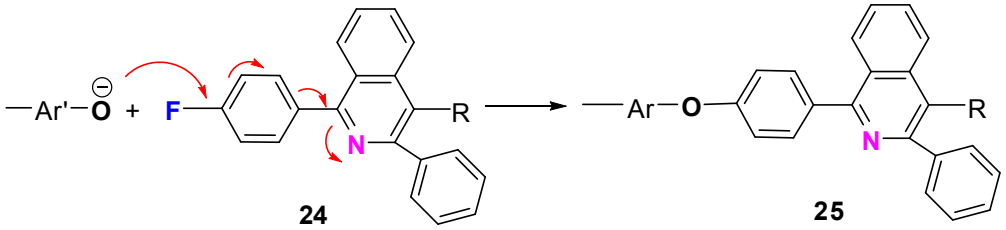
The electron-poor pyridazine ring in 1,4-bis(4-fluorophenyl)phthalazine (22) activated the –F atom for nucleophile to attack results the formation of ether linkages (23).[25,26] The intermediate Meisenheimer complex was stabilised by the resonance effects Scheme-10.



Scheme–10: Phthalazine Activated the Nucleophilic Displacement Reaction

Activation by Isoquinolines Rings

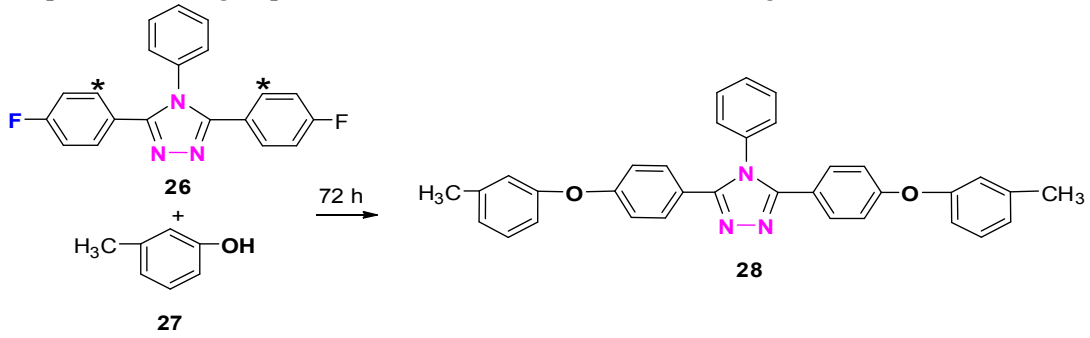
The fluoro-substituted isoquinolines (24) was undergoing nucleophilic aromatic substitution reactions with phenoxide ions.[27] The electron-deficient pyridine moiety of the isoquinoline ring activated the fluoroarene towards nucleophilic displacement reactions. The activating groups stabilised the Meisenheimer-type transition state Scheme–11.



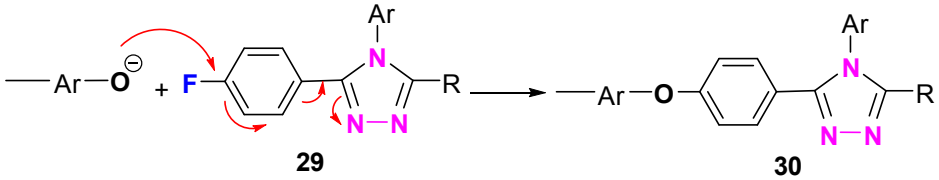
Scheme–11: Isoquinoline-activated Nucleophilic Displacement Reaction

Activation by 1.2.4-Triazoles Rings

The electronic effect of l,2,4-triazol (26) was evaluated by ^{1}H-NMR[28], the *ortho* protons appeared at δ 7.4 ppm. Compared to other groups, triazole had weak electron-withdrawing effects.



Scheme–12: Reaction between 1.2.4-triazoles Compound and *m*-cresol

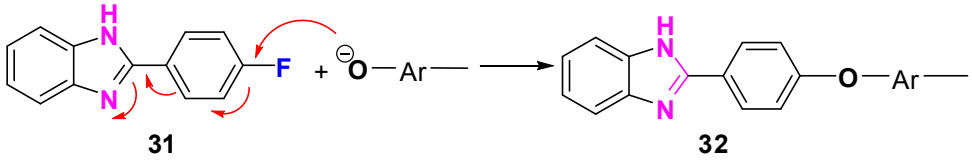


Scheme–13: 1.2.4-triazoles Activated Nucleophilic Displacement Reaction

To study the utility of the 1,2,4-triazole compounds (26), a model reaction between 1.2.4-triazoles compound (26) and *m*-cresol (27) was performed at 185 °C (Scheme-12). The reaction time (72 h) was significantly longer due to the poor activation of triazole. The model reaction and the ^{1}H-NMR studies indicated that fluorotriazole was a weakly activated compound. The triazole 29 activated the nucleophilic displacement reaction by stabilising the Meisenheimer intermediate results the formation of compound 30, Scheme-13.

Activation by Benzimidazoles Rings

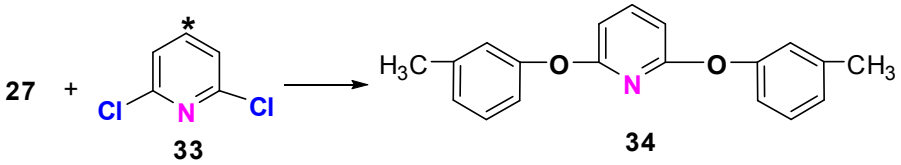
In 2-(4-fluorophenyl)benzimidazole (31), the imidazole moiety can draw the electrons towards itself, activating the –F atom for the nucleophilic displacement reactions. Benzimidazole stabilised the Meisenheimer-type reaction intermediate analogous to conventional activating groups (Scheme–14). [29,30]



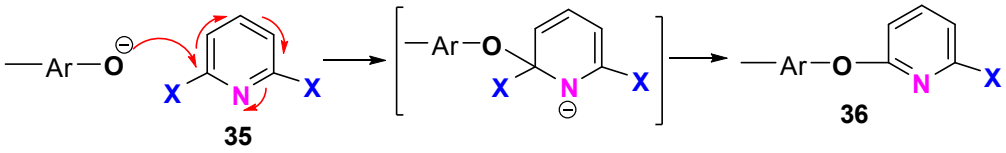
Scheme–14: Benzimidazoles Activate Nucleophilic Displacement Reactions

Activation by Pyridine Rings

The electron-withdrawing ability of the pyridine ring (33) was estimated by ^{1}H-NMR.[31,32] The protons *para* to the nitrogen atom in the pyridine (33) appeared at δ 7.65 ppm, which was almost the same as that of protons *ortho* (δ 7.9 ppm) to a –CO– group in 4,4'-difluorobenzophenone (10). The sample reaction between dichloropyridine (33) and *m*-cresol (27) and the generation of bis(3-methylphenoxy)pyridine (34) at high temperature indicated that the pyridine rings facilitated the nucleophilic substitution reactions (Scheme–15). The 2- and 6-positions of pyridine (35) was equally activated to nucleophilic attack, and the intermediate was stabilised by the resonance (Scheme–16).



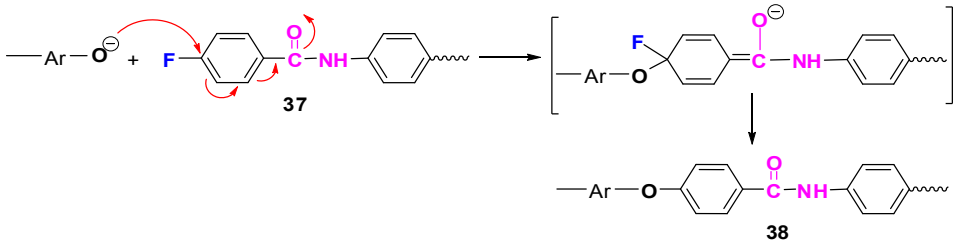
Scheme–15: Reaction between the Pyridine Compound and *m*-cresol



Scheme–16: Pyridine-Activated Nucleophilic Displacement Reaction

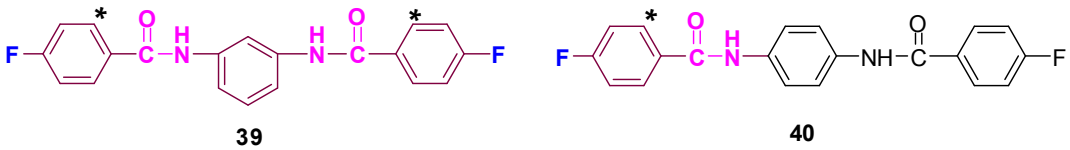
Activation by Amide Groups

The electron-withdrawing power of the amide moiety (–CO-NH–) (37) was analogous to conventional activating –SO_2– and –CO– groups.[33-37] Facile displacement occurred at 2- or 4- positions results the formation of new ether compounds (38). The –CO-NH– group stabilised the Meisenheimer complex as shown in Scheme–17.

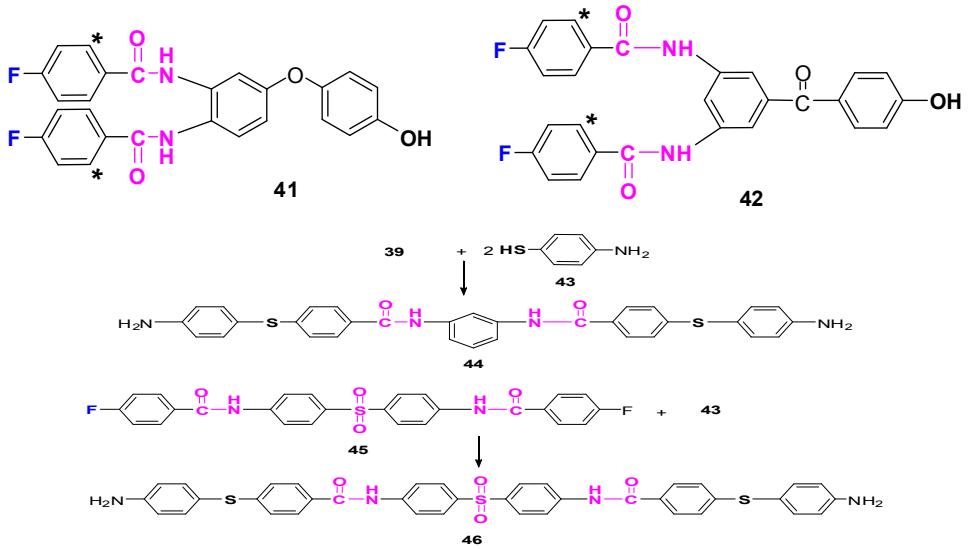


Scheme-17: Stabilization of Meisenheimer Intermediate by the Amide Group

The activation power of the –CO-NH– group was estimated by J. L. Hedrick[35], based on the Hammett sigma values and ^{1}H-NMR analysis. The Hammett sigma values of the –CO-NH– (0.36) and –CO– (0.50) group showed that they were electronically similar. The ^{1}H-NMR analysis of bisfluoramide 39 and 40 showed that the *ortho* protons had a chemical shift of 8.1 ppm. On comparing the chemical shift value (δ = 8.1 ppm) with the protons *ortho* (δ= 7.9 ppm) to the –CO– group in 4,4'-difluorobenzophenone (10), the –CO-NH– group was more effective in activating the nucleophilic displacement reaction.

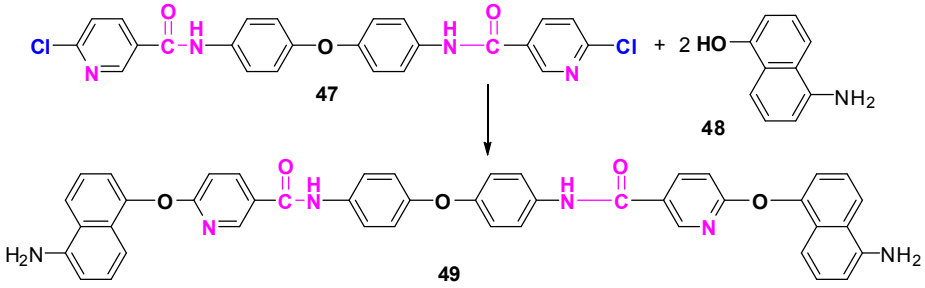


According to F. W. Harris *et al.*[38] the ^{1}H-NMR spectrum of the –CO-NH– containing compounds 41 and 42 showed that the *ortho* protons had chemical shifts at 8.03 ppm and 8.10 ppm, respectively. These chemical shift values were similar to the values obtained by J.L. Hedrick for the bisfluoramide 39 and 40. This analysis suggested that the –CO-NH– group was more effective in activating the nucleophilic displacement reaction.



Scheme–18: Synthesis of Diamines *via* Nucleophilic Displacement of Fluorine Atoms

J. Yang *et al.* in the year 2011[39] reported the synthesis of diamines 44 (yield: 83.4%) and 46 (yield:78.6 %) from 39 and 45, respectively, through the amide-activated nucleophilic displacement reactions with 4-aminothiophenol (43) at 155 °C in 4h (Scheme–18). Since fluorine was the best leaving group, the reaction occurred quantitatively in a short time. E. Gharekhanil *et al.*[40,41] reported the synthesis of diamines (49) with 90 % yield from dichlorodiamides (47) and 5-aminonaphthols (48) at 165 °C in 21h through nucleophilic displacement reactions (Scheme-19). Since chlorine was a poor leaving group, the –CO-NH– groups were not sufficient to activate the chlorine atoms; an additional electron-withdrawing pyridine group was involved in nucleophilic displacement reactions.



Scheme-19: Synthesis of Diamine *via* Nucleophilic Displacement of Chlorine Atoms

Amide-Activated Nucleophilic Displacement Reactions

The reactions between conventional activated halides and bisphenols having an amide moiety in NMP at 180 °C demonstrated that the –CO-NH– linkage was stable during the high-temperature nucleophilic reactions.[33,34,42] Since the –CO-NH– group was stable at high temperature and has high electron-withdrawing ability, it was utilised for high-temperature nucleophilic displacement reactions. This review covers the amide-activated nucleophilic fluoro and nitro displacement reactions for polyamide synthesis.

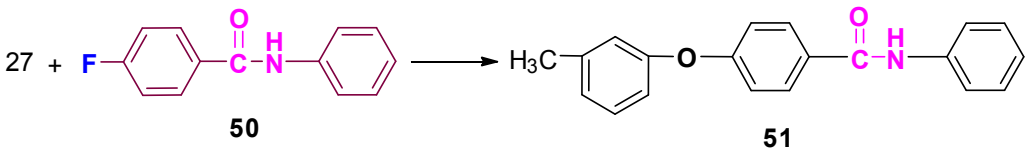
Amide-Activated Nucleophilic Fluoro Displacement Reactions for Polyamide Synthesis

The –CO-NH– activated nucleophilic fluoro displacement reaction was utilized for the preparation of a variety of poly(ether-amide).

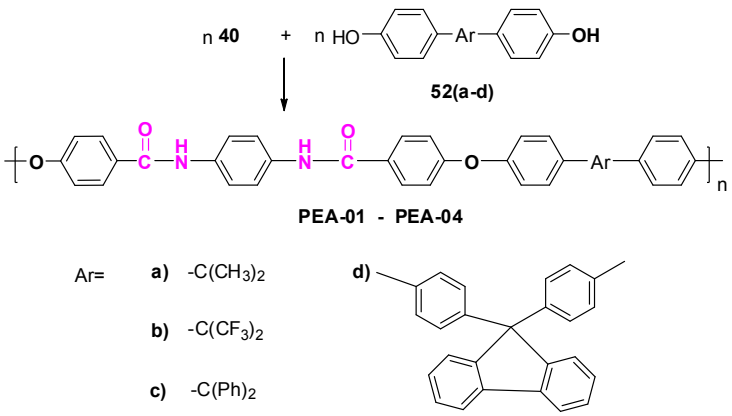
Synthesis of Poly(ether-amide)s *via* Amide-Activated Fluoro Displacement Reactions

In the year 1991, J. L. Hedrick[33] carried out a model reaction between N-(fluoro benzoyl) aniline (50) and *m*-cresol (27) at 180 °C (Scheme-20). Quantitative formation (yield >90 %) of the products 51 indicated that the amide group was an effective activating group for nucleophilic fluoro displacement reactions. This model reaction also suggested that the –CO-NH– moiety was stable at high temperature. Based on the model reaction, J. L. Hedrick[33] synthesized poly(ether-amide)s (PEA-01–PEA-04) starting from

bisfluoramide 40 and bisphenols 52(a-d) through amide-activated nucleophilic displacement reactions at 180–190°C (Scheme-21). The formation of high M. Wt poly(ether-amide)s (inherent viscosity-η_{inh} = 0.42 to 0.73 dL/g**,** Table-1) indicated an effective nucleophilic displacement polymerisation reaction.



Scheme-20: Model Amide-Activated Nucleophilic Displacement Reactions



Scheme-21: Synthesis of poly(ether-amide)s

Synthesis of AB-Type Poly(ether-amide)s *via* Amide-Activated Fluoro Displacement Reactions

M. Lucas and J. L. Hedrick[34] synthesized amide-containing AB monomers 53, 54 and carried out the amide-activated self-nucleophilic displacement reactions at 180-190 °C (Scheme-22). The formation of high M. Wt (Table-1) AB- poly(ether-amide)s (PEA-5, η_{inh} = 0.50 and PEA-6, η_{inh} = 1.45) indicated that the –CO-NH– group activated the nucleophilic fluoro displacement reactions more effectively.

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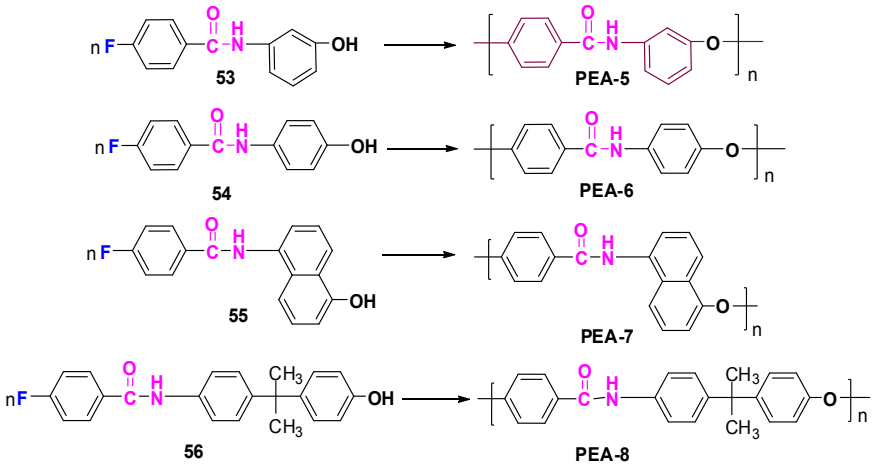


Scheme–22: Synthesis of AB- poly(ether-amide)s from Amide-Containing AB-Type Monomers

The author of this review article reported [43] the synthesis of AB-typ poly(ether-amide)s PEA-7 and PEA-8 from amide-containing AB monomers 55 and 56, respectively, through self-nucleophilic displacement reactions at 170 °C. The η_{inh} of PEA-7 and PEA-8 was comparable with the η_{inh} of the PEA-5 and PEA-6 reported by M. Lucas and J. L. Hedrick[36] (Table-1). The η_{inh} of PEA-7 and PEA-8 was also comparable with the η_{inh} of PEA-1 to PEA-4 derived from AA and BB monomers reported by J. L. Hedrick.[33]

Table-1: Reactions of AA-BB and AB Type Monomers

Polymer	monomer	type of monomer	Temperature (°C)	η_{inh} [a] dL /g
PEA-1	40 and 52a	AA- BB	180-190	0.60*
PEA-2	40and 52b	AA- BB	180-190	0.42*
PEA-3	40and 52c	AA- BB	180-190	0.73*
PEA-4	40and 52d	AA- BB	180-190	0.43*
PEA-5	53	AB	180-190	0.50*
PEA-6	54	AB	180-190	1.45*
PEA-7	55	AB	170	0.40ψ
PEA-8	56	AB	170	0.52ψ

[a] Measured with 0.5 g / dL * = in NMP ψ = in DMSO

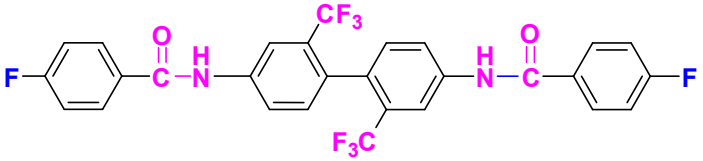
Enhancing Amide Activation by the –CF_3 Group in Nucleophilic Displacement Reactions

J. L. Hedrick *et al*. [35] in the year 1993 reported the synthesis of three bisfluoramide monomers 39, 40 and 57. They carried out the nucleophilic fluoro displacement polymerisation with various bisphenols 58a-d at 180–190°C (Scheme-23).

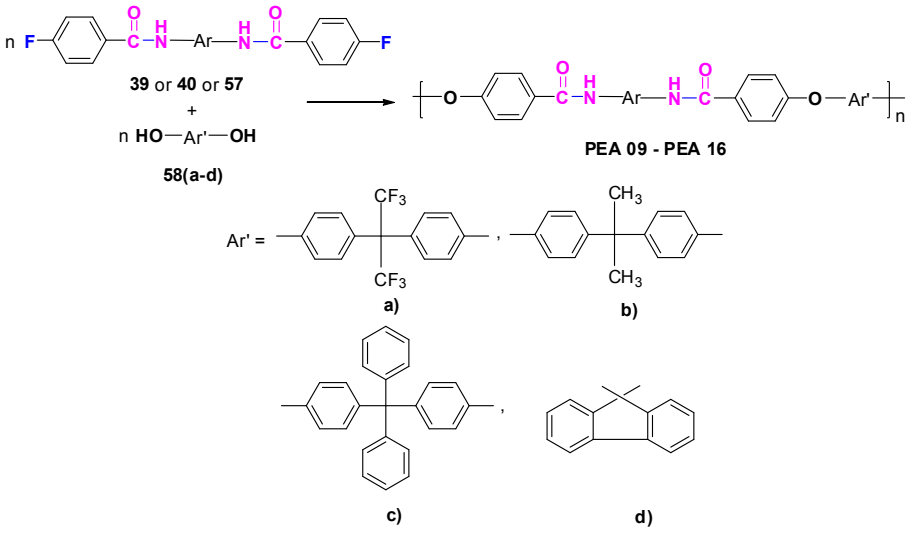
Table-2: Reactions of Bisfluoroamide and Bisphenols

Polymer	bisfluoramide	bisphenol	η_{inh}[a] dL /g
PEA-09	39	58a	0.48
PEA-10	39	58b	0.60
PEA-11	39	58c	0.73
PEA-12	39	58d	0.43
PEA-13	40	58a	0.78
PEA-14	40	58b	0.48
PEA-15	57	58a	1.17
PEA-16	57	58b	1.19

[a] = measured with NMP as solvent



57

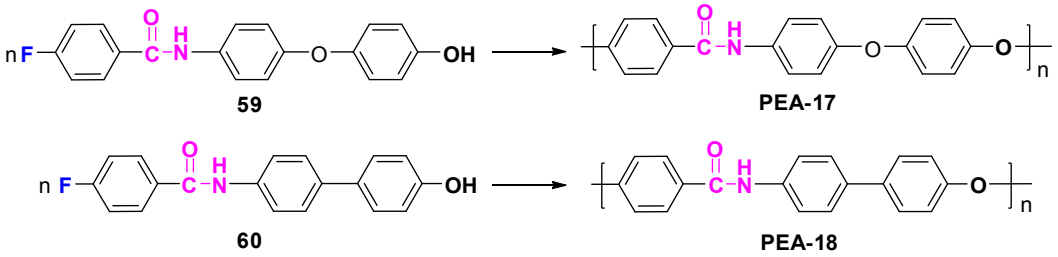


Scheme–23: Reaction of Bisfluoramides with Various Bisphenols

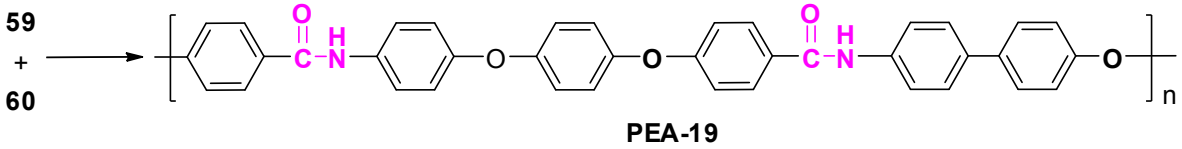
The poly(ether-amide)s PEA-09 – PEA-16 derived had η_{inh}, 0.43–1.45 dL/g (Table-2), indicating an effective nucleophilic fluoro displacement reaction. Among the polymers, PEA-15 (η_{inh}=1.17dL/g) and PEA-16 (η_{inh}=1.19 dL/g) derived from bisfluoramide 57 have high M.Wt. The high M.Wt polymers formation was due to the existence of additional–CF_3 groups in the bisfluoramide 57, which enhanced the nucleophilic displacement reactions more effectively.

Synthesis of Linear and Co-poly (ether-amide)s from Amide-Containing AB-Type Monomers

F.W. Harris *et al.*[38] communicated the synthesis of AB monomers 59 and 60. Monomers 59 and 60 were self-polymerised at 180 °C to afford linear AB-poly(ether-amide)s PEA-17 and PEA-18, respectively (Scheme-24). The η_{inh} of the PEA-17 and PEA-18 was 1.49 dL/g and 0.57 dL/g, respectively. They also reported the synthesis of *co*-polymer PEA-19 from AB-type monomers 59 and 60 in the ratio 50:50, and the η_{inh} was found to be 0.86 dL/g (Scheme-25). The high M. Wt AB-type linear and AB-type *co*-poly(ether-amide)s formation was due to effective nucleophilic fluoro displacement reactions activated by amide groups.



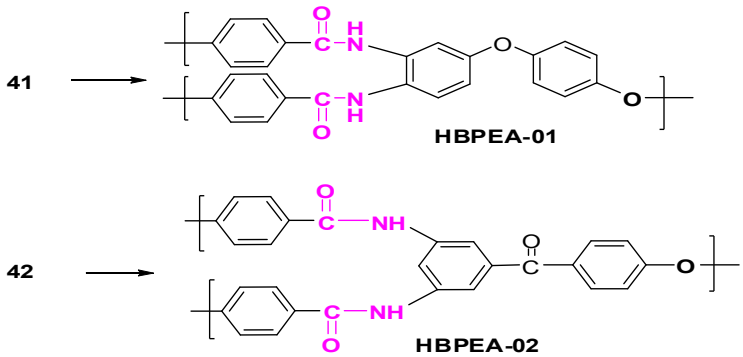
Scheme–24: Synthesis of Linear Poly(ether-amide)s from AB- Type Monomers



Scheme–25: Synthesis of Co-poly(ether-amide)s from AB- Type Monomers

Synthesis of Hyperbranched Poly(ether-amide)s from AB_2 and A_2B Monomers

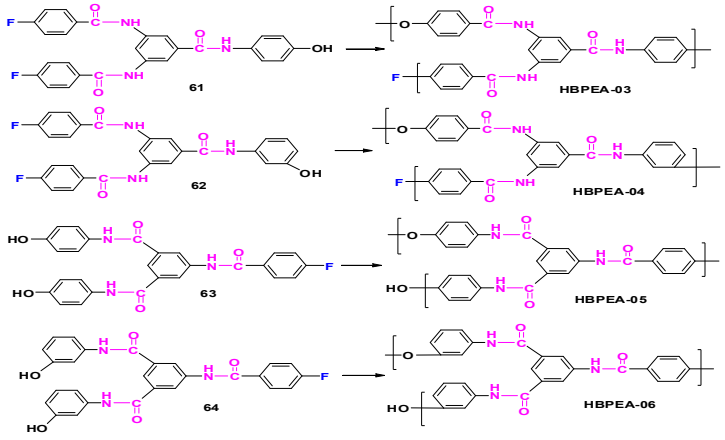
In continuation of their research, F.W. Harris *et al.*[38] communicated the synthesis of AB_2-type monomers 41, 42 and were self-polymerised at 180 °C into hyperbranched polymer HBPEA-01 and HBPEA-02, respectively (Scheme-26). The GPC analysis and the η_{inh} measurement indicated the formation of low M. Wt polymers (Table-3).



Scheme–26: Synthesis of Hyperbranched Polyamides from AB_2 and A_2B Monomers

In this regard, S.Y. Kim *et al.* in the year 2005 [44] reported the synthesis of amide containing AB_2-type monomers 61, 62, A_2B -type monomers 63 and 64. The AB_2 and A_2B monomers were converted into corresponding hyperbranched poly(ether-amide)s (HBPEA-03 to HBPEA-06) at 180 °C for 2 h (Scheme-27). The GPC analysis indicated the polyamides HBPEA-03– HBPEA-06 had high M. Wt (Table-3). The

high M. Wt. polymer formation may be due to the existence of three–CO-NH– group in the monomers (61-64) which effectively activated the nucleophilic displacement reactions.



Scheme–27: Synthesis of Hyperbranched Polymers Through Nucleophilic Displacement Reaction

Table-3: Synthesis of a Hyperbranched Polymer

Polymer	monomer	η_{inh}[a] dL/g	M_n GPC analysis
HBPEA-1	41	0.34	14,200
HBPEA-2	42	0.24	10,030
HBPEA-3	61	0.62	112 400
HBPEA-4	62	---	96 900
HBPEA-5	63	---	78 300
HBPEA-6	64	---	102 200

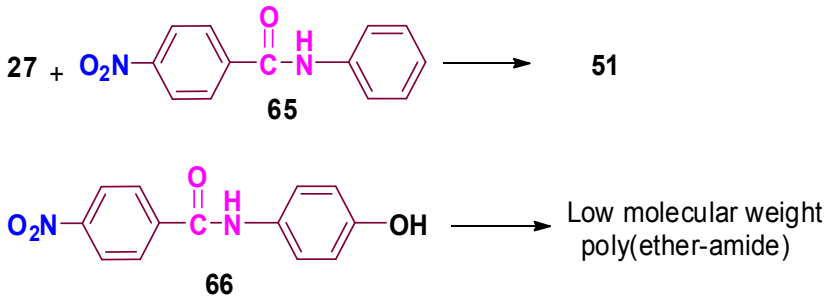
[a] = measured in *m*-cresol as solvent

Amide-Activated Nucleophilic Nitro Displacement Polymerisation Reactions

The activation power of the –CO-NH– group and the combined activation effect of the –CO-NH– and –CF_3 groups for the nucleophilic –NO_2 displacement reactions are reviewed.

Nucleophilic Nitro Displacement Reactions by the Activation Effect of Amide Groups

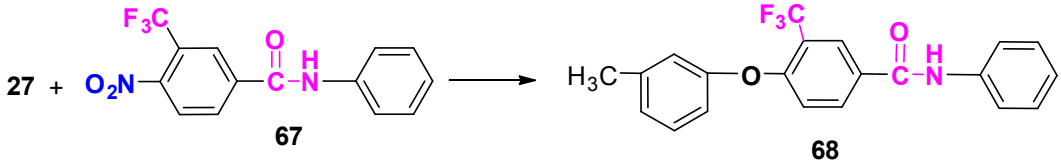
S.Y.Kim *et al*. [45] in the year 2002 studied the –CO-NH– activated nucleophilic –NO_2 displacement reactions. They conducted a sample reaction between 27 and 65 at 150 °C (Scheme -28). Following a 10 h of reaction, they achieved only 80 % yield, which indicated that the rate of nucleophilic –NO_2 displacement reactions activated by –CO-NH– group was slow. Further, they observed the formation of low M. Wt. polyamides from the –CO-NH– containing AB-type monomer (66) (Scheme-28). These results clearly showed that the activation power of the –CO-NH– group was not sufficient for the nucleophilic –NO_2 displacement reaction and further indicated that an additional electron-withdrawing group was needed for the displacement of the –NO_2 group.



Scheme–28: Amide-Activated Nucleophilic Nitro Displacement Model Reaction

Enhancing Amide Activation by the –CF_3 Group for Nitro Displacement Reaction

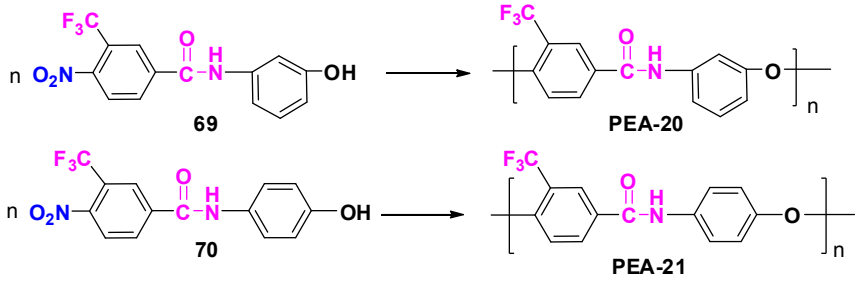
The same research group, S.Y. Kim *et al*., further investigated the combined activation power of –CO-NH– and –CF_3 groups in the nucleophilic –NO_2 displacement reactions.[45] They carried out a model reaction between 67 and *m*-cresol (27) at 100 °C, the product 68 was formed with 96 % yield (Scheme-29). The reason for the quantitative conversion at mild reaction conditions was due to the combined activation effects of –CO-NH– and –CF_3 groups. This study indicated that for –NO_2 as leaving group, –CO-NH– group alone was not sufficient, an additional electron-withdrawing group was required for effective nucleophilic displacement reactions. The –CF_3 group was identified as an additional activating group for the nucleophilic –NO_2 displacement reactions.



Scheme–29: Model Amide and Trifluoromethyl Activated Nucleophilic Nitro Displacement Reaction

Synthesis of Poly(ether-amide)s *via* Nucleophilic Nitro Displacement Reaction

S. Y. Kim *et al.*[42] outlined the preparation of AB-poly(etheramide)s PEA-20, PEA-21 from AB-type monomers 69 and 70, respectively, at 120 °C (Scheme-30). The M. Wt of PEA-20 and PEA-21 were 5.4 x10^4 and 4.2 x 10^4 respectively. This data indicated that nucleophilic –NO_2 displacement by the combined effect of –CO-NH– and –CF_3 group was feasible and was comparable with the –CO-NH– activated fluoro displacement reactions.



Scheme–30: Synthesis of AB-type PEA by Nitro Displacement Reaction

Advantages of Nucleophilic Displacement Reactions in Polyamide Synthesis

Poly(ether-amide)s are generally synthesised from diacids and diamines through the conventional methods. But many aromatic diacids will undergo decarboxylation at elevated temperature, aromatic diamines will be easily oxidised and tend to sublime. This results in the requirement of low-temperature polymerisation methods, but at low temperature, the post precipitation of polyamides occurs, leading to low yield with low molecular weight, which adversely affects the properties of the polymers. Moreover, the reactivity of aromatic acid is too low, so acid chloride is employed, which is moisture sensitive and results in a low yield. In Higashi–Yamazaki's phosphorylation methods, the synthesis involves the use of the harmful solvent pyridine. To overcome these difficulties, poly(ether-amide)s are best prepared through amide-activated nucleophilic displacement reaction. In this technique, the desired amide is introduced in the bisfluoride monomers and polymerised with bisphenols. In this method, the polymer formed shows good solubility due to the generation of ether linkages, and the polymerisation proceeds homogeneously. The high solubility of the poly(ether-amide)s helps to produce high yield with high molecular weight, which in turn enhances the properties of polymers.

CONCLUSION

(i) The activation power of the various groups is analysed by ^{1}H-NMR; the groups having high activation power are effective in nucleophilic displacement reactions.

(ii) ^{1}H-NMR analysis indicated that the amide carbonyl group is more effective than the –CO– group in 4,4-difluorobenzophenone for activating the nucleophilic displacement reaction.

(iii) The activation power of the amide group is sufficient for nucleophilic displacement of –F atoms. (iv) The activation power of amide group is not sufficient for the displacement of –Cl or $–NO_2$ group an additional electron withdrawing group like $–CF_3$ is required and the reaction occurred quantitatively and (v) The amide group is an effective activating groups and can be utilized for the synthesis of drugs, ethers, diacids, diamines, diols and high molecular weight polymers.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production.* All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Thiruvasagam Ponnusamy https://orcid.org/0000-0003-2230-5756

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