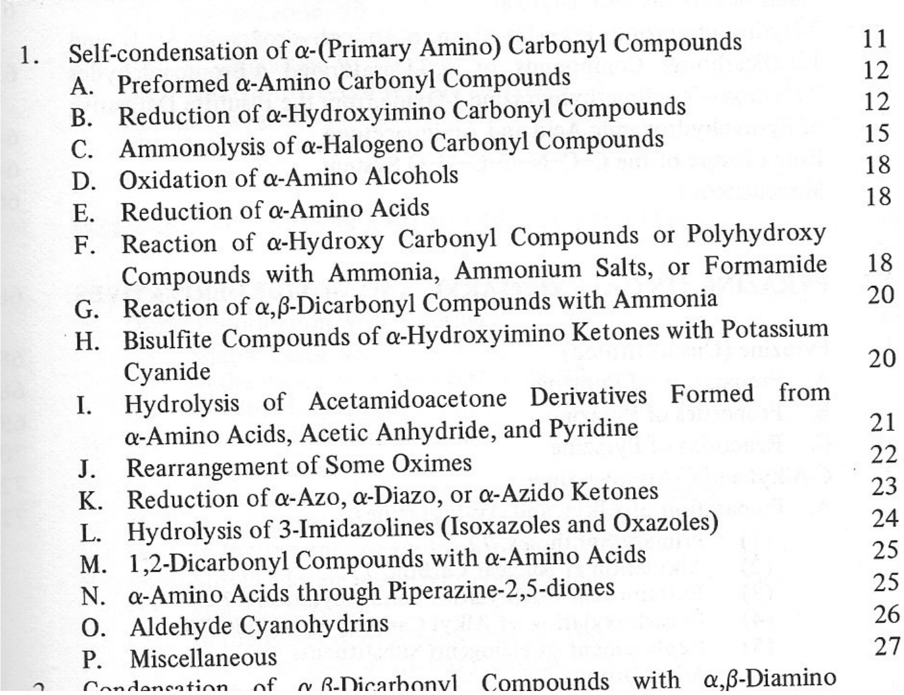
Alpha-Amino Ketone based Polymeric Pyrazines

By: Robert B. Login (rloginconsulting.com)

Pyrazine chemistry had its start long ago in the 19th century. It is a vast chemical technology as witness by the following books.

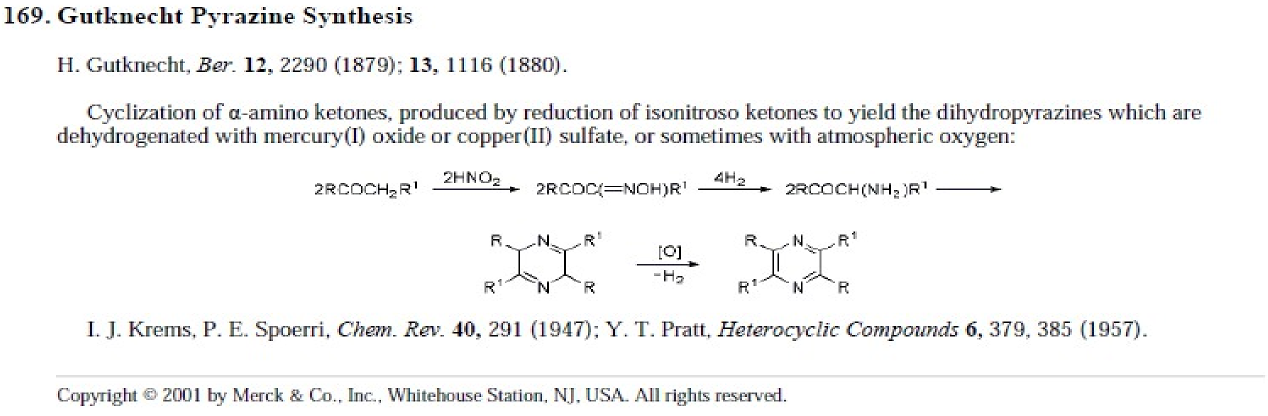
Barlin, G. B. "The Pyrazines: The Chemistry of Heterocyclic Compounds: A series of monographs."*John Wiley & Sons, New York",* 41 (1982): 1-10. (687p book!) Contents illustrates most useable methods.



II. PRIMARY SYNTHESES OF PYRAZINES 11

Brown, D. J. "The Pyrazines: Supplement I, Volume 58." (2002). (557p book!)

Although there are two name reactions associated with its synthesis, both of the above references illustrates numerous other reactions used to prepare various pyrazines and their derivatives.



169. Gutknecht Pyrazine Synthesis

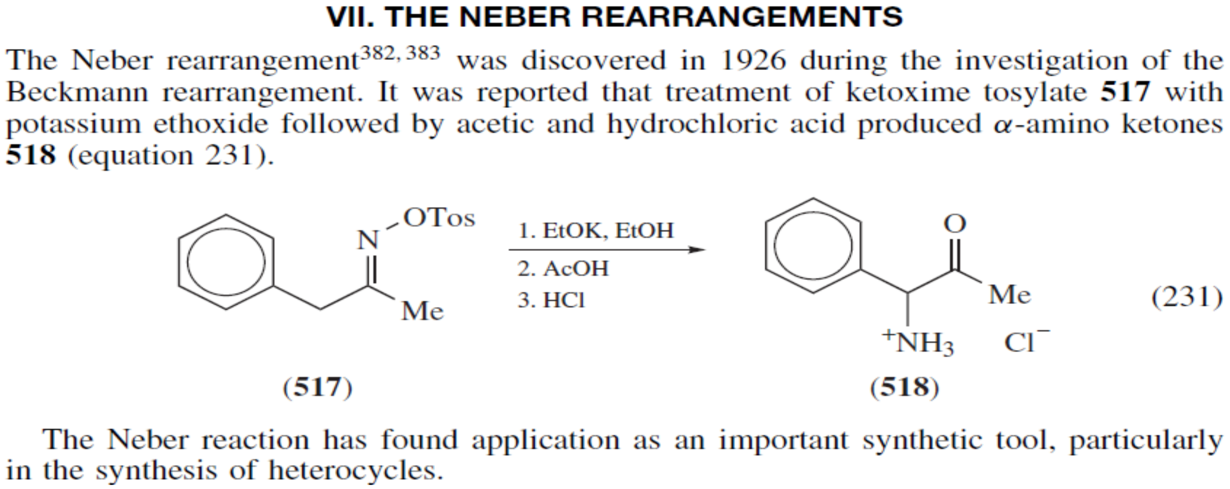
H. Gutknecht, *Ber.* **12,** 2290 (1879); **13,** 1116 (1880).

Cyclization of α-amino ketones, produced by reduction of isonitroso ketones to yield the dihydropyrazines which are dehydrogenated with mercury(I) oxide or copper(II) sulfate, or sometimes with atmospheric oxygen:

$$2RCOCH_2R^1 \xrightarrow{2HNO_2} 2RCOC(=NOH)R^1 \xrightarrow{4H_2} 2RCOCH(NH_2)R^1 \longrightarrow$$

I. J. Krems, P. E. Spoerri, *Chem. Rev.* **40,** 291 (1947); Y. T. Pratt, *Heterocyclic Compounds* **6,** 379, 385 (1957).

Alpha amino ketones are important intermediates in pyrazine synthesis and are also available from the Neber rearrangement.



VII. THE NEBER REARRANGEMENTS

The Neber rearrangement[382, 383] was discovered in 1926 during the investigation of the Beckmann rearrangement. It was reported that treatment of ketoxime tosylate **517** with potassium ethoxide followed by acetic and hydrochloric acid produced α-amino ketones **518** (equation 231).

The Neber reaction has found application as an important synthetic tool, particularly in the synthesis of heterocycles.

O'Brien, Connor. "The rearrangement of ketoxime O-sulfonates to amino ketones (The Neber rearrangement)."*Chemical Reviews",* 64.2 (1964): 81-89.

Berkowitz, William F., "The Neber Rearrangement", *Organic Reactions",* (2012).

Rappoport, Zvi, and Joel F. Liebman."*The chemistry of hydroxylamines, oximes and hydroxamic acids*.", Vol. 1. John Wiley & Sons, 2008.

The amine must be trapped as its salt or else the reaction goes directly to dihydropyrazine and with air oxidation, to pyrazine.

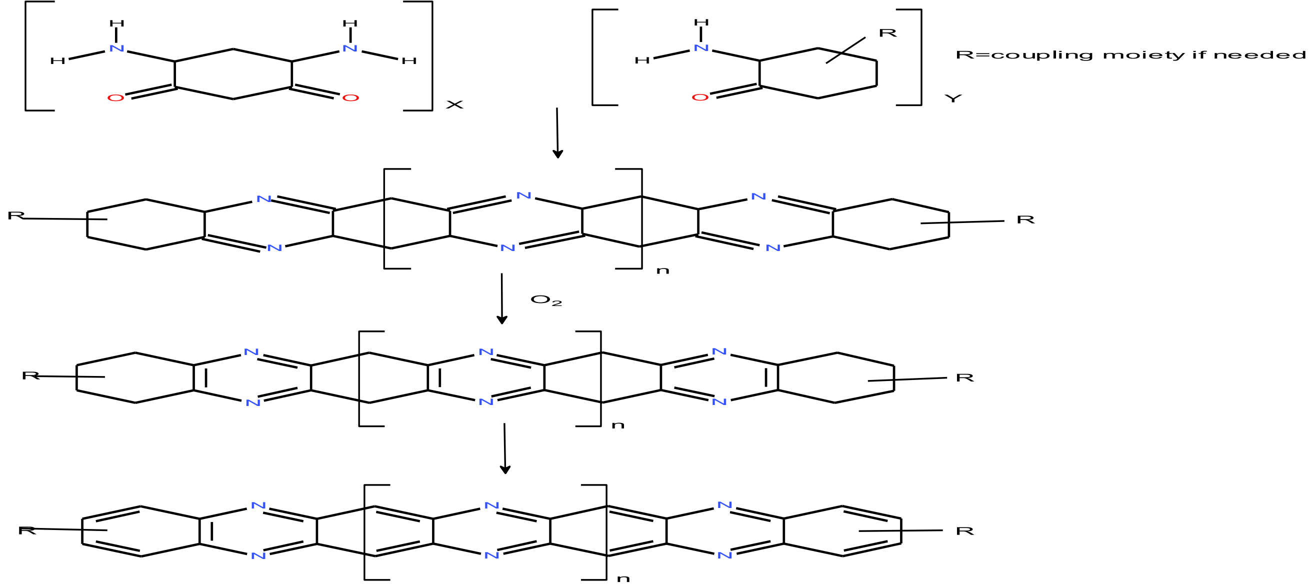
A recent review is quite instructive as to medicals:

B Miniyar, Pankaj, et al. "Unequivocal role of pyrazine ring in medicinally important compounds: A review."*Mini reviews in medicinal chemistry",* 13.11 (2013): 1607-1625.

Pyrazine has been used in polymeric motifs. I found many references to derivatives used in ladder(Azaacene) polymers with numerous electronic applications.
There are hundreds of references but the following are representative.

Bunz, Uwe HF. "The larger linear n-heteroacenes."*Acc. Chem. Res",* 48.6 (2015): 1676-1686.
Lu, Xuefeng, et al. "Controlling the Charge Transfer in D–A–D Chromophores Based on Pyrazine Derivatives."*The Journal of organic chemistry",* 79.14 (2014): 6480-6489.
More, Sandeep, Rajesh Bhosale, and Aurelio Mateo-Alonso. "Low-LUMO Pyrene-Fused Azaacenes."*Chemistry-A European Journal",* 20.34 (2014): 10626-10631.
Stępień, Marcin, et al. "Heterocyclic Nanographenes and Other Polycyclic Heteroaromatic Compounds: Synthetic Routes, Properties, and Applications."*Chem. Rev",* 117.4 (2017): 3479-3716.
Mateo-Alonso, Aurelio. "Pyrene-fused pyrazaacenes: from small molecules to nanoribbons."*Chemical Society Reviews",* 43.17 (2014): 6311-6324.
Stępień, Marcin, et al. "Heterocyclic Nanographenes and Other Polycyclic Heteroaromatic Compounds: Synthetic Routes, Properties, and Applications."*Chem. Rev",* 117.4 (2017): 3479-3716.

But I have found none with the following ideas:



Scheme 1: I think that the cyclohexanes can be easily oxidized further to aromaticity as indicated.

The R group can be suitable for one of the cross-coupling reactions. It can be coupled to some other conductive polymer type. The pyrazaacenes are electron acceptors and can be coupled to electron donors to improve semiconductor performance. A recent review covers the progress in this type of reaction.

Morin, Pierre-Olivier, Thomas Bura, and Mario Leclerc. "Realizing the full potential of conjugated polymers: innovation in polymer synthesis."*Materials Horizons",* 3.1 (2016): 11-20.

Further more the relatively new DHAP (direct heteroarylation polycondensation) is being used instead of the older cross-coupling.

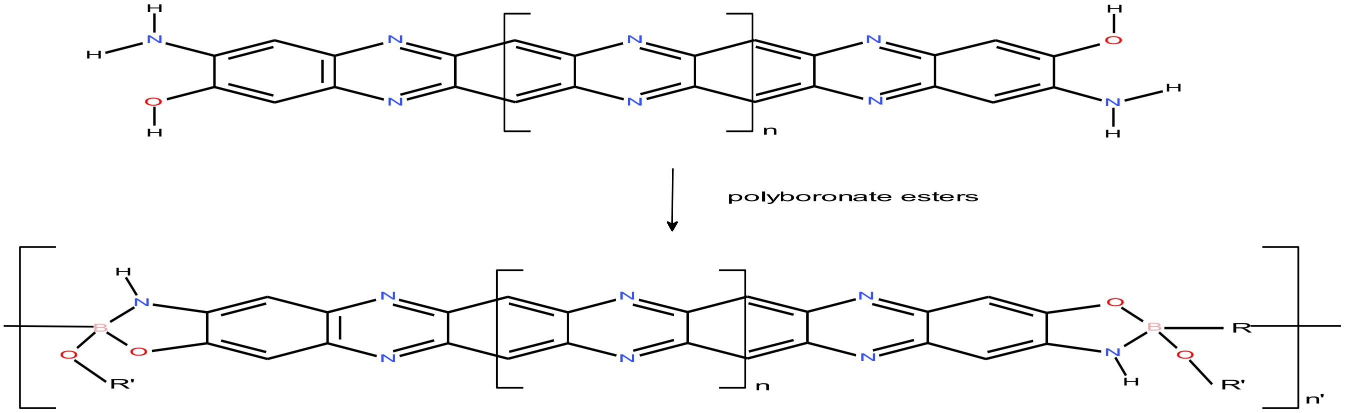
"These π-conjugated polymers are usually synthesized by transition metal-catalyzed crosscoupling techniques such as Suzuki–Miyaura and Migita– Kosugi–Stille couplings. However, these conventional synthetic techniques show disadvantages such as the necessity of prefunctionalization of monomers (arylene diboronic acids and distannyl arylenes) using flammable butyllithium, and particularly for Stille coupling, the difficulty of purifying organotin monomers and the formation of toxic trialkyltin byproducts. To synthesize π-conjugated polymers through an economy-efficient and environmentally-benign approach, the carbon–hydrogen (C–H) direct arylation polycondensation (DAP) reaction has attracted increasing attention recently."

Shao, Jinjun, et al. "Direct arylation polycondensation for efficient synthesis of narrow-bandgap alternating D–A copolymers consisting of naphthalene diimide as an acceptor."*Polymer Chemistry",* 6.38 (2015): 6836-6844.

Yu, Simiao, et al. "Eco-friendly direct (hetero)-arylation polymerization: scope and limitation."*Journal of Materials*

Chemistry C”, 5.1 (2017): 29-40.

If only the difunctional aminoketone is polymerized without the capping monomer, then the resulting polymer would have amines in the end groups. This end phenol amine could be chain extended with polyboronate esters to form all sorts of supermolecular structures. A linear one is highlighted in scheme 2 however.



Scheme 2: Terminal derivatives for chain extension.

The end amine groups that would terminate the polymerization can alternatively be acylated with long chain carboxylic acids. Such fatty amide derivatives would enhance process-ability by improving solvent solubility.

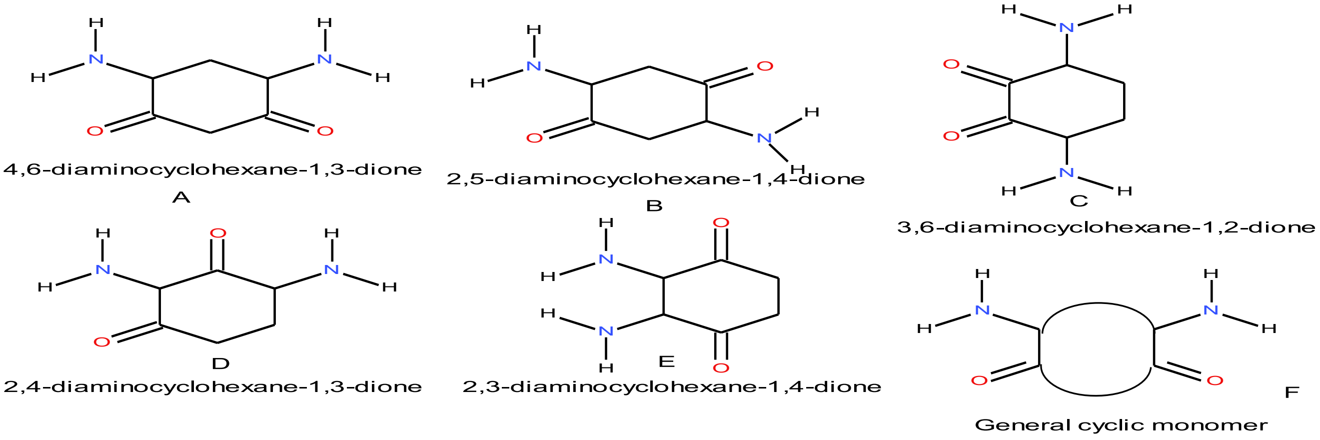
According to Clar's sextet rule these pyrazaacene linear polymers have only one sextet ring indicating the desired smaller electronic band gaps desired for semiconductor polymers.

Portella, Guillem, Jordi Poater, and Miquel Sola. "Assessment of Clar's aromatic π-sextet rule by means of PDI, NICS and HOMA indicators of local aromaticity."*Journal of physical organic chemistry”,* 18.8 (2005): 785-791.

Misra, Anirban, D. J. Klein, and T. Morikawa. "Clar theory for molecular benzenoids."*The Journal of Physical Chemistry A”,* 113.6 (2009): 1151-1158.

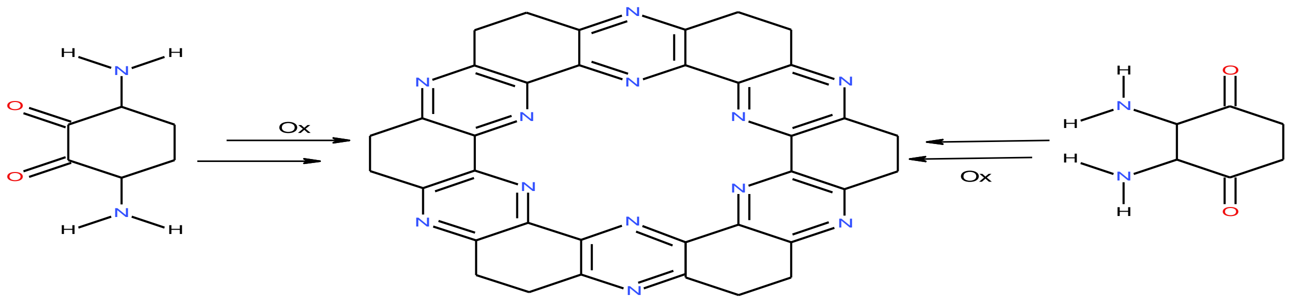
However, this type of pyrazaacene is easily reduced because so doing results in two aromatic Clar rings.

Various alpha amino ketones could be employed by this reaction.

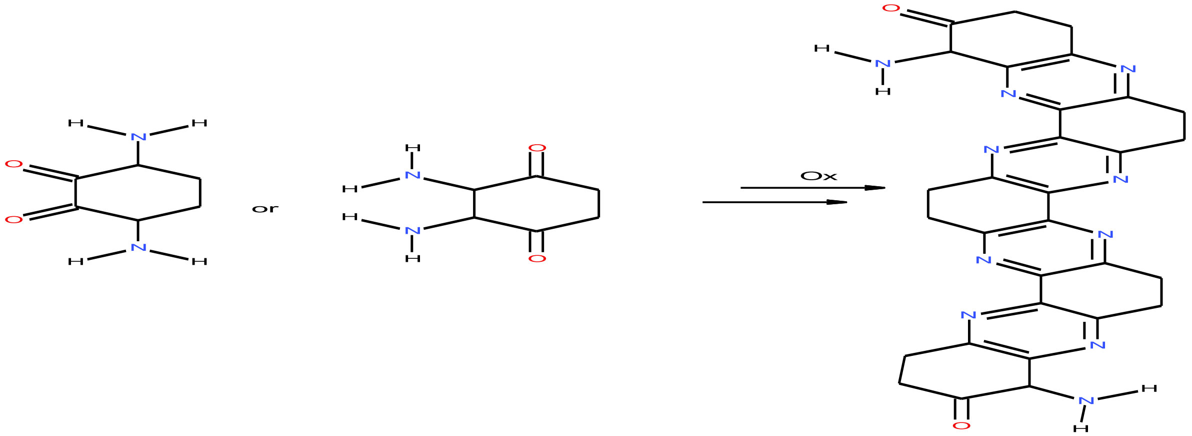


Scheme 3: Monomer D is problematic as it may not function as difunctional monomer.

C and E could result in a cyclic pyrazaacenes.



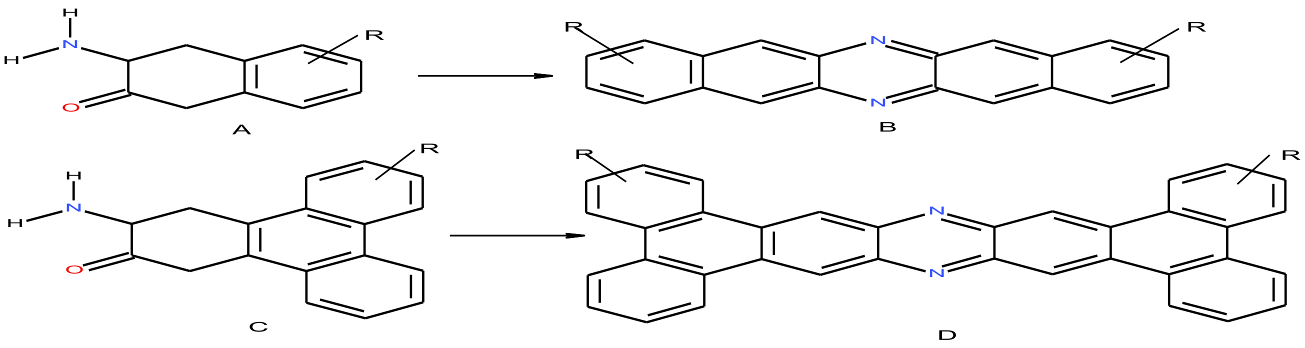
Scheme 4: Further oxidation would result in a cyclic pyrazaacene.



Scheme 4' Probably what would happen vs. wished for cyclic; however, possibly the cyclic would occur if an ion or metal species complexed with the pyrazine nitrogens directing ring formation.

Many further reactions are possible if the cyclohexane ring is derivatized with a typical cross-coupling R group or R=H if suitable for DHAP. A sufficient number of such derivatized monomers (or none if DHAP would work) would be required mixed with the unsubstituted to afford the desired post reactions such as coupling to polythiophenes to afford A-D semiconductors.

The above scheme 3 monomers would form stable amine salts that would polymerize upon neutralization. Even larger and smaller ring are possible as would be implied in the above general cyclic structure with either cis or trans amines(cis is illustrated by F). Pyrazine itself is water soluble as are the above as amine salts; therefor, water would be an ideal solvent for the polymerization because the polymer(oligomer) might also be soluble in it.



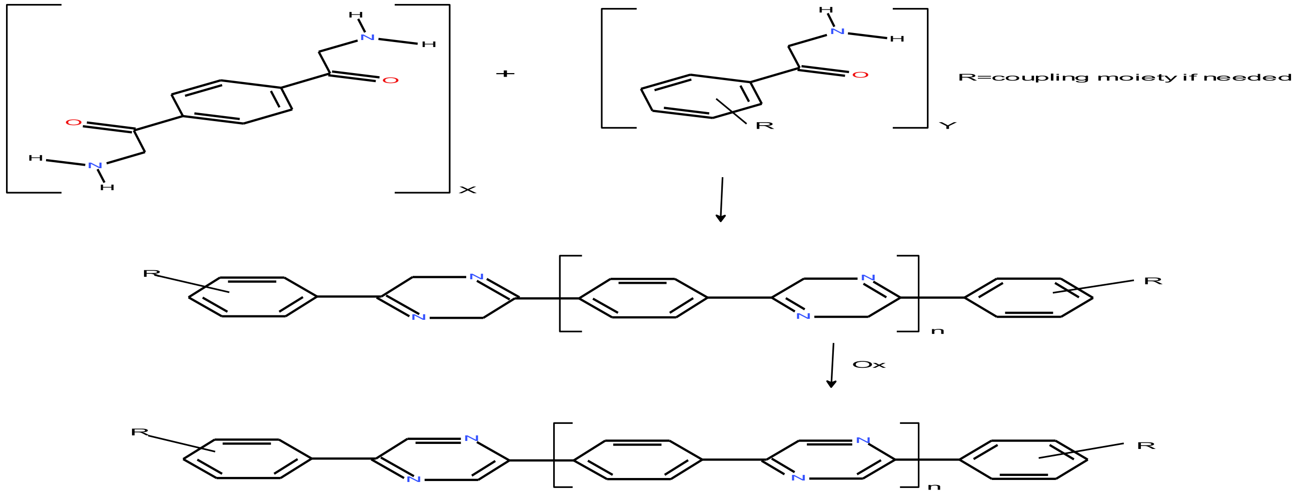
R= a coupling moiety for Suzuki and other coupling reactions...if needed

Scheme 5: B & D are the result of further oxidation.

Monofunctional alpha-amino ketones can be utilized as in scheme 5. This illustrates the flexibility of this pyrazaacene reaction. DHAP coupling can be used here also for various D-A combinations.

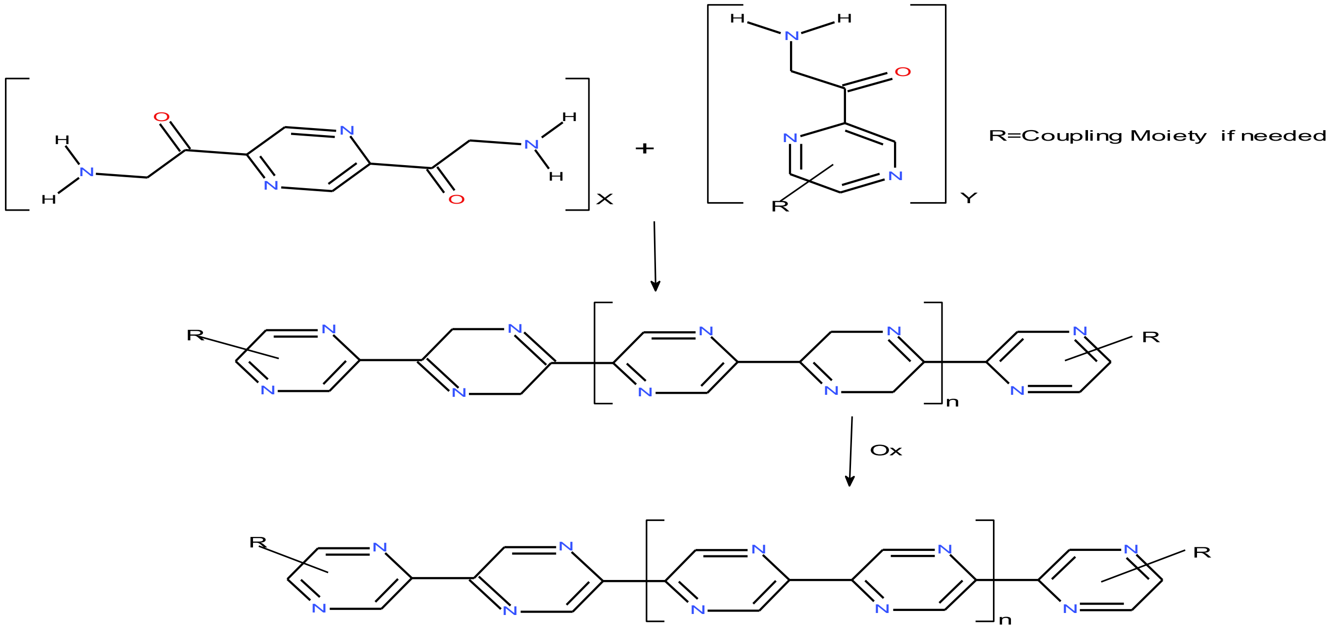
Lee, Seongmin, Thomas G. LaCour, and Philip L. Fuchs. "Chemistry of Trisdecacyclic Pyrazine Antineoplastics: The Cephalostatins and Ritterazines, "*Chemical reviews",* 109.6 (2009): 2275-2314.

Other **non-cyclic alpha-amino ketones** attached as disubstituted aromatics of all types could be polymerized. For example:

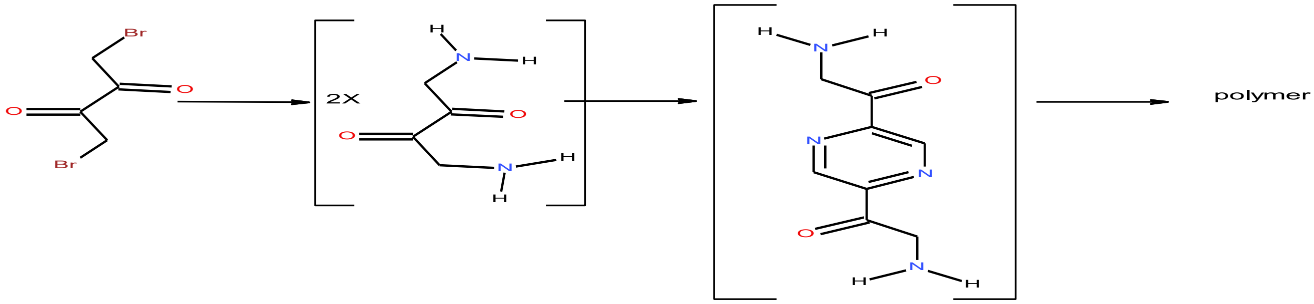


R=coupling moiety if needed

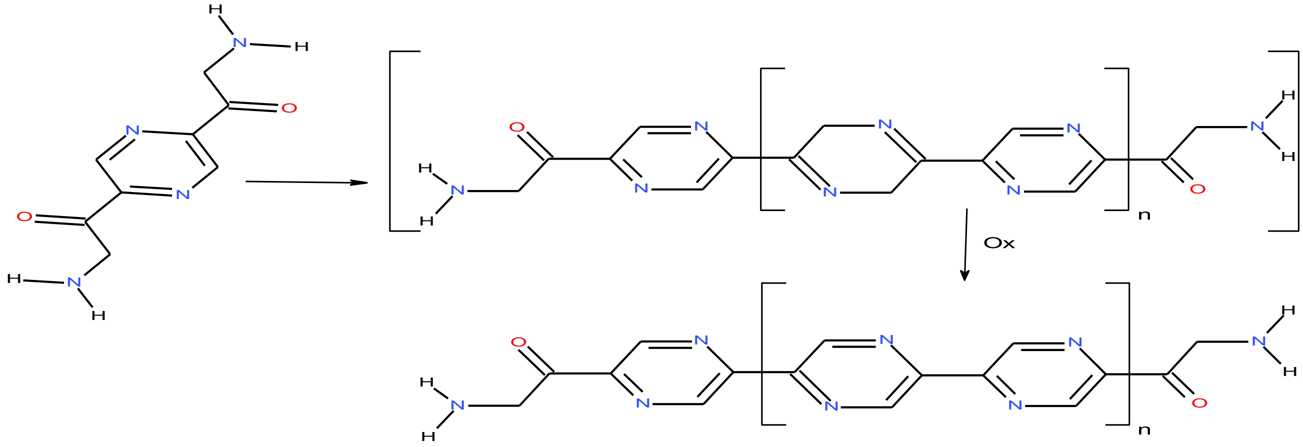
Scheme 6: Alternating polymers. Note, I will show the alpha-amino carbonyls as above but it is possible to reverse said carbonyl and amine groups and still end up with the same polymers.



scheme 7: Non-cyclic alpha-aminoketones

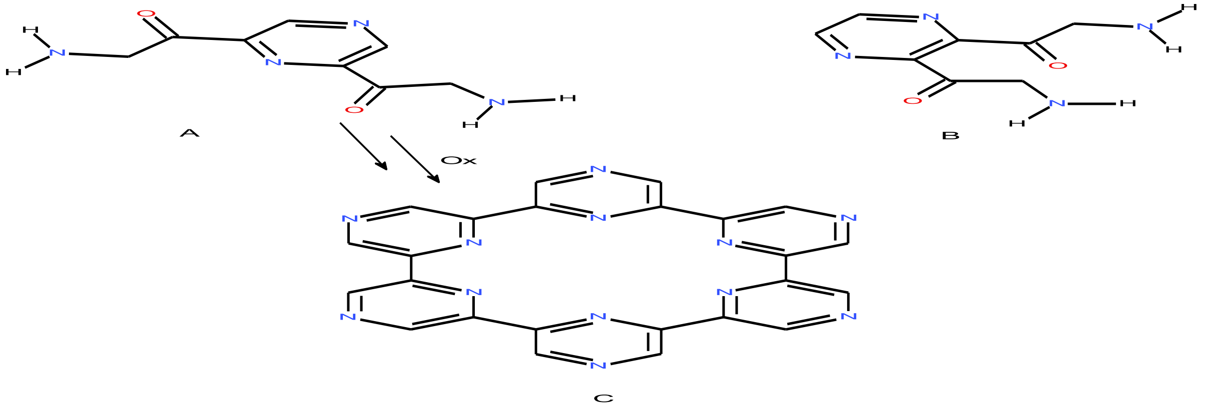


Scheme 8: Suggested monomer synthesis possibility. Ketones might have to be protected (ketal) before NH3.

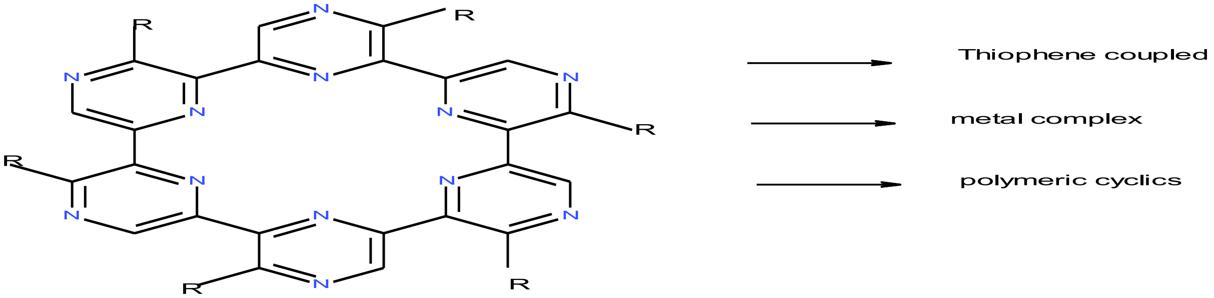


Scheme 9: Polymerization without capping monomer. This assumes that the terminal groups will stand up to the mild oxidation conditions or the amine terminals can be derivatized before oxidation.

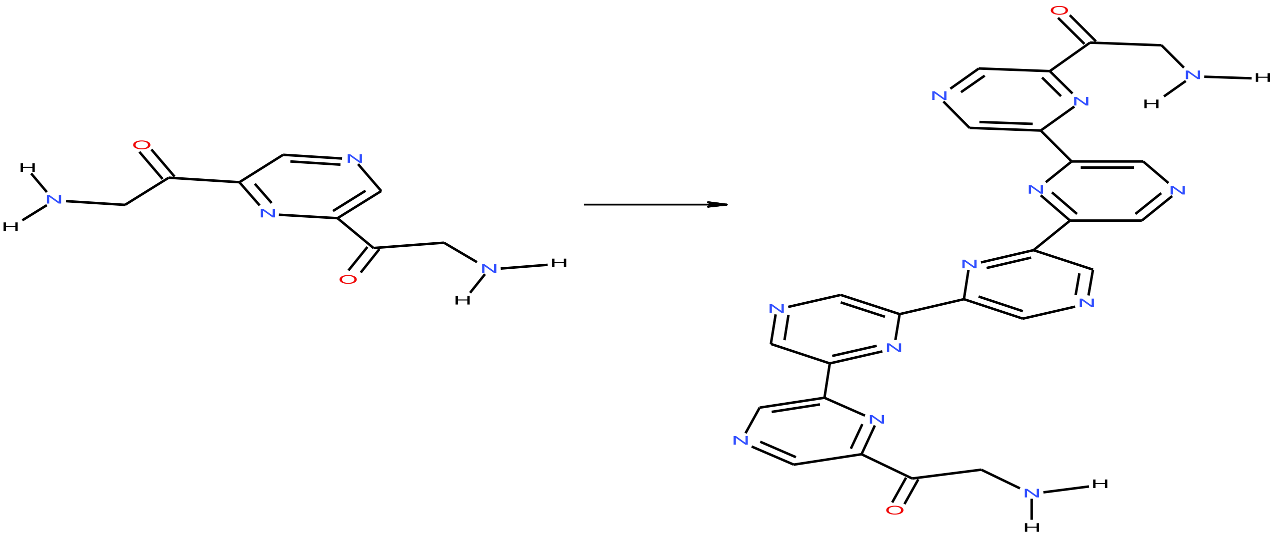
Again the terminal amines can be derivatized in order to improve processing or to couple to other polymers or to acrylic acids or other radical polymerizable monomers to form polymerizable oligomeric monomers.



Scheme 10: Monomer A could produce a cyclic pyrazine while monomer B will not function in this reaction probably going a different route to non-pyrazine derivatives?

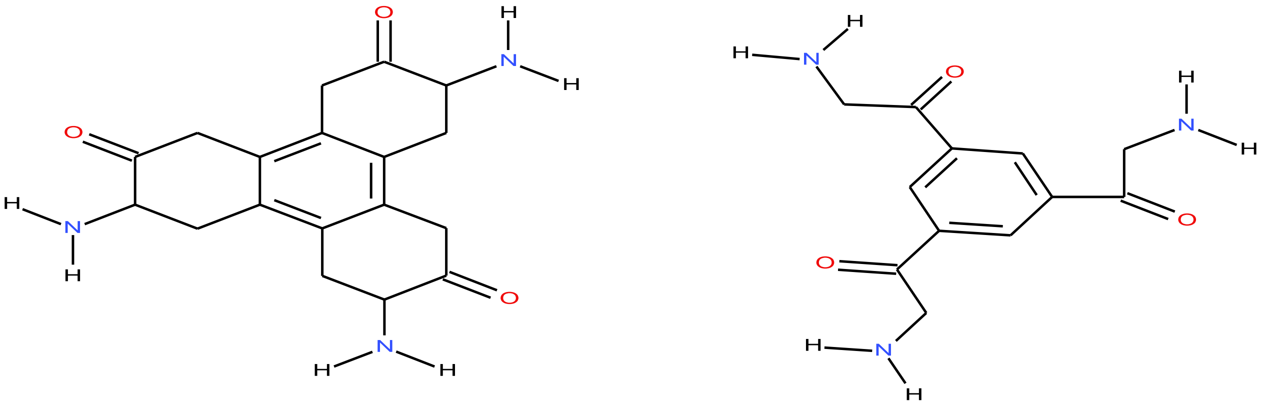


Scheme 11: Possible derivatives for post reactions. An R cross-coupling group is illustrated on every pyrazine ring but this is not necessary, a sufficient number are required depending on the goal.



Scheme 12: The cyclic of scheme 11 is probably wishful thinking and the condensation goes as shown above; however, as previously mentioned, a complexing ion or metal species might direct cyclic formation like with the crown ethers.

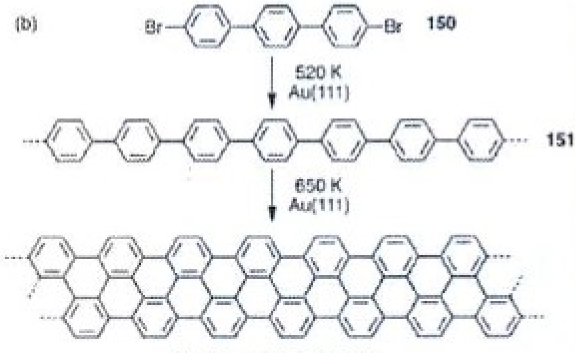
Tri alpha-amino ketones are also possible forming branched structures.



Scheme 13: Trifunctional possibilities illustrating the variety of poly alpha-amino ketones one could envision.

A potential problem is if the mono functional aminoketones employed to terminate pyrazaacene chains self condense resulting in an impurity. This should be minor depending on using a large number of repeating difunctional units, that would make this reaction less likely.

Additional possibilities concerning subsequent reactions could be considered. For example:

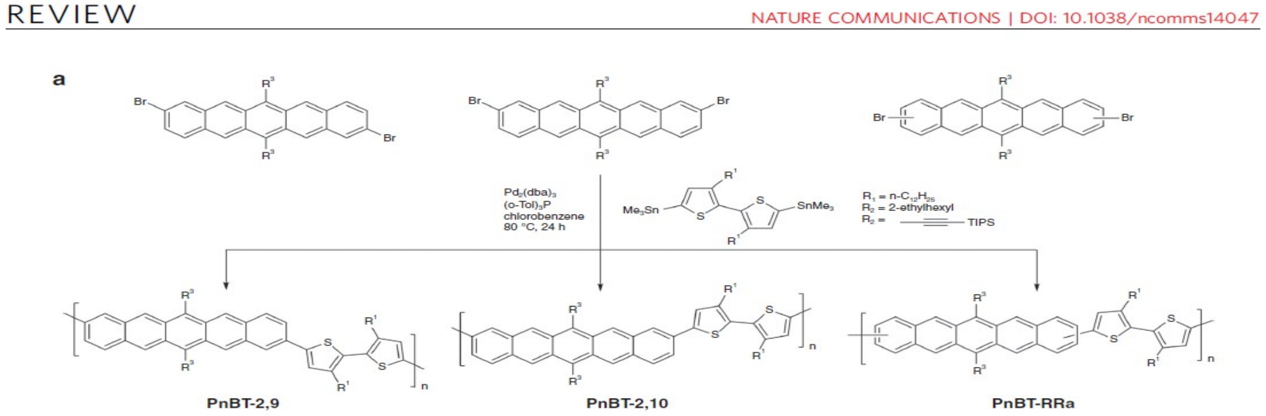


N = 6 armchair GNR 152

Narita, Akimitsu, et al. "New advances in nanographene chemistry."*Chemical Society Reviews",* 44.18 (2015): 6616-6643.

Basagni, Andrea, et al. "Molecules–oligomers–nanowires–graphene nanoribbons: A bottom-up step wise on-surface covalent synthesis preserving long-range order."*Journal of the American Chemical Society",* 137.5 (2015): 1802-1808.

This suggests that nanowires could result from the above pyrazaacene proposals (If these polymers would stand up to the conditions that are required?).



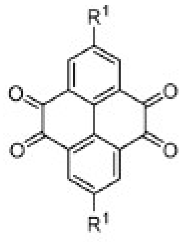
REVIEW

NATURE COMMUNICATIONS | DOI: 10.1038/ncomms14047

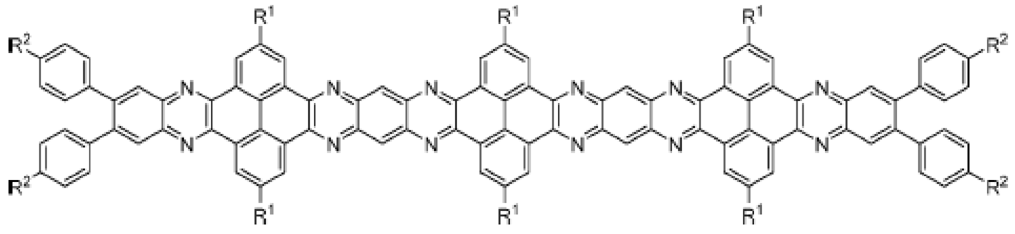
Above is an example of the R moieties used for coupling (DHAP would avoid Sn) that I have included to illustrate this possibility that I have alluded to several times. The reason for doing this coupling is to attach donors to acceptors. This D-A leads to superior semiconductors.

Ying, Lei, Fei Huang, and Guillermo C. Bazan. Regioregular narrow-band gap-conjugated polymers for plastic electronics."*Nature Communications”,* 8 (2017).

The pyrazaacene literature does not employ alpha-amino ketones?
To synthesize more complicated polymers or condensates, diketones of one structure are condensed with diamines of another structure, for example:



Using the above tetra-ketonee with tetra-amines, the following pyrazaacene can be synthesized. This is the typical chemistry employed by practically every reference I have seen. None that I have found employ the alpha-amino carbonyl method?



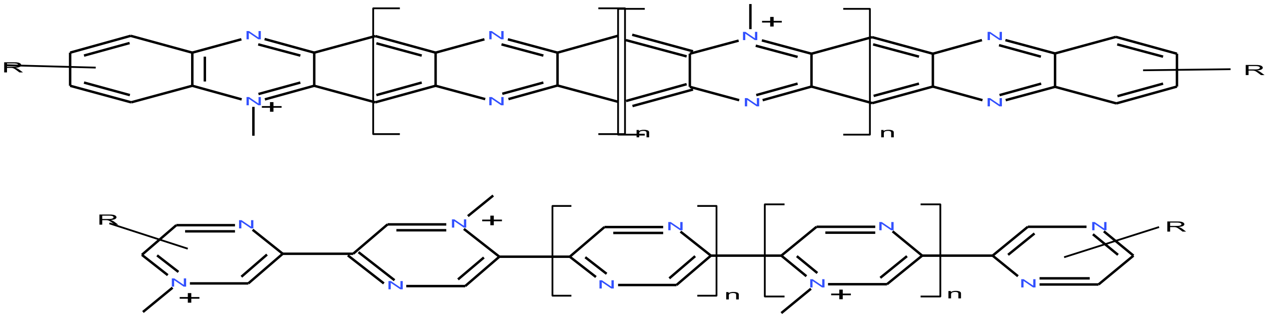
C33.4
a $R^1 = H$, $R^2 = OC_{10}H_{21}$
b $R^1 = t\text{Bu}$, $R^2 = OC_{10}H_{21}$

In conclusion, I have looked at many references concerning pyrazaacene synthesis and I have not found any that prepare these polymers from alpha amino ketones? As I have shown, employing this alternative alpha-amino ketone chemistry would lead to a variety of pyrazaacene polymers in homopolymer, block or cyclic polymer motifs.

The following reference is the latest review of this chemistry:

Stępień, Marcin, et al. "Heterocyclic Nanographenes and Other Polycyclic Heteroaromatic Compounds: Synthetic Routes, Properties, and Applications."*Chem. Rev*", 117.4 (2017): 3479-3716.

Quaternary Derivatives

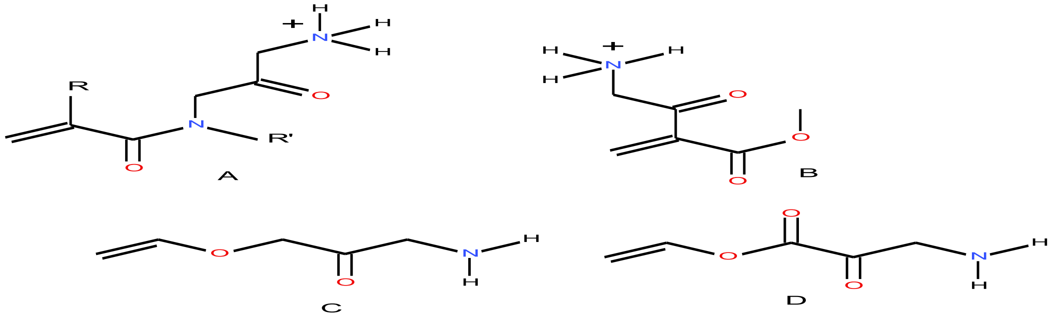


Scheme 14: Two examples of converting pyrazines to quaternary derivatives. Pyrazine is well known to form mono-quats. Many kinds of alkylating agents can be employed such as methyl chloride or bromide, diethyl sulfate etc.

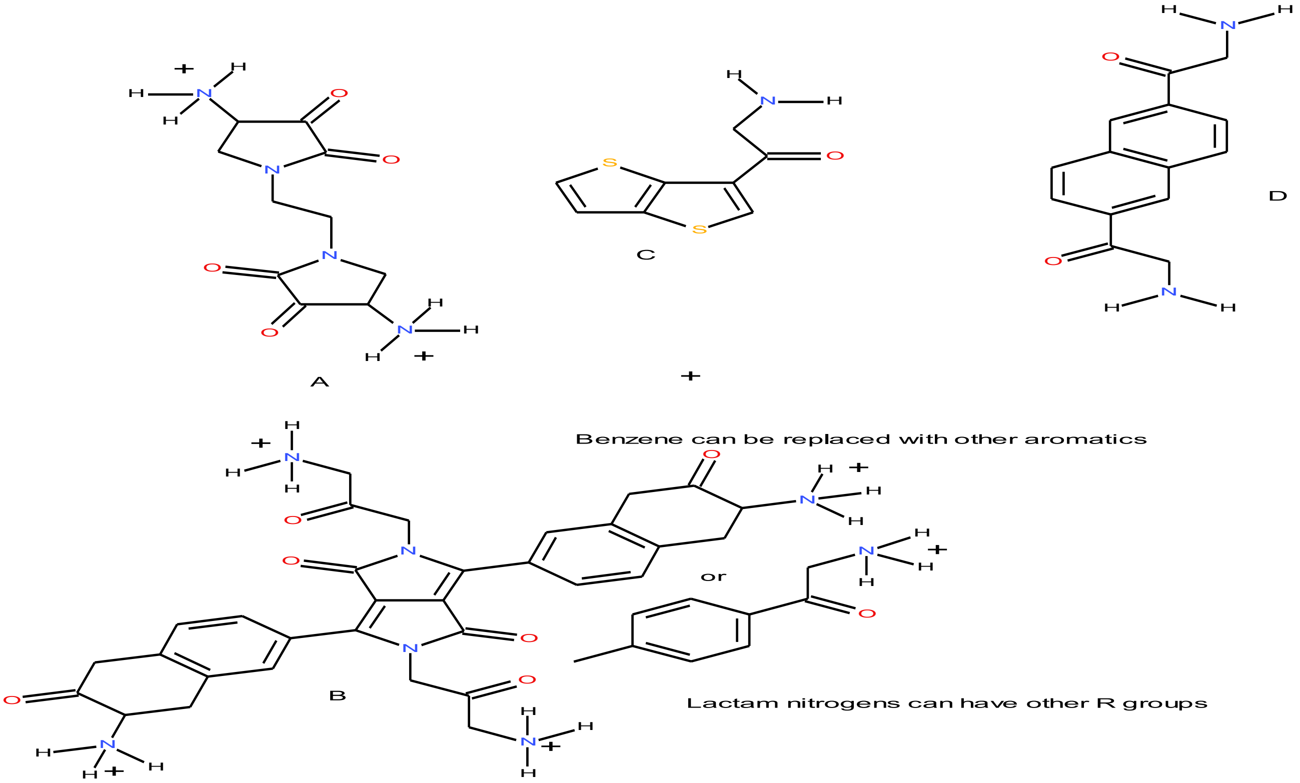
Gao, Ye, and M. Shreeve Jean’ne. "Quaternization of pyrazine, pyridazine, and pyrimidine with alkyl and polyfluoroalkyl halides: Formation of low melting salts."*Synthesis”,* 2004.07 (2004): 1072-1082.

These quat polymers might have biocidal properties? I don't think anyone has looked at them? Obviously, any of the pyrazaacene ideas can also be (partially) quaternized.

Vinyl Monomers



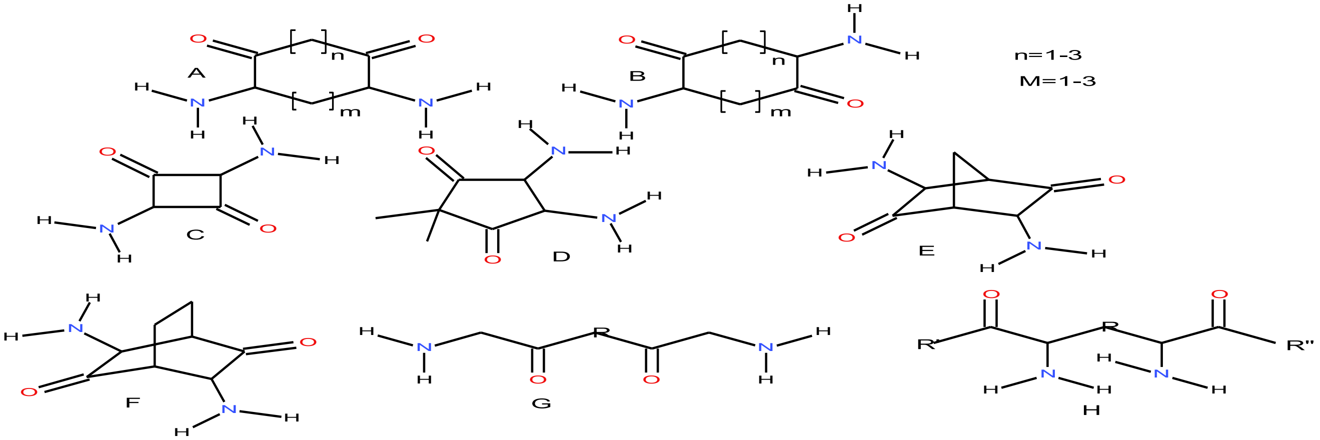
Scheme 15: A & B would copolymerize with many other water soluble monomers. Post polymerization, neutralization would release the amines and cross-link the copolymer with pyrazines.



Scheme 16: Trying to suggest structures that might be feasible. D would lead to a pyrazine copolymer that on further oxidation could lead to a graphene analog.

Stępień, Marcin, et al. "Heterocyclic Nanographenes and Other Polycyclic Heteroaromatic Compounds: Synthetic Routes, Properties, and Applications."*Chem. Rev*", 117.4 (2017): 3479-3716.

C could cap pyrazaacene types affording thiophene moieties capping the pyrazaacenes. A is just out of my imagination while B is a way to incorporate pyrazaacenes in this dye.



Scheme 17: Monomer possibilities. R can be almost anything, alkyl, aromatic, heterocyclic etc. Some of these might be difficult to synthesize but I leave that open.

Thank you for reading this proposal.
Dr. Robert B. Login …. rloginconsulting.com