MACROCYCLE FORMATION VIA ARYLNITRENIUM IONS: POSSIBLE INTRAMOLECULAR RECOGNITION

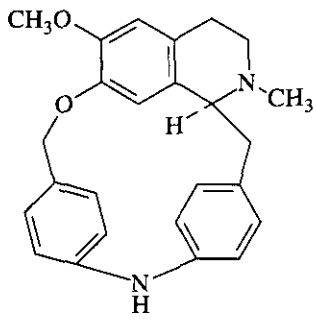
Rudolph A. Abramovitch* and Qing Shi

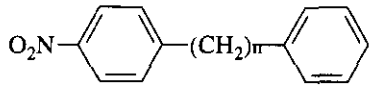
Department of Chemistry, Clemson University, Clemson, SC 29634-1905, U.S.A.

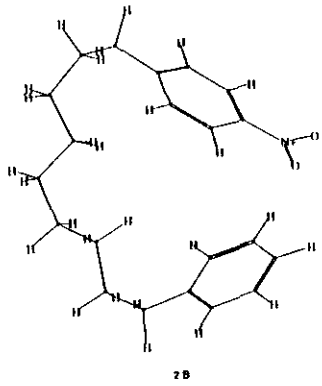
Abstract - MMX calculations on 1-(4-nitrophenyl)-9-phenylnonane indicate that it has a global minimum energy conformation in which the aryl rings are within easy bonding distance, which is confirmed by 2D NOESY, ultraviolet and fluorescence spectroscopy; the corresponding arylnitrenium ion cyclizes to give mainly the 18-membered ring 4,4′-nonamethylenediphenylamine, which results suggest that when electron-deficient and electron-rich aryl rings are joined by a long, flexible chain there exists an intramolecular attractive interaction between them that pre-orients them for cyclization.

We previously reported the remarkable formation (in reasonable isolated yield) of a sixteen-membered highly strained ring (**1**) by an intramolecular electrophilic aromatic amination by an arylnitrenium ion under normal concentration conditions.[1] Of the various possible explanations considered,[1] the preferred one was that there existed an attractive interaction between the highly electron-deficient arylnitrenium ion (or its protonated azide precursor) and an electron rich benzyloxy group, such that the two rings were pre-oriented favorably, resulting in a lower activation energy and favorable entropy for intramolecular cyclization. If this were the case, then this phenomenon of intramolecular recognition may have generality, and might be used as the basis for designing novel approaches to desirable macrocycles.

Intramolecular formation of macrocyclic rings from flexible chains can present formidable problems since it might be expected that stretched out conformations would be favored for the immediate precursors. There has been considerable interest in such processes in recent years owing to the existence of a number of macrocyclic natural products which exhibit useful biological activity e.g. vancomycin,[2a] RA-VII (an antitumor hexapeptide),[2b] arnabinol, [2c] combretastatin D-2,[2d] myricanone,[2e] and the lythraceae alkaloids, including lagerine,[2f] to name but a few. High dilution techniques have usually been employed. An example of intramolecular electrophilic substitution is the formation of macrocycles via the Friedel-Crafts acylation.[3] Free-radical macrocyclization,[4] macrolactonization,[5] and intramolecular Ullmann reactions[6] have also been used. We now report preliminary studies aimed at determining whether intramolecular recognition can be used to effect macrocylizations with arylnitrenium ions.

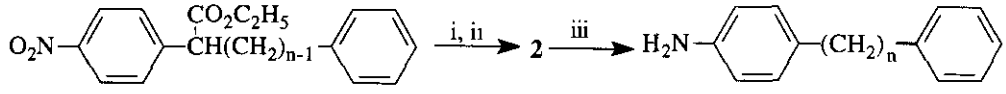






1 **2 a:** n = 9 **b:** n = 4 **2B**

Computer molecular modelling (MMX) cannot be carried out for arylnitreniums since no parameters are available for $-\overset{+}{N}-$. As an approximation, we modelled 1-(4-nitrophenyl)-9-phenylnonane (**2a**), a compound having a flexible chain and electron-poor and electron-'rich' aromatic groups at either end. MMX force field calculations indicated that the bent conformation **2B** was the global energy minimum,[7] preferred slightly over the 'linear' conformation. If the nitro group is replaced either by NH_2 or by H, then the linear conformation is found to be the global energy minimum, as expected. Conformation **2B** suggested that the N-atom was within 3.79-4.95Å of the ortho and para-positions of the ring at the other end. Modelling of p-$O_2NC_6H_4(CH_2)_4C_6H_5$ (**2b**), predicted it to have a preferred bent conformation, though with the shorter chain the inter-ring distances increased, not unexpectedly. Similar results were obtained if NO_2 was replaced by $\overset{+}{N}H_4$ in these molecules. When the more recent synthetic methods used to synthesise **2** either failed or gave very low yields we turned to the microwave-induced alkylation of ethyl p-nitrophenylacetate with $Ph(CH_2)_nI$ on n-$Bu_4\overset{+}{N}F^-/Al_2O_3$ to give **3**,[8] whose hydrolysis and decarboxylation proved uneventful and proceeded in reasonable yield (**2a**: 70%; **2b**: 38%).



3 a: n = 9 **b:** n = 4 **4 a:** n = 9 **b:** n = 4

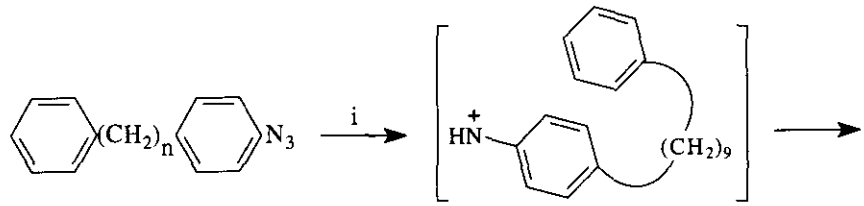
(i) NaOH/H_2O/EtOH/reflux. (ii) Quinoline/Cu powder/reflux. (iii) Ra-Ni/H_2/room temperature

The conformation of **2a** in solution was studied using 2D NOESY. In $CDCl_3$ solution, off-diagonal cross coupling between the two phenyl-ring protons [δ 7.39 (m- to NO_2) and δ 7.28-7.13] and between the two terminal methylene protons (δ 2.69 and δ 2.57) was observed. This indicates that these protons are within 5Å of each other,[9] and that the two terminal aryl groups are indeed quite close to each other in solution. 2D NOESY of **2b** showed similar cross-coupling patterns. No cross coupling peaks were observed for **4** (n = 9), which agrees with the hypothesis that bending is due to attraction between terminal electron-withdrawing and electron-donating group.

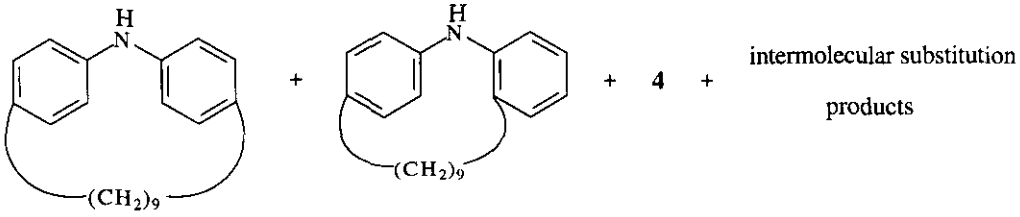
The UV-VIS spectra of **2a** in both acetonitrile and hexane solution (conc. 1.03×10^{-2} mol/l) were determined. In MeCN, a weak, broad red-shifted band between 400-500 nm was observed. Such a band was not present in the spectrum of a 1:1 (mole/mole) mixture of toluene and p-nitrotoluene in MeCN, nor was it present in the spectrum of **2b**. Ten-fold dilution of the solution of **2a** in MeCN and increasing the path-length 10 fold

resulted in no change in the intensity of that band, eliminating the possibility that it arose by intermolecular interaction. We assign this band to an intramolecular charge transfer absorption.[10] Clearly, the aryl rings in **2b** are not close enough for this charge transfer to occur. Similarly, **4a** does not exhibit such a peak in the UV-VIS. The solution of **2a** in hexane also did not exhibit a charge transfer peak, suggesting that the polar MeCN, which does not solvate the hydrocarbon chain, causes the latter to undergo the equivalent of hairpin looping,[11] whereas the non-polar hexane allows a less bent conformation. Similarly, the fluorescence spectrum of **2a** in MeCN exhibited a broad red-shift peak at 450-500 nm, suggesting that intramolecular charge transfer also existed in the excited state.[12]

Acid-catalyzed decomposition of azide (**5a**) (from **4a**) at 0°C gave a mixture. GC/ms indicated the presence of intramolecular cyclization products (**6**, **7**) and a small amount of hydrogen abstraction product (**4a**). These were separated by tlc[13] to give **6** (44%)[14] and **7** (2%).[15] Traces of **4a** (comparison with authentic sample) and of intermolecular dimeric and trimeric[16] reaction products were also isolated by tlc. No other intermolecular products were detected.



5a: n = 9



6 **7**

(i) Hexafluoroisopropanol/cat. CF_3SO_3H-CF_3COOH , 0°C then room temperature

The acid-catalyzed decomposition of azide (**5b**) (n = 4) gave a complex mixture in which only a very small amount of intramolecular cyclization product (m/z 223) was detected by GC/ms, together with the H-abstraction product (**4b**) and of a trifluoroacylated cyclization product [m/z 319 (M^+), 222 (M^+-CF_3CO)]. Mainly tar was formed. This would suggest that, as predicted by the MMX calculations and the absence of a charge transfer band in the UV-VIS, the aromatic rings in the nitrenium ion are not close enough to give meaningful yields of ring-closed product(s).

If these two examples of using MMX computations prove to be general, then this novel way of effecting intramolecular macrocyclizations, guided by the principle of intramolecular recognition and by molecular modelling, may have wide-spread application. Another example could be the recent synthesis of 12- to 16-membered propargylic alcohols through Lewis acid-promoted electrophilic ring-closure.[17] Post facto modelling of the corresponding formyl-O-protonated precursor to the 12-membered ring shows that the global

MMXE minimum is indeed the bent structure in which the reacting alkene functionsits right under the $\rangle C=\overset{+}{O}H$ group.[18] Further work is needed to determine whether or not this type of computation has predictive value.

We thank the National Science Foundation (grant # CHE - 9015972) for support of this work, and Dr. Dan Bearden for extensive help with the 2D and other nmr experiments.

REFERENCES

1. R. A. Abramovitch, P. Chinnasamy, K. Evertz,and G. Huttner, J. Chem. Soc., Chem. Commun., 1989, 3. (Concentration: 50 mg of azide in 2 ml. CH_2Cl_2).

2. (a) D.A. Evans and C.J. Dinsmore, Tetrahedron Lett., 1993, **43**, 6029. (b) H. Itokawa, J. Suzuki, Y. Hitotyanagi, K. Kondo, and K. Takaya, Chem. Lett., 1993, 695. (c) X-S. Yaa, Y. Ehizuka, H. Noguchi, F. Kiuchi, M. Shibya, Y. Itaka, H. Seto, and U. Sankawa, Chem. Pharm. Bull., 1991, **39**, 2956. (d) D.L. Boger, S.M. Sakuya, and D. Yohannes, J. Org. Chem. 1991, **56**, 4204. (e) D.A. Whiting, and A.F. Wood., Tetrahedron Lett., 1978, 2335. (f) K. Fuji, K. Ichikawa, and E. Fujita, J. Chem. Soc., Perkin Trans. 1, 1980, 1066.

3. (a) W.H. Schubert, W.A. Sweeney, and H.K. Latourette, J. Am. Chem. Soc., 1954, **76**, 5462. (b) R. Huisgen and U. Rietz, Chem. Ber., 1957, **90**, 2768.

4. (a) C. Walling, Tetrahedron, 1985, **41**, 3887. (b) B. Giese, Angew. Chem., Int. Ed. Engl., 1983, **22**, 753.

5. G. Illuminati and L. Mandolini, Acc. Chem. Res., 1981, **41**, 95. E.J. Corey, K.C. Nicolaou, and L.S. Melvin, J. Am. Chem. Soc., 1975, **97**, 653, 654.

6. D. L. Boger and D. Yohannes, J. Org. Chem.,1991, **56**, 1763.

7. Using PC MODEL from Serena Software. The computations were carried out on a 486/33 PC. To ensure that a global minimum energy had been reached, the various local minimal structures were altered repeatedly until the lowest energy conformation was reached consistently. Though these computations do not take into account the influence of solvent they do allow changes in the dielectric constant. The latter has been changed from 1.5D to 30.0D without much change resulting in the global energy minimum conformation.

8. R. A. Abramovitch, Q. Shi, and D. Bogdal, Synth. Commun., in press.

9. K. Wüthrich, J. Biol. Chem., 1990, **265**, 22059. D. Neuhaus and M.P. Williamson, "The Nuclear Overhauser Effect in Structural and Conformational Analysis", 1989, VCH Publishers, Inc, New York.

10. M. A. Winnik, Acc. Chem. Res., 1985, **18**, 73. M. Sisido, T. Mitamura, and Y. Imanishi, Macromolecules, 1976, **9**, 316. K. Mutai, H. Tukada, and R. Nakagaki, J. Org. Chem., 1991, **56**, 4896.

11. X.K. Jiang, W.Q. Fan, and T.Z. Hui, J. Am. Chem. Soc., 1984, **106**, 7202.

12. X-K, Jiang, Y-Z Hui, and Z-X Fei, J. Am. Chem. Soc.,1987, **109**, 5862.

13. Preparative tlc plates (Kieselgel 60 PF_{254}); elution with ethyl acetate/hexane (1:4, v/v).

14. **6**: $C_{21}H_{27}N$, m/z 293.2147. ^1H Nmr($CDCl_3$): δ 7.11 (d, J=8.3 Hz, 4H), 6.98 (d, J=8.3 Hz, 4H), 5.51 (s, 1H, exch. with D_2O), 2.57-2.50 (m, 4H), 1.55-1.42 (m, 4H), 0.92-0.82 (m, 4H), 0.56-0.45

(m, 2H), 0.06 - (-0.16) (m, 4H). ^{1}H-^{13}C DEPT ($CDCl_3$): 2 4° carbon peaks (δ 148.90, 138.53); 2 3° carbon peaks (δ 129.46, 123.22), 5 2°C peaks (δ 35.75, 31.27, 30.93, 30.45, 28.17. N-Benzenesulfonyl deriv.: mp 134°C; m/z 433 (M^+). ^{1}H Nmr ($CDCl_3$): δ 7.89 (d, J=8.2 Hz, 2H), 7.63-7.49 m, 3H), 7.12 (d, J=8.4 Hz) 7.00 (d, J=8.4 Hz, 4H), 2.55 (t, J=6.1 Hz, 4H), 1.49-1.41 (m, 4H), 0.81-0.71 (m, 4H), 0.47-0.44 (m, 2H), 0.18-(-0.09) (m, 4H). Proton peaks assigned by DQFCOSY nmr.

15. **7**: m/z 293(M^+). ^{1}H Nmr ($CDCl_3$): δ 7.25 (m, 2H), 7.15 (m, 2H), 7.10-6.88 (m, 4H), 5.51 (s, NH), 2.60-2.48 (m, 4H, NH), 2.60-2.48 (m, 4H), 1.55 (m, 4H), 1.25 (m, 10H).

16. Electrospray mass spect. (positive ion mode) on an API III Biomolecular mass analyzer; 50% (v/v) aq. MeCN solution containing 0.1% HCO_2H and 2 mM ammonium formate. Dimer: 606 ($M+NH_4^+$); trimer: 899 ($M+NH_4^+$).

17. J. A. Marshall and M.W. Andersen, J. Org. Chem., 1993, **58**, 8912.

18. R. A. Abramovitch, unpublished result.

Received, 9th May, 1994