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An Approach to Electronic Communication Through Transannular Hydrogen Bond : Synthesis of Cyclic Diamines Bearing Donor and Acceptor Groups

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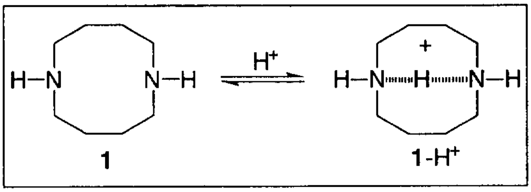
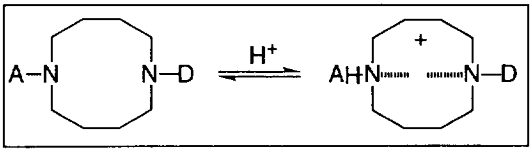
Abstract: The synthesis of medium-size monocyclic diamines based on a 1,6-diazacyclodecane core and bearing either nitrophenyl acceptor and methoxyphenyl donor groups or two donor or acceptor groups was achieved and their structure studied in the solid state by X-ray crystallography.

Around the eighties, Alder *et al* demonstrated, in an elegant manner, that medium size bicyclic diamines,[1] in particular 1,6-diazabicyclo[4.4.4]tetradecane, form robust transannular hydrogen bonds. In the latter case, the solid state structure of its monoprotonated form confirmed the inclusion of the proton within the cavity of the bicyclic compound.[2] Furthermore, based on NMR and IR studies, the intrabridgehead hydrogen bond was proposed to be linear and of the single minimum type.[3] Medium-ring monocyclic diamines, upon protonation, also leads to transannular hydrogen bond. In particular, 1,6-dimethyl-1,6-diazacyclodecane, a dimethylated analogue of **1**, undergoes such a phenomenon. In solution, as a consequence of the transannular hydrogen bond, the first protonation constant of the above mentioned compound was found to be so high (>12) that it could not be determined in water.[4] In the solid state, the X-ray analysis of the monoprotonated form of the dimethyl derivative of **1** confirmed the presence of the intramolecular H-bond.[4] Dealing with 1,6-diazacyclodecane **1**, our own study revealed the same type of behaviour (scheme 1).[5]



Scheme 1 : *Formation of a transannular H-bond*

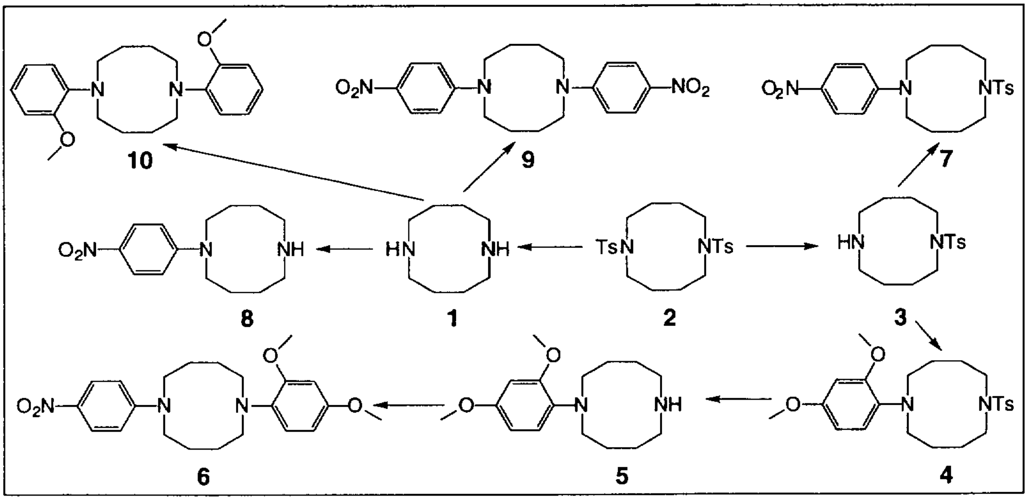
Based on these observations, it appeared interesting to study the possible effect of a transannular H-bond in Non-Linear Optics (NLO).[6] In other terms, is it possible to affect the second order polarisability of a molecule in which the donor and the acceptor groups may interact through an H-bond? It should be noted that most of the organic materials displaying NLO properties are, so far, based either on aromatic cores, or aromatic moieties interconnected through conjugated double bonds.[6]



Scheme 2 : *Possible communication between a donor and a acceptor through intramolecular H-bond*

In order to test this idea, one may consider, as a backbone, compound **1**, possessing two secondary amines and, thus, allowing a double functionalisation. The attachment of a donor group to one of the two amines and an acceptor moiety to the other nitrogen affords a molecule in which, upon protonation, the communication between the donor and the acceptor groups may occur through an intramolecular H-bond (scheme 2). To our knowledge, this concept has not been proposed earlier. In this vein, the compound **6** was designed. It is worth noting that most of the materials studied for their NLO properties are based on a aromatic core bearing donor and acceptor moieties.[6] The compound **6** may also be regarded as two interconnected aniline moieties bearing a methoxy as the donor and a nitro as the acceptor groups.

We report here the synthesis of compound **6** as well as two other reference compounds both based on **1** and bearing two nitrophenyl acceptor (**9**) and two methoxy donor (**10**) groups (scheme 3).



Scheme 3 : *Synthetic strategy*

The stepwise strategy for the synthesis of compound **6** bearing both the donor and the acceptor groups was based on our previous observation.[7] Indeed, during our investigation of the synthesis of cyclic analogues of naturally occurring polyamines such as spermine, we found that the treatment of the diprotected compound **2** by HBr/AcOH in the presence of phenol affords the monotosyl compound **3** in high yield.[7] Following the one-pot published procedure by Barton *et al*,[8] upon arylation of **3** by 2,4-dimethoxyphenyllead triacetate in the presence of $(AcO)_2Cu$ in CH_2Cl_2 at room temperature, compound **4** was obtained only in 13 % yield. This rather poor yield was further increased to 36 % by slow addition of the lead complex in CH_2Cl_2 to a solution of **3** and cooper acetate in CH_2Cl_2.[9] The lead complex was generated by plumbylation of resorcinol using $Pb(OAc)_4$.[10] The removal of the tosyl group on **4** leading to compound **5**[11] was achieved in 81 % yield by reductive method using lithium in liquid ammonia. In order to avoid the cleavage of the methoxy groups, the reaction time appeared to be crucial. Treatment of compound **5** with *p*-fluoronitrobenzene in DMSO afforded the desired compound **6**[12] in 67 % yield.[13] The synthesis of **6** by another strategy consisting of initial functionalisation of **3** by *p*-fluoronitrobenzene in DMSO leading to the compound **7**[14] failed. Indeed, in our hand, the deprotection of the latter, affording the compound **8**, by HBr/AcOH and phenol did not occurred. Nevertheless, compound **8**[15] could be prepared in 68 % yield by direct condensation of **1** with 1 equivalent of *p*-fluoronitrobenzene in DMF. Unfortunately, the arylation of **8** leading to compound **6** using the above mentioned Barton's method[8] failed. This observation may perhaps be due to some electronic communication between the two amino groups in **8**.

Dealing with the synthesis of symmetrical compounds **9** and **10** bearing two acceptor or two donor groups respectively, the common starting material was the unprotected compound **1**. Compound **9**[16] was prepared in 76 % yield by condensation of **1** with *p*-fluoronitrobenzene in DMSO at 100 °C. Compound **10**[17] was obtained in 13 % yield upon treatment of **1** with BuLi in THF followed by reaction with veratrol.[18]

The precursors **4** and **7** as well as the final compounds **6** and **10** were characterised by X-ray analysis, which confirmed the proposed structures. We only partially mention some of the characteristics for the final compounds **6** and **10** (figure 1). A detailed structural study of all compounds will be presented elsewhere.

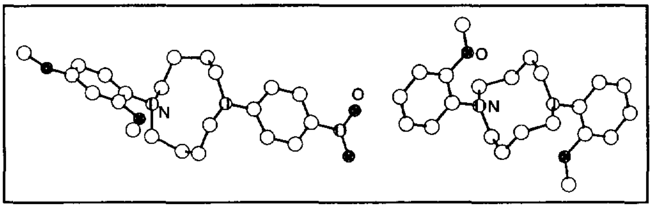


Figure 1 : *X-ray structures of* **6** *(left) and* **10** *(right). Selected bond distances : for* **6** *N-N = 3.37 Å, N-C (NO_2Ph) = 1.36 Å, N-C (MeOPh) = 1.43 Å; for* **10** *N-N = 3.21 Å, N-C (MeOPh) = 1.47 Å*

In summary, the synthesis of medium-ring monocyclic diamines bearing nitrophenyl and / or methoxyphenyl groups was achieved. Furthermore, their structures were confirmed by X-ray analysis. The protonation of the above mentioned compounds as well as their NLO behaviour will be reported elsewhere.

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9 To a solution of compound **3**[7] (0.6 g, 2 mmol) and copper acetate (36 mg, 0.2 mmol) in dry CH_2Cl_2 (5 ml), a solution of 2,4-dimethoxyphenyllead triacetate[10] (1.15 g, 2.2 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise (3 h.) under argon. The reaction mixture was stirred at rt. for 48 h. before it was filtered over celite. The pure compound **4** (0.31 g, 36 % yield) was obtained by chromatography (Al_2O_3, hexane/CH_2Cl_2 7/3) as a white solid which was further washed with hexane (3x30 ml). M. p. 130-132 °C; ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.79 (m, 8H, $NCH_2\mathit{CH_2CH_2}CH_2N$); 2.42 (s, 3H, CH_3, Ts); 3.11-3.19 (m, 8H, NCH_2, CH_2NTs); 3.73 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 6.39 (dd, 1H, 2.7 Hz, 8.6 Hz, Ar), 6.45 (d, 1H, 2.7 Hz, Ar); 6.93 (d, 1H, 8.5 Hz, Ar); 7.30 (d, 2H, 8.0 Hz, Ts); 7.64 (d, 2H, 8.2 Hz, Ts); ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 21.6 (CH_3); 23.8, 24.6, 50.1, 50.4 (CH_2); 55.0, 55.5 (OCH_3); 100.0, 103.2, 121.5, 128.0, 129.4, 132.9, 133.8, 143.1, 155.3, 155.9 (Ar).
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11 Into a solution of compound **4** (0.16 g, 0.37 mmol) in dry THF (20 ml), 100 ml of NH_3 was condensed at -78 °C before Li (110 mg, 15.8 mmol) was added and the reaction mixture was further stirred at - 78 °C for

4 h. under argon. The reaction was quenched at -78 °C by addition of absolute EtOH (1.4 ml). The mixture was allowed to reach the rt. leading to the removal of NH_3. The reaction residue was cautiously treated with a mixture of THF/H_2O 50/50. THF was removed and the mixture extracted with CH_2Cl_2 (4x30 ml). The solvent was removed. The residue was partitioned in a mixture of Et_2O (40 ml) and HCl (40 ml, 6N). The aqueous layer was further washed with Et_2O (3x20 ml) before it was evaporated to dryness leaving the desired compound **5** (106 mg, 81 % yield) as a slightly coloured solid. Compound **5** was used in the next step without further purification.

12 To a solution of **5** (106 mg, 0.3 mmol) in DMSO (8 ml) NaOH (45 mg, 1.1 mmol) and *p*-fluoronitrobenzene (60 mg, 0.42 mmol) was added and the mixture heated to 70 °C overnight. The mixture was allowed to cool to rt. before H_2O (50 ml) was added. The solution was acidified (HCl, pH 1) and washed with CH_2Cl_2 (3x50 ml). The aqueous layer was basified with (NaOH, pH 13) and the desired product extracted with CH_2Cl_2 (3x50 ml). The solvent was removed and the pure compound **6** (80 mg, 67 % yield) was obtained by chromatography (Al_2O_3, CH_2Cl_2/hexane 1/1). M. p. 134-135 °C; ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.6 (m, 4H, NCH_2CH_2); 1.95 (m, 4H, NCH_2CH_2); 3.02 (t, 4H, 5.4 Hz, NCH_2); 3.8 (m, 10H, NCH_2, OCH_3); 6.41 (dd, 1H, 2.7 Hz, 8.6 Hz, Ar), 6.49 (d, 1H, 2.7 Hz, Ar); 6.67 (d, 2H, 9.4 Hz, Ar); 6.97 (d, 1H, 8.6 Hz, Ar); 8.1 (d, 2H, 9.4 Hz, Ar); ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 24.9, 27.1 (NCH_2CH_2); 53.3, 53.7 (NCH_2); 54.8, 55.5 (OCH_3); 100.0, 103.4, 112.5, 122.3, 125.8, 134.3, 137.0, 155.2, 155.4, 156.4 (Ar).

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14 To a solution of **3** (296 mg, 1 mmol) in DMSO (5 ml) *p*-fluoro-nitrobenzene (282 mg, 2 mmol) was added and the mixture heated to 100 °C for 20h. The mixture was allowed to cool to rt. before H_2O (150 ml) and acetone (50 ml) were added. The volume was reduced leading to a yellow precipitate which was filtered. The pure compound **7** was obtained by chromatography (Al_2O_3, CH_2Cl_2/hexane 1/1). M. p. 172-173 °C; ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.81 (m, 4H, $TsNCH_2CH_2$); 2.04 (m, 4H, CH_2CH_2NAr); 2.43 (s, 3H, CH_3); 3.07 (t, 4H, CH_2NTs, 5.3 Hz); 3.86 (t, 4H, NCH_2, 6.0 Hz); 6.61 (d, 2H, Ar, 9.5 Hz); 7.34 (d, 2H, Ts, 8.0 Hz); 7.68 (d, 2H, Ts, 8.3 Hz); 8.10 (d, 2H, Ar, 9.5 Hz); ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 21.6 (CH_3); 25.0, 27.8, 52.8, 53.6 (CH_2); 127.8, 129.8, 133.3, 143.9 (Ts); 111.0, 126.0, 136.3, 153.8 (Ar).

15 To a solution of the dihydrochloride of **1** (215 mg, 1 mmol) in DMF (10 ml), K_2CO_3 (1.38 g, 10 mmol) was added and the stirred mixture was heated to 80 °C. To this, a solution of *p*-fluoro-nitrobenzene (141 mg, 1 mmol) in DMF (2 ml) was added dropwise and the mixture further stirred at 80 °C for 4 h. The solvent was removed and the pure compound **8** (180 mg, 68 % yield) was obtained by chromatography (Al_2O_3, CH_2Cl_2, 3 % MeOH/CH_2Cl_2). M. p. 101-103 °C, ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.57 (m, 4H, NCH_2CH_2); 1.88 (m, 4H, $ArNCH_2CH_2$); 2.78 (t, 4H, 5.4 Hz, NCH_2); 3.70 (t, 4H, 5.6 Hz, $ArNCH_2$); 6.60 (d, 2H, 9.5 Hz, Ar); 8.09 (d, 2H, 9.5 Hz, Ar). ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 26.8, 28.7 (CH_2CH_2); 49.4, 55.4 (NCH_2); 111.6, 125.9, 136.8, 142.9, 154.5 (Ar).

16 100 mg (0.46 mmol) of the dihydrochloride salt of **1** was dissolved in H_2O (10 ml) and the free base **1** was extracted into $CHCl_3$ (3x10 ml). The solvent was removed and the residue was dissolved in DMSO (10 ml). To this, *p*-fluoro-nitrobenzene (135 mg, 0.96 mmol) was added and the mixture heated to 100 °C for 24h. The mixture was allowed to cool to rt. before H_2O (150 ml) and acetone (50 ml) were added. The volume was reduced leading to a yellow precipitate which was filtered. The pure compound **9** was obtained by chromatography (Al_2O_3, CH_2Cl_2/hexane 9/1). M. p. 234-236 °C; ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.95 (m, 8H, CH_2CH_2); 3.49 (m, 8H, NCH_2); 6.64 (d, 4H, 9.5 Hz, Ar); 8.12 (d, 4H, 9.5 Hz, Ar); ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 25.7 (NCH_2CH_2); 53.2 (NCH_2); 110.9, 125.7, 137.1, 152.7 (Ar).

17 To a solution of the dihydrochloride salt of **1** (100 mg, 0.46 mmol) in dry THF (10 ml) *n*BuLi/hexane(1,3 ml, 1.6 M) was added under argon at 0 °C. The temperature was maintained at 0 °C for 30 min and the mixture further stirred at rt. for 1 h. To this, 1,2-dimethoxybenzene (200 mg, 1.45 mmol) was added and the mixture was refluxed for 3 days. The reaction mixture was allowed to cool to rt. before H_2O (30 ml) was added and the mixture acidified with Conc. HCl (pH 1). The mixture was washed with toluene (3x30 ml) and the aqueous layer basified with NaOH (pH 13) before the desired compound was extracted into toluene (3x30 ml) and the solvent removed. The pure compound **10** (22 mg, 13 % yield) was obtained by chromatography (Al_2O_3, CH_2Cl_2/hexane 1/1). M. p. 159-161 °C; ^1H (300 MHz, $CDCl_3$, 25 °C): δ (ppm) : 1.59 (m, 8H, NCH_2CH_2); 3.33 (m, 8H, NCH_2); 3.87 (s, 6H, OCH_3); 6.8-7.0 (m, 8H, Ar); ^{13}C (50.32 MHz, $CDCl_3$,, 25 °C): δ (ppm) : 23.9 (NCH_2CH_2); 50.0 (NCH_2); 55.1 (OCH_3); 111.5, 120.4, 121.8, 140.8, 154.1 (Ar).

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