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Diastereoisomerism In 1,3,5-Triazine Through Nitrogen Substituents

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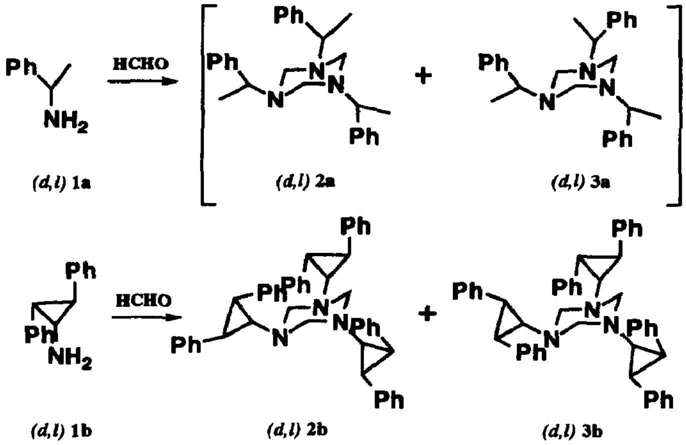
***Abstract*:** The reaction of formaldehyde with (*d,l*) α-methylbenzylamine resulted in a mixture of products of which the desired 1,3,5 triazines **2a** and **3a** could not be isolated. On the other hand, the reaction of (*d,l*) 2,3 (*trans*)-diphenylcyclopropanamine **1b** with formaldehyde results in the formation of the diasteromeric nonsymmetrical 1,3,5-triazine **2b** and the symmetrical 1,3,5-triazine **3b**. These triazines were isolated and their structures were determined by NMR. The stereochemical outcome is discussed.

Changes in the substitution patterns on carbon atoms that lead to (i) conformational cycloenantiomers in hexaisopropylbenzene and (ii) cycloenantiomers in cyclohexaalanyls have been described previously.[1-5] Mislow has developed conventions that illustrate cyclodirectionality in the above cases. Similar opportunities to demonstrate interesting stereochemical outcomes exist when the substitution pattern is manipulated on the nitrogen atoms of symmetrical triazines. Optical diastereomers of symmetrical triazine generated by the use of optically active α-methylbenzylamine and formaldehyde have already been reported.[6] However, the diastereoisomerism resulting from alternating the chiral substituents on nitrogen atoms remains to be demonstrated. This manuscript describes one such finding. When (±) - α - methyl benzylamine **1a** was treated with formaldehyde it resulted in several products. Dozens of chromatographic procedures were evaluated to separate the desired compounds **2a** and **3a**. None led to the desired results. In some cases decomposition was demonstrated with the help of 2-D tlc. A 400 MHz NMR analysis (including COSY and NOESY techniques) at 20° to 90° revealed a probable existence of the desired compounds. However, due to the complexity of these spectra (presumably, in part due to the existence of byproducts) an unequivocal assignment remained elusive. The optically active diastereomers described above [6a,b] were obtained in pure form by low temperature crystallization. Thus, it was theorized that sterically demanding substituents on nitrogen may improve the stability of these triazenes, and thus allow their separation by chromatography. To this end when (±)-*trans*-(2,3)-diphenylcycloprona-1-amine, **1b**, was treated with formaldehyde, it generated, as expected, two distinct compounds **2b**, and **3b** in addition to polymeric materials as observed by thin layer chromatography. These two compounds were isolated and subjected to structure determination.

The reactions of ammonia with aldehydes (excluding formaldehyde), and ketones generate triazines in which the ring carbons carry subtituents resulting in conformationally restricted triazines. Several examples of these studies can be found in the literature in which Nuclear Magnetic Resonance (NMR) spectroscopy led to elucidation of the structures of these triazines and to determination of the energy barriers for the axial/equatorial, or the chair/boat interconversions.[7-13] When amine **1b** was treated with formaldehyde, two new compounds (along with some polymeric material) resulted. Although the present work involves the reaction between the substituted amine and formaldehyde, it was important to establish that the existence of these new compounds (**2b**, and **3b**) was not due to conformational rigidity.



Toluene solutions of isolated compounds **2b**, and **3b** were heated to 100°C. The tlc patterns[14] of these compounds remained unchanged after heating. NMRs of these compounds in d_6-DMSO, d_8-THF, and d_4-MeOH were obtained. Regardless of the solvent, the spectra of compound **2b** were more complex than the spectra of compound **3b**. A temperature dependent (20°C to 110°C) NMR study in d_6-DMSO was also undertaken. This study showed that at temperatures of 50°C or higher (for CMR) and 75°C or higher (for PMR) spectra with excellent line resolutions resulted. This real time/temperature NMR work indicated that at no temperature did the signal from one compound appear in the sample of the other. When these heated (110°C) NMR samples were cooled to arbitrarily predetermined temperatures of 90°, 75°, and 50°C, they regenerated the spectra that were independently obtained at those temperatures for these compounds. Thus compounds **2b**, and **3b** did not result from conformational rigidity. The interpretation of these spectra clearly indicated the symmetrical nature of compound **3** and the nonsymmetrical nature of compound **2**. The NMR data is listed in the experimental section. The COSY, and NOESY NMR of **2b** further verified these structures.

The use of a *d+l* substrate for the formation of the trimer resulted in only two diastereomers. This is in accordance with theory.[15a] In the above reaction compounds **2b**, and **3b** were formed in the ratio of 2:1. This is in agreement with the higher ratio (3:1) of the nonsymmetrical compound predicted by theory.[15b] Inspection of models of these compounds as well as MM2 energy minimization approximations indicated that in the case of unsymmetrical compound **2b** there is a crowding of two of the six phenyl rings. This crowding is absent in the case of compound **3b** as all six phenyl rings are oriented in a cyclic fashion. Thus, extending Mislow's concept to the above compounds, a lack of cyclodirectionality in compound **2b** results in a steric crowding. This steric hindrance retards the formation of the unsymmetrical compound to some degree resulting in a slightly lower than the expected ratio. Conversly, for the symmetrical compound **3b**, the cyclodirectionality of the phenyl rings lowers the crowding, resulting in a lack of interference during its formation.

In summary, the reaction of an amine substituted with at least one chiral carbon and formaldehyde results in the formation of two distinct 1,3,5-triazines. The use of a hindered amine imparted stability to the resultant triazines, which allowed their separation. The structures of these triazines were determined, and the ratio of their formation was explained based on statistical and stereochemical grounds.

EXPERIMENTAL SECTION

Formaldehyde and α-methyl benzylamine were purchased from Aldrich.

(*d,l*) 2,3 (*trans*)-diphenylcyclopropanamine hydrochloride salt (1b•HCl): This was synthesized as described previously.[16-19] For the purpose of this study the following NMR data was obtained on this compound. NMR (Room Temperature) : (d_6-DMSO) δ:2.77 (t, J=8Hz,CH), 2.885 (d of d, J=4, and 7 Hz, CH), 3.17 (q, J=4Hz, CH), 7.2-7.5 (m, Ar, 10H),8.7 (br,NH_2,). CMR: (d_6-DMSO) δ:26.78 (CH), 26.8,20.5 (CH),126.5(N-CH),127.1(Ar),128.4(Ar),129.4(Ar),133.8(Ar-q),138.7(Ar-q).

(*d,l*)-(nonsymmetrical,and symmetrical)-1,3,5-Tris (2,3 (*trans*)-diphenyl-1-cyclopropyl) hexahydro-1,3,5-triazine (2b, and 3b, respectively): A suspension of 3.75g of **1•HCl** in 200ml ether was stirred and treated with ca 15ml of saturated aq. Na_2CO_3 solution. The alkaline aqueous layer was removed and it was extracted with 50ml ether. The combined ether layer was dried over anhydrous $MgSO_4$ and then concentrated to give 3.3g of **1** as a free base.

This solid was dissolved in 90 ml MeOH and to it 1.2ml 37% aq. HCHO solution was added over ca. 5 minutes. The resultant suspension was stirred for 2hr at room temperature. This was concentrated under reduced pressure to a oil. This oil was dissolved in 100ml CH_2Cl_2, washed with 2x20 ml H_2O, followed by 15ml sat. $NaHCO_3$ solution, dried over anhyd Na_2SO_4 and then it was concentrated to 4.45g of a viscous oil. This solid was chromatographed using flash grade silica gel with benzene[18] as a eluant to obtain 1.5g of the less polar (*d,l*)-(nonsymmetrical)-1,3,5-Tris (2,3 (*trans*)-diphenyl-1-cyclopropyl)hexahydro-1,3,5-triazine (**2b**) as a white solid, and 0.8g of more polar (*d,l*)-(symmetrical)-1,3,5-tris (2,3 (*trans*)-diphenyl-1-cyclopropyl)hexahydro-1,3,5-triazine (**3b**) as a white solid. The analytical data on these compounds are reported below.

(*d,l*)-(nonsymmetrical)-1,3,5-Tris (2,3 (*trans*)-diphenyl-1-cyclopropyl)hexahydro-1,3,5-triazine (**2b**):
m.p. 85-90°C (turns to glassy solid), 101-103°C (glassy solid collapsed). MS (FAB/DMSO) 662.8 (M^+). IR: (KBr) ν 3025,1602,1497 cm^{-1}. Elemental: Calcld for $C_{48}H_{45}N_3$: C:86.90; H:6.78; N:6.32. Found: C:86.81; H:6.84; N:6.36. NMR : (d_6-DMSO, 90°C) δ: 2.14 (t, J=7Hz, C-CH , 2H), 2.26 (d of d, J=4 and 6Hz, C-CH, 2H), 2.34-2.42 (m, C-CH, 2H), 2.54 (d of d, J=4 and 7Hz,N-CH, 2H), 2.80 (d of d, J=4 and 8Hz,N-CH, 1H), 3.04 (s, N-CH_2, 2H), 3.30 (d, J=11Hz, N-CH_2, 2H), 3.50 (d, J=11Hz, N-CH_2, 2H), 6.85-7.35 (m, Ar, 30H). CMR: (d_6-DMSO, 50°C) δ: 31.3 (CH), 31.7 (CH), 33.9 (CH), 34.0 (CH), 49.6 (CH), 50.0 (CH), 71.7 (CH_2), 72.1 (CH_2), 125.3 to 128.1 (Ar-CH), 137.2 (Ar-qC), 141.2 (Ar-qC). Note: All signals had two peaks with a ratio of 2:1, indicating that one of the cyclopropyl rings had a different orientation compared to to the remaining two orientations. This supports the ^1H NMR data listed above for this compound.

(*d,l*)-(symmetrical)-1,3,5-Tris (2,3 (*trans*)-diphenyl-1-cyclopropyl)hexahydro-1,3,5-triazine (**3b**):
m.p. 93-94°C (turns to glassy solid), 104-108°C (glassy solid collapsed). MS (FAB/DMSO) 662.7 (M^+). IR: (KBr) ν 3025,1602,1497 cm^{-1}. Elemental: Calcld for $C_{48}H_{45}N_3$: C:86.90; H:6.78; N:6.32. Found: C:87.14; H:6.86; N:6.34. NMR: (d_6-DMSO, 90°C) δ: 2.05 (d of d, J=4, and 6Hz,C-CH, 3H), 2.19 (t, J=6Hz,C-CH, 3H), 2.42 (d of d, J=4 and 7Hz,N-CH, 3H), 3.2 (s, N-CH_2, 6H), 7.05-7.40 (m, Ar,30H). CMR: (d_6-DMSO, 50°C) δ: 30.2 (CH), 33.6 (CH), 49.2 (CH), 71.8 (CH_2), 125.5 to 128.3 (Ar-CH), 136.8 (Ar-qC),141.1 (Ar-qC).

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14. Our subsequent thin layer chromatography work suggests that 10% ether in hexane, 5% EtOAc in hexane, and 1:1 mixture of hexane/CH_2Cl_2 also separate these compounds.
15. (a) This should result in symmetrical trimer pairs (*ddd+lll*) and the unsymmetrical trimer pairs *ddl+lld*; *dld+ldl*; and *ldd+ddl*. However, since these entities are connected in the case of unsymmetrical trimers, their order is inconsequential, rendering them equal. This explains the formation of two sets of compounds. (b) At the onset of reaction of formaldehyde with **1b**, the probability of *d* (or *l*)-**1b** forming a dimer either with *d*, or *l*-**1b** is equal. The reaction of the *dd* (or *ll*) dimer with *d* (or *l*)-**1b** to generate **3b**, and with *l* (or *d*)-**1b** to generate **2b** progresses with equal probability. On the other hand the reaction of the *dl* dimer with either *d* or *l*-**1b** results in **2b**. Thus the theoretical ration of **2b**:**3b** is 3:1.
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