Reductive Deoxygenation of Aryl Aldehydes and Ketones and Benzylic, Allylic, and Tertiary Alcohols by ZnI2-NaCNBH3

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Sodium cyanoborohydride in the presence of zinc iodide is found to exhibit unique and selective reducing properties. The reagents reduce aryl aldehydes and ketones as well as benzylic, allylic, and tertiary alcohols to the corresponding hydrocarbons.

Reductive deoxygenation of aryl aldehydes and ketones is a widely employed transformation in organic synthesis and various methods have been developed for this useful transformation.[1] However, many of the direct methods like the Wolf–Kishner[2] and the Clemensen[3] reductions utilize harsh reaction conditions that are incompatible with the high degree of selectivity required for polyfunctional compounds. Mixed hydride reagents such as lithium aluminum hydride or sodium borohydride in combination with strong Lewis acids[4,5] are widely applicable but hardly selective. Catalytic hydrogenolysis,[6-8] diborane,[9,10] lithium in ammonia,[11] and organosilicon hydrides[12] are mild reducing agents but are incompatible with compounds having double or triple bonds. There are also other reagents like the unusual mixture of hydrogen iodide and red phosphorous[13] which are not generally applicable.

Indirect methods such as the reduction of tosylhydrazones of aldehydes and ketones[14,16] and the desulfurization of thioketals and thioacetals by Raney nickel[15]

are in general mild and selective. However these methods involve multistep sequences and the yields are variable.

The combination of sodium borohydride or sodium cyanoborohydride with metal salts for the purpose of modifying their reducing ability and selectivity has been well documented.[5,16-18] However none of the reported combination of sodium borohydride or sodium cyanoborohydride with metal salts can reduce aryl or alkyl carbonyls directly. Sodium cyanoborohydride has been used in combination with zinc chloride to reduce aryl aldehydes and ketones but only the corresponding alcohols were isolated.[16] Even the corresponding aryl tosylhydrazones under the same conditions were reduced with difficulty and the resulting aryl alkanes were obtained only in very low yield.

We now wish to report a mild and selective method of direct deoxygenation of aryl aldehydes and ketones using sodium cyanoborohydride in the presence of zinc iodide in dichloroethane that complements the collection of existing methods. The present system reduces with ease a wide variety of aryl aldehydes and ketones directly to the corresponding aryl alkanes and many functional groups can be tolerated. Moreover, the NaCNBH3/ZnI2 system is also capable of reducing benzylic, allylic, and tertiary alcohols to the corresponding hydrocarbons. The reaction conditions are mild, the reagents are easy to handle, and the operations are simple to perform.

Results and Discussion

Reduction of Aryl Ketones and Aldehydes. In order to establish the optimum reaction conditions for reductions, several common solvents such as ether, methanol, tetrahydrofuran, and dichloroethane were examined with benzophenone as a model compound. With 1.5 mol equiv of zinc iodide and 7.5 mol equiv of NaCNBH3, only dichloroethane gave the completely reduced diphenylmethane in nearly quantitative yield. In ether and methanol, benzophenone was only reduced partially to the alcohol. In tetrahydrofuran, there was no reduction at all.

The optimum ratio of reagents has also been examined. With 0.1 mol equiv of zinc iodide, there was almost no reduction. For some reactive systems 1 mol equiv of zinc iodide was found to be sufficient, but 1.5 mol equiv appeared to be the optimum in most cases. For reactive systems, 2–3 mol equiv of sodium cyanoborohydride were

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sufficient, but 7.5 mol equiv appeared to be generally applicable to all cases. Since zinc chloride in combination with sodium cyanoborohydride was reported to be a selective reducing agent for reducing aldehydes and ketones to the corresponding alcohols in ether,[16] it was compared with zinc iodide, zinc bromide, and titanium tetrachloride in refluxing dichloroethane, the solvent found to be superior to ether in the deoxygenation of benzophenone. The results showed that zinc iodide is superior to the other salts investigated. Zinc bromide and titanium tetrachloride gave mainly diphenylmethane with some alcohol present after 3 days of reaction, while zinc chloride gave an almost 1:1 starting material and alcohol ratio with no traces of the hydrocarbon. Thus, this unique combination of dichloroethane as solvent and zinc iodide provides an extremely useful synthetic method for direct deoxygenation of aryl aldehydes and ketones.

Based on the reduction studies carried out on benzophenone, all subsequent reductions were carried out with 1.5 mol equiv of zinc iodide and 7.5 mol equiv of sodium cyanoborohydride in dichloroethane. The reaction time and temperature depends on the substrate being reduced. Table I summarizes the reduction of a wide range of aryl aldehydes and ketones to the corresponding hydrocarbons. From Table I, it is evident that electron-rich carbonyls like indole-3-carboxaldehyde (entry 12), benzofuran-2-carboxaldehyde (entry 11),[19] flavone (entry 14), and those aryl aldehydes and ketones having a p-methoxy or a p-thiomethyl substituent on the ring (entries 2, 3, 5, 7, 8) were reduced much more readily and in most cases at room temperature. Unsubstituted aryl carbonyls (entries 1, 4, 6) and those having electron-withdrawing substituents (entries 9, 10) on the ring required a higher temperature. The reduction is very selective. Aryl halides (entries 3, 8) and aliphatic and aromatic esters (entries 7–9) are not reduced. Methoxy and thiomethyl substituents remain intact. In the case of p-nitrobenzaldehyde, the carbonyl is severely deactivated by the p-nitro group, and the reduction of the nitro group competes. Benzoquinone (entry 13) was only reduced to the dihydro compound. It is interesting to note that in the case of p-anisaldehyde (entry 8) and indole-3-carboxaldehyde (entry 12), small amounts of dimer were also isolated. To determine if the dimer obtained was formed from the product of the deoxygenation process or during the course of the reduction, 3-methylindole (the product of the reduction of indole-3-carboxaldehyde) was subjected to the same reaction conditions. After 20 h of reflux, no trace of the dimer was observed, indicating that dimerization occurred prior to the formation of the hydrocarbons. The dimerization and the mechanism of the deoxygenation process will be discussed in more details in the section on mechanism.

Reduction of α,β-Unsaturated Enones. The reductive deoxygenation of α,β-unsaturated enones by zinc iodide and sodium cyanoborohydride was briefly investigated. Cholest-4-en-3-one and isophorone were reduced to a complex mixture of saturated and unsaturated alcohols, olefins, and dienes when subjected to the same reduction conditions as the aryl carbonyls (refluxing dichloroethane, 20 h). Cinnamaldehyde gave only 15% of trans β-methylstyrene, the rest of the product being polymeric material. These results are similar to those obtained with aluminum chloride in combinations with lithium aluminum hydride.[21,22] In view of the complex

mixtures obtained from these reductions, further studies were not pursued.

Reduction of Benzylic, Allylic and Tertiary Alcohols. The zinc iodide/sodium cyanoborohydride system is also capable of reducing benzylic, allylic, and tertiary alcohols to the corresponding hydrocarbons. Table II summarizes the results of a few selected examples. Benzylic alcohols behaved in a manner similar to that of the aryl carbonyl analogues and were reduced to the hydrocarbons in good yields (entries 1, 2). Allylic alcohols were reduced to the corresponding olefins with some isomerization of the double bond and formation of some dienes (entries 3, 4). Entry 4 also demonstrates the stability of a secondary aliphatic alcohol to the reaction conditions. 3,5,5-Trimethyl cyclohex-2-en-1-ol (entry 5) on the other hand gave 80% of a dimer with only a trace amount of the desired cyclohexene. The reaction appeared to be almost instantaneous. This unexpected result is discussed in more detail in a later section. Adamantanol was reduced quantitatively to adamantane.

Reduction of Aliphatic and Alicyclic Alcohols and Carbonyls. To probe the limitations of the zinc iodide/sodium cyanoborohydride reduction system, the deoxygenation of aliphatic and alicyclic alcohols and carbonyls was studied. Table III summarizes the findings with several selected alcohols and ketones. Cyclododecanone and camphor (entries 1, 2) were reduced only to the corresponding alcohols after 20 h of reflux in dichloroethane. Upon an extended reflux period (96 h), cyclododecanone gave about 8% of cyclododecane along with polymeric material. Cyclohexanol was not deoxygenated after 20 h in refluxing dichloroethane (entry 3) and gave polymeric material after 72 h. On the other hand, 4-methoxyphenethyl alcohol gave 8% of 4-ethylanisole, 26% of 4-methoxyphenethyl iodide, and 24% of 4-hydroxy-phenethyl iodide under similar conditions (entry 4). Borneol gave a complex mixture of unidentified polymeric material. Thus, the sodium cyanoborohydride/zinc iodide system does not reduce aliphatic or alicyclic alcohols readily and reduces aliphatic ketones only to their corresponding alcohols in low yields. Most attempts to force deoxygenation resulted in extensive decomposition.

Reductive Deoxygenation of Aryl Aldehydes and Ketones by Sodium Borohydride in Combination with Zinc Iodide. It was of interest to see if sodium borohydride could replace sodium cyanoborohydride in the reductive deoxygenation of aryl aldehydes and ketones in the presence of zinc iodide. The results of a few selected substrates are listed in Table IV. Except for highly activated substrates, sodium borohydride is not a suitable replacement for sodium cyanoborohydride. Upon refluxing over an extended period of time (>20 h), sodium borohydride appears to react with the zinc salt to give a gray precipitate, which could be a mixture of zinc metal, zinc borohydride, and other species. The reducing power appeared to be significantly reduced as was exemplified by the reduction of 2-naphthaldehyde (entry 3).

Mechanism. The mechanism or even the active species of this reducing system is still not clear. Kim et al.[16] speculated that combining zinc chloride with sodium cyanoborohydride in a 2:1 molar ratio afforded a mixture of Na[ZnCl(BH₃CN)₂], Na₂[ZnCl₂(BH₃CN)₂], Na[Zn(BH₃CN)₃], and Zn(BH₃CN)₂ rather than pure Zn(BH₃CN)₂. In our system, since a 5:1 molar ratio of sodium cyanoborohydride to zinc iodide was used, the most likely pre-

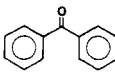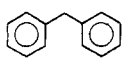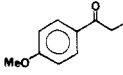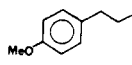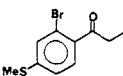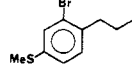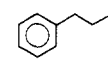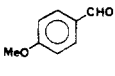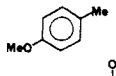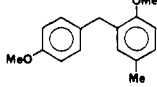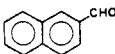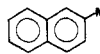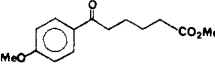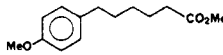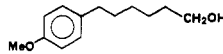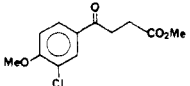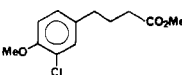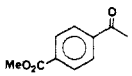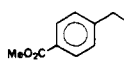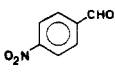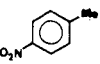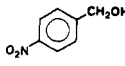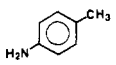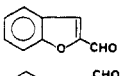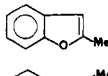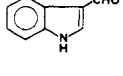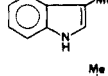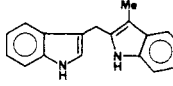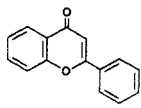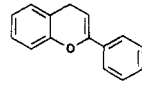(19) This compound was kindly supplied by Dr. R. Zamboni of Merck Frosst Canada.

(20) This compound was kindly supplied by Jacques-Yves Gauthier of Merck Frosst Canada.

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(22) Brewster, J. H.; Bayer, H. O. J. Org. Chem. 1964, 29, 116 and references cited therein.

Table I. Reductive Deoxygenation of Selected Aryl Carbonyl Compounds with Zinc Iodide/Sodium Cyanoborohydride in Dichloroethane[a]
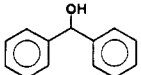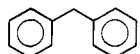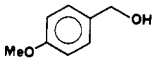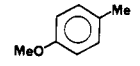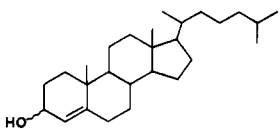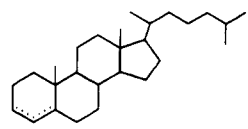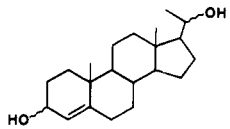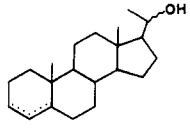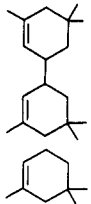
ENTRY	COMPOUND	TEMP °C	TIME hours	PRODUCT	YIELD %[b]	b.p. °C[c] (mm)
1	(benzophenone)	83	48	(diphenylmethane)	>95	150 (3)
2	(4-MeO propiophenone)	22	20	(4-MeO propylbenzene)	82	100 (20)
3	(2-Br-4-MeS propiophenone)	83	20	(2-Br-4-MeS propylbenzene)	70	155 (3)
4	(propiophenone)	83	48	(propylbenzene)	64	159 (760)
5	(4-MeO benzaldehyde, CHO)	22	20	(4-MeO-Me)	51	174 (760)
				(dimer, OMe, Me)	2.3[d]	
6	(naphthalene CHO)	83	72	(naphthalene Me)	66	140 (1)
7	(4-MeO aryl, CO$_2$Me chain)	22	20	(4-MeO aryl chain CO$_2$Me)	61[d]	
				(4-MeO aryl chain CH$_2$OH)	10[d]	
8	(4-MeO-3-Cl aryl, CO$_2$Me)	22	65	(4-MeO-Cl aryl CO$_2$Me)	58[d]	
9	(MeO$_2$C acetophenone)	83	20	(MeO$_2$C ethylbenzene)	47	150 (3)
10	(O$_2$N benzaldehyde CHO)	83	20	(O$_2$N-Me)	24[d]	
				(O$_2$N CH$_2$OH)	20[d]	
				(H$_2$N CH$_3$)	11[d]	
11	(benzofuran CHO)	83	20	(benzofuran Me)	50[d]	
12	(indole CHO)	83	1	(indole Me)	52[d]	
				(bis-indole dimer, Me)	12[d]	
13	(naphthoquinone)	83	20	(naphthalene diol, OH/OH)	66[d]	
14	(flavone)	22	20	(2-phenylchroman)	70[d]	

[a] 1.5 mol equiv of zinc iodide and 7.5 mol equiv of NaCNBH$_3$ were used. [b] Yields are isolated by distillation except where otherwise stated. [c] All values are in accord with those found in the literature. [d] Yields are isolated by chromatography on silica gel.

vailing reducing species is still sodium cyanoborohydride. We have also demonstrated that at least a stoichiometric equivalent of zinc iodide is needed for the deoxygenation process to take place, indicating that zinc iodide is actively participating in the process and not just present as a regenerating catalyst. The observation that dimers of various natures were formed during several of the reductions, strongly suggests that radical species are involved in the

Table II. Reductive Deoxygenation of Benzylic, Allylic, and Tertiary Alcohols with Zinc Iodide/Sodium Cyanoborohydride in Dichloroethane[a]

ENTRY	COMPOUND	TEMP °C	TIME hours	PRODUCT	YIELD %	b.p. °C (mm)
1		83	48		>95[c]	150 (3)
2		22	20		>90[c]	174 (760)
3		22	20		60[b]	
4		22	20		28[b]	
5		22	1		80[b]	
					Traces	
6		83	20		>95[d]	

[a] 1.5 Molar equiv of zinc iodide and 7.5 mol equiv of NaCNBH₃ were used. [b] Yields are isolated by chromatography on silica gel. [c] Yields are isolated by distillation. [d] Recrystallized.

Scheme I

Scheme II

Scheme III
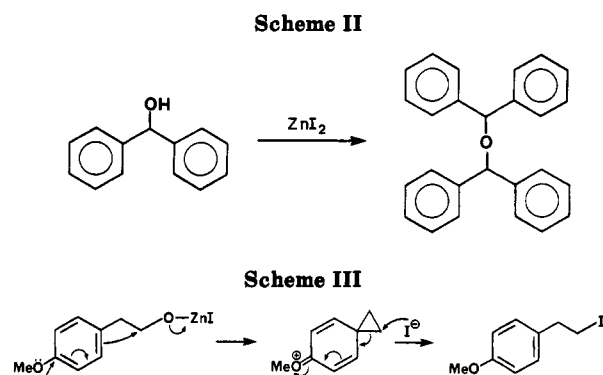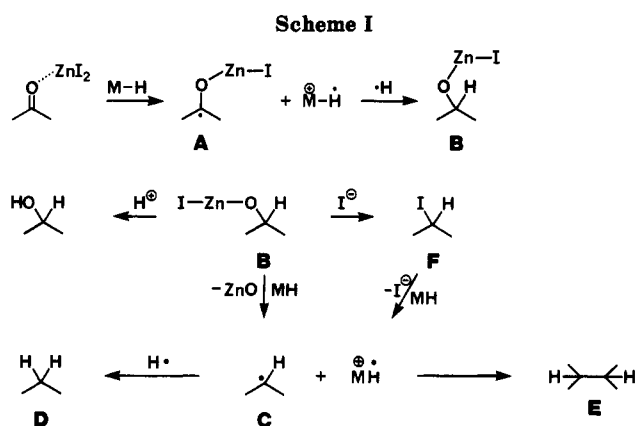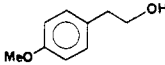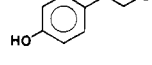
course of this reaction. This further suggests that the reaction involves an electron-transfer process that gives rise to radical intermediates since the reduction of aryl ketones, alcohols, and halides by metal hydrides via a single electron transfer (SET) mechanism are well documented.[23]

The mechanism proposed for this reduction is illustrated in Scheme I. First, cyanoborohydride anion transfers a single electron to the carbonyl–zinc iodide complex, giving rise to an intermediate A, which, after picking up a hy-

drogen radical, gives rise to alkoxide B. Alkoxide B receives another electron from the reducing reagent to give the radical C which in turn can accept a hydrogen radical to give the deoxygenated product D or dimerizes to E. Alkoxide B may also be displaced by iodide, leading to the iodo intermediate F which accepts an electron from cyanoborohydride to give the same radical C. The alkoxide intermediates have been observed in all cases and isolated as the corresponding alcohol in some cases. 4-Methoxyphenethyl iodide was isolated from the reaction of 4-methoxyphenethyl alcohol with zinc iodide and sodium cyanoborohydride, but no other iodo intermediate have been isolated. It is possible that benzylic iodo intermediates if formed would be too reactive to be observed. In an attempt to prove the intermediacy of iodo derivatives, benzhydrol was allowed to react with zinc iodide alone. The only product isolated was bis(diphenylmethyl) ether
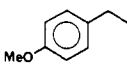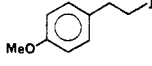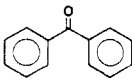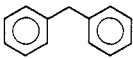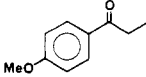
(23) (a) Ashby, E. C.; De Priest, R. N.; Boel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545 and references cited therein. (b) Ashby, E. C.; Goel, A. B. *Tetrahedron Lett.* **1981**, 1879. (c) Ashby, E. C.; Goel, A. B.; De Priest, R. N. *J. Am. Chem. Soc.* **1980**, *102*, 7779.

Table III. Reduction of Aliphatic and Alicyclic Carbonyls and Alcohols by Zinc Iodide/Sodium Cyanoborohydride in Dichloroethane[a]

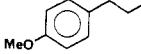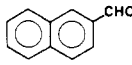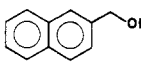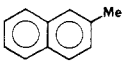| ENTRY	COMPOUND	TEMP °C	TIME hours	PRODUCT	YIELD %[b]	b.p. °C[c] (mm)
1		83	20		c	
		83	96		8	
2		83	20		c	
		83	72	Polymers		
3		83	20			
4		83	96		8	
					26	
					24	
5		83	72	Polymers		

[a] 1.5 mol equiv of zinc iodide and 7.5 mol equiv of NaCNBH₃ were used. [b] Yields are isolated by chromatography. [c] Not isolated.

Table IV. Reductive Deoxygenation of Aryl Aldehydes and Ketones by Zinc Iodide/Sodium Borohydride in Dichloroethane[a]

ENTRY	COMPOUND	TEMP °C	TIME hours	PRODUCT	YIELD %	b.p. °C (mm)[c]
1		83	48		>95[b]	
2		83	20		51[b]	
3		83	48		>90[c]	
					Trace	

[a] 1.5 mol equiv of zinc iodide and 7.5 mol equiv of NaBH₄ were used. [b] Yields are isolated by distillation. [c] Yields are isolated from chromatography.

(Scheme II). Diphenylmethyl iodide, prepared from a known procedure[24] was reduced to diphenylmethane in a much slower rate than benzhydrol. These results seem to indicate that the reaction does not pass through an iodo intermediate. The formation of 4-methoxyphenethyl iodide from 4-methoxyphenethyl alcohol, which is the only aliphatic alcohol giving rise to an appreciable quantity of iodide, may be rationalized by the fact that such a compound could form a spiro cyclopropyl intermediate[25] as shown in Scheme III. Such an intermediate is then at-

Scheme IV
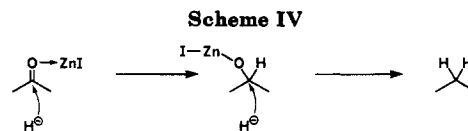
tacked by an iodide anion to produce 4-methoxyphenethyl iodide.

Zinc iodide also appears to play an important role in promoting the electron-transfer process. In the absence of zinc iodide, benzophenone and isophorone were only very slowly reduced to the alcohol, and no reduction to the hydrocarbon was observed. As mentioned, zinc iodide alone reacted with benzhydrol to give a dimeric ether (Scheme II), and borneol reacted with zinc iodide to give

(24) Muizebelt, W. J.; Noyes, R. M. *J. Am. Chem. Soc.* 1970, *92*, 6012.
(25) (a) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* 1962, *85*, 567. (b) Jenny, E. F.; Winstein, S. *Helv. Chem. Acta* 1958, *41*, 807.

a complex mixture of dimer, trimers, and tetramers under forcing conditions.

Even though the formation of dimers in some cases supports the electron-transfer mechanism, one cannot rule out completely the simple hydride reduction of polar intermediates as demonstrated in Scheme IV. It is not unlikely that both mechanisms are operating, depending on the nature of the substrate.

Zinc iodide thus appears to be an effective coreagent with sodium cyanoborohydride because it is a sufficiently strong oxygenophile to function first as a Lewis acid to catalyze the reduction steps and finally to form the very stable zinc oxide in the last step.

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Varian EM390 spectrometer, and infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Reported boiling points are those observed during distillation with a Kugelrohr apparatus and are uncorrected. Melting points were measured on a Buchi 510 melting point apparatus. Low-resolution mass spectral analyses were performed by the Morgan-Schaffer Corporation, Montreal, and elemental analyses were performed by Guelph Chemical Laboratories Ltd, Guelph, Ontario. All reactions as well as column chromatography were monitered routinely with the aid of thin-layer chromatography using precoated silica gel GF plates (Analtech).

Sodium cyanoborohydride and zinc iodide (98+%) were purchased from Aldrich Chemical Co, Ltd, and were used without purification. Dichloroethane was used without purification. Most of the compounds used in this study were commercial products, and some compounds were prepared from known procedures. The products obtained were readily available materials in most cases.

If not, identification was based on ^{1}H NMR, IR, mass spectra, and elemental analyses.

Since the reactions performed are all similar in many aspects, a typical reaction is describe as a specific example.

Method A: Preparation of 4-Propylanisole. To a stirred solution of 4-methoxypropiophenone (1.64 g, 10 mmol) in 1,2-dichloroethane (50 mL) at room temperature were added solid zinc iodide (4.8 g, 15 mmol) and sodium cyanoborohydride (4.7 g, 75 mmol). The reaction mixture was stirred at room temperature for 20 h. It was then filtered through Celite. The Celite was washed with dichloromethane (100 mL). The combined filtrate was evaporated to dryness, and the residue was distilled, bp 100 °C (20 mm), to yield 4-propylanisole (1.23 g, 82%), identical with an authentic sample on the basis of IR, TLC, mass spectrum, ^{1}H NMR data.

Method B: Preparation of 4-Nitrotoluene. To a solution of 4-nitrobenzaldehyde (1.51 g, 10 mmol) in 1,2-dichloroethane (50 mL) at room temperature were added solid zinc iodide (4.8 g, 15 mmol) and sodium cyanoborohydride (4.7 g, 75 mmol). The reaction mixture was refluxed for 20 h. It was then cooled and poured into an ice-cold mixture of saturated ammonium chloride solution containing 10% by volume of 6 N HCl (200 mL). The mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The residue was chromatographed on silica gel, eluting with 20% ethyl acetate in hexane and gave 4-nitrotoluene (330 mg, 24%), 4-nitrobenzyl alcohol (300 mg, 20%), and 4-methyl aniline (118 mg, 11%). The IR, ^{1}H NMR, TLC, and mass spectral data of each products agreed with those of authentic material.

The Question of Homoaromaticity in 1,6-Dihydro-1,2,4,5-tetrazines

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1,6-Dihydro-1,2,4,5-tetrazines exist as rapidly interconverting boat conformations in solution. In the 3,6-dimethyl derivatives alkylated on N_1 with small or medium-sized groups the equilibrium is strongly biased toward the conformation with C_6-Me endo, but in the *N-tert*-butyl derivative the opposite conformation is completely dominant. ^{1}H NMR spectroscopy shows the C_6 endo substituents to be strongly shielded and the exo substituents to be strongly deshielded. The individual conformations thus have dramatically different spectra (e.g., 6 has δ_H, δ_{Me} 2.08, 1.93; 9 has δ_H, δ_{Me} 6.00, 0.71). The conformational balance is about equal in the tri-isopropyl compound 30 whose time-averaged C_6-H absorption at δ 3.87 (298 K) separates into two absorptions at δ 5.40 and 2.53 below 190 K. If the N_1 substituent, regardless of its size, is conjugatively electron withdrawing, only the conformation with C_6-H exo is detectable (δ typically 6.2 to 6.7). Since 1-acetyl-1,6-dihydro-1,2,4,5-tetrazine (32), whose two boat conformations must be equally populated, shows no resolution of these down to 173 K the inversion barriers must be very much lower in the *N*-acyl than in the *N*-alkyl derivatives. Crystal structure determinations of 1-(hydroxymethyl)- and 1-acetyl-3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazines (5 and 14) confirm the opposite arrangements of the C_6 substituents in the boat conformations. Despite the nonplanarity of the five atoms N_1 to N_5 and the relatively large separations between N_1 and N_5 (2.29 Å in 5 and 2.35 Å in 14), we suggest that a case can be made for the operation of a homoaromatic ring current in these systems to account for the remarkable proton shielding and deshielding observed.

Introduction

Recently, van der Plas and co-workers have described a remarkable NMR shielding of a proton on C_6 in the low temperature spectrum of 1,6-dihydro-1,2,4,5-tetrazines (1), an effect they attributed to homoaromaticity.[1-3] They

supposed that C_6 was out of plane with respect to a planar array of the other five ring atoms, which were capable of sustaining a ring current and thus shielding the C_6 proton above them. Such a homotetrazole arrangement is depicted in 2.

(1) Counotte-Potman, A.; van der Plas, H. C.; van Veldhuizen, B *J. Org. Chem.* **1981**, *46*, 2138.

(2) Counotte-Potman, A.; van der Plas, H. C.; van Veldhuizen, B *J. Org. Chem.* **1981**, *46*, 3805.

(3) Counotte-Potman, A.; van der Plas, H. C.; van Heldhuizen, B.; Landheer, C. A. *J. Org. Chem.* **1981**, *46*, 5102.