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INVESTIGATIONS OF THE MECHANISM OF NUCLEOSIDE SYNTHESIS. I. ^{13}C-NMR STUDIES OF DIHYDRO-*s*-TRIAZINE-$SnCl_4$ COMPLEXES.

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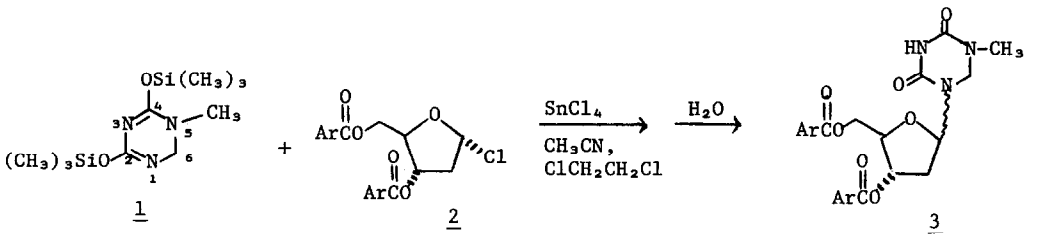
^{13}C-NMR has been employed to demonstrate and define the nature of Sn^{IV} octahedral complexes of bissilyl triazines as a further investigation of nucleoside condensation mechanisms.

We have been intrigued by some observations relating to earlier chemistry from this laboratory involving the Lewis acid mediated condensation of the silylated dihydro-*s*-triazine 1 with the deoxyribosyl chloride 2 in the synthesis of the antiviral, antibiotic dihydro-5-azathymidine, 3. These observations included (1) that the nucleoside anomeric ratio changed as a function of reaction temperature, (2) that the ratio of Lewis acid "catalyst" ($SnCl_4$) to triazine was approximately 1:2 for optimum yield, and (3) that deoxyribosyl chloride decomposition was not observed when the triazine and $SnCl_4$ were premixed in the optimum ratio. We are independently examining several aspects of this chemistry and report herein our findings involving the interaction of $SnCl_4$ with 1.



1 + 2 → 3

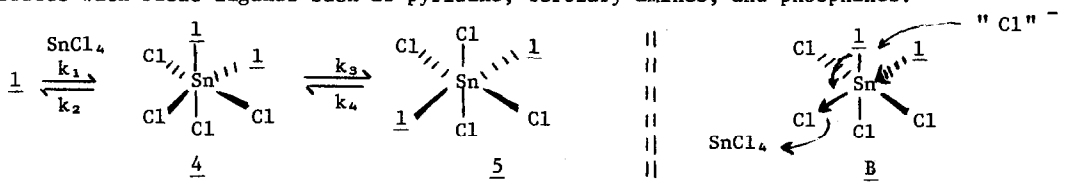
We have examined the changes which occur in the ^{13}C-NMR spectrum of the bissilyl triazine,[1] 1, upon incremental addition of $SnCl_4$ in CD_3CN and $CDCl_3$.[2,3] The results for CD_3CN are tabulated in Table I and a visual representation of the $CDCl_3$ case is exhibited in Figure A. To unambigously substantiate the assignments for C_2 and C_4, the $^{13}C_2$-enriched triazine was prepared[4], silylated, and subjected to the same complexation study with $SnCl_4$ in CD_3CN.

Several immediate observations are (1) ultimately all shifts are downfield in both solvents,[6] (2) multiple peaks develop during initial additions of $SnCl_4$ which then condense ultimately to four new carbon resonances, (3) relaxation times of C_2 and C_4 tend to shorten relative to C_6 and NCH_3 as more $SnCl_4$ is added, and (4) no changes occur after the addition of approximately 0.4 equivalents of $SnCl_4$ in $CDCl_3$ and 0.55 equiv. in CD_3CN. The question arises then regarding the nature of this possible complexation phenomenon in respect to stoichiometry, geometry, and liganding site on the triazine ring.

The data contained in the Table and Figure, and the above observations, strongly implicate a 2 triazine (1): 1 $SnCl_4$ stoichiometry since no spectral shifts are noted after approximately 0.5 equiv.[7] of "catalyst." Apparently two new species ($a_1b_1c_1d_1$ and $a_2b_2c_2d_2$) are formed and co-occur with the starting material when $SnCl_4$ is the limiting reagent. As more $SnCl_4$ becomes available, 1 is completely converted through $a_1b_1c_1d_1$ to $a_2b_2c_2d_2$. In fact, *one can prepare the 2:1 complex in*

chloroform by evaporation in vacuo to a white solid which, after washing with hexane, exhibits identical ^{13}C-NMR resonances as in Table I (0.55 eq.), identical condensation chemistry with 2 to give 3, and appears to be less moisture sensitive than either 1 or $SnCl_4$.[8]

To explain the 2:1 stoichiometry an octahedral complex, 5, is suggested. The resulting 2:1 complex exhibits only four resonances similar to but downfield from 1, indicative of *trans* geometry with D_{4h} symmetry. There are a number of precedents for the $4d^{10}$ Sn^{IV} tetrahalides to form 1:2 adducts with basic ligands such as pyridine, tertiary amines, and phosphines.[9-13]



The rationale for the structure of the intermediate (a_1-d_1) could possibly arise by advocating (1) an initial 1:1 complex (trigonal bipyramid for example), or (2) a trigonally or tetragonally distorted *cis* octahedral complex accounting for both a_1-d, and a_2-d_2, or (3) a 1:1 complex (O_h, with halogen bridging), or (4) a *cis* octahedral complex (4) in equilibrium with 5. First, although we cannot disprove it, it would seem unlikely that a 1:1 complex would be the intermediate when there is initially a large excess of ligand and the *trans*-octahedral (2:1) complex already exists at the early stages of $SnCl_4$ addition.[8] Secondly, the possibility of a distorted *cis*-octahedral complex exhibiting the assymmetry necessary to generate the a_1-d_1 peaks and the a_2-d_2 peaks, which would then coalesce (through re-arrangement) to the a_2-d_2 peaks only of the *trans*-octahedron, likewise appears unlikely since one would predict such a structure would actually generate two sets of resonances, both different from a_2-d_2. Therefore, a reasonable conclusion is that we are witnessing an equilibrium situation between starting material, a *cis*-octahedral complex (4), and a final *trans* complex (5).[14,15] In ancillary support of this is the observation from Table I that the major chemical shift change occurs in going from intermediate-4 to 5 (4: $\Delta\delta$-C_2, 1.45; C_4, 1.04; C_6, 2.25; NCH_3, -0.14; 5: C_2, 4.8; C_4, 4.8; C_6, 3.2; NCH_3, 1.9 relative to 1) suggesting a partial shielding effect in the intermediate consistant with neighboring (*cis*) ligands.

The phenomenon of 4 $\xrightarrow{SnCl_4}$ 5 is supported by Figure B. It is evident that as 1 becomes the limiting reagent there is a more rapid, concommitant change in the ratio of 5 to 4. (This also implies that k_1 and k_3 are quite close, *i.e.*, 4 favorably competes with 1 for $SnCl_4$.) It seems plausible that the conversion of *cis* to *trans* O_h geometry, as a function of added $SnCl_4$, results from a *trans*-labilizing effect[16] of the *cis* octahedron to the more thermodynamically stable *trans*, B.

The nearly equivalent downfield shifts of C_2 and C_4 might initially suggest N_3 complexation on ligand 1 since this would involve an equidistant positioning of Sn^{IV} to C_2 and C_4, analoguous to pseudocontact shifts with lanthanides. However, if one examines the possible canonical structures available from either N_1 or N_3 "protonation" with $SnCl_4$, it is apparent that electron density can only be influenced (lowered) at both C_2 and C_4 by N_1 complexation (consistent with downfield, deshielded shifts).

These data support the proposition that the reactant in the condensation of 1 with 2 is in fact the *trans*-O_h complex, 5, with N_1 as the suggested complexation site. These results then address two of the three observations noted at the beginning of this communication. The possible implications

TABLE I: ^{13}C-NMR SHIFTS[a] OF 1 UPON ADDITION OF $SnCl_4$[b]

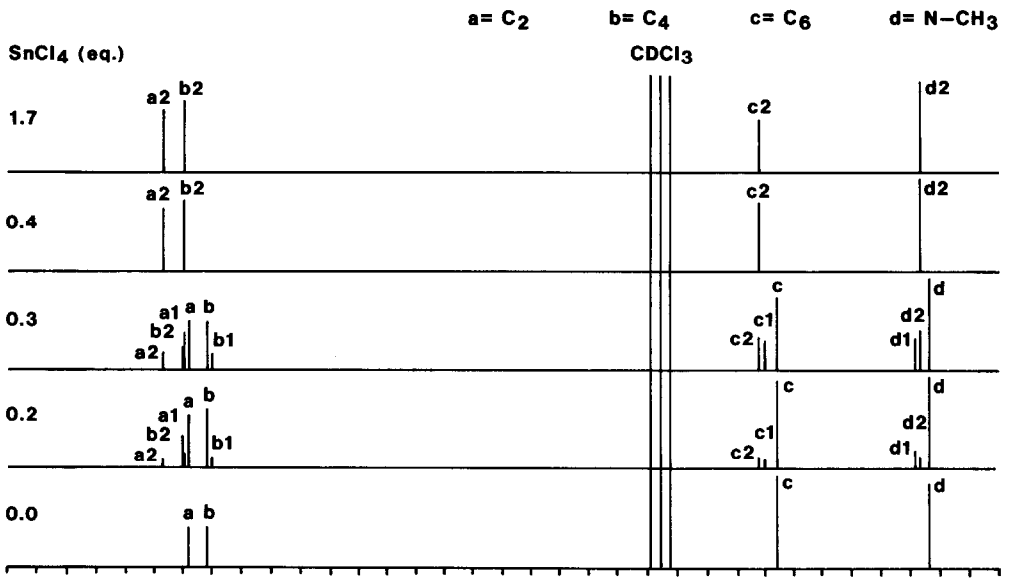
Equivalents of $SnCl_4$ →	0	0.2	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.8	1.0	1.5	2.0	Δ	Δ, $CDCl_3$
C_2	42.43	47.30 43.88 **42.43**[c]	47.28 43.89 42.42	47.26 43.88 42.40	**47.25** **43.88** 42.38	47.21 43.88	**47.22** 43.90	47.21	47.24	47.31	47.33		47.38	4.8	4.9
C_4	39.00	43.75 40.06 **39.02**	43.73 39.98 38.99	43.69 40.01 38.97	**43.69** **39.96** 38.96	43.64 39.93	**43.65** 39.95	43.63	43.66	43.74	43.75		43.81	4.8	4.4
CD_3CN															
C_6	59.14	**59.14** 56.89 55.91	59.16 56.96 56.00	59.06 56.89 55.88	59.14 **56.94** **55.96**	59.10 **56.93** **55.91**	56.90 **55.87**	56.88 **55.87**	55.95	55.90	55.89	55.83	55.80	3.2	3.3
$N\text{-}CH_3$	85.41	83.54 **85.43** 85.55	83.65 85.41 85.58	83.45 85.26 85.44	**83.60** 85.40 **85.54**	**83.46** 85.31 **85.46**	**83.42** 85.42	**83.39** 85.35	83.55	83.49	83.51	83.42	83.37	1.9	2.1

a) Reported relative to ^{13}CN of the CD_3CN solvent which was approximately 117 ppm (± 0.5 ppm), relative to TMS, throughout the additions of $SnCl_4$ (actually the values for C_6 and $N\text{-}CH_3$ are negative).

b) Concentration of substrate was 1M in CD_3CN.

c) The "boxed" values indicate the predominate peak(s).

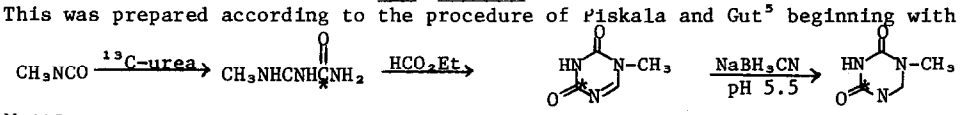
Figure A. ^{13}C-NMR Shifts of Bis(trimethylsilyl)triazine



of this for Lewis-acid assisted nucleoside synthesis in general, extension of this to other pyrimidines and triazines, and examination of other facets in the conversion of 1 + 2 → 3 are currently under investigation

References

1. H.I. Skulnick, J. Org. Chem., 43 (1978).
2. All spectra were obtained on a Varian CFT-20 NMR spectrometer with a 1.023 sec. acquisition time, pulse delay 3.00 sec. Acetonitrile-d_3 was dried over activated 3A molecular seives and chloroform-d over 4A seives. The process of preparing samples and solutions for NMR was done in an argon-filled dry box. H.F. Vorbrüggen, et al., in "Chem. and Biol. of Nucleosides and Nucleotides," p. 251-262 (ed. R.E. Harmon et al.), Academic Press, N.Y. (1978) report preliminary complexation studies of $Me_3SiSO_3CF_3$ and $SnCl_4$ with several pyridines and a pyrimidine.
3. A.K. Bose and P.R. Srinivasan, Tet. Letters, 1571 (1975) report $TiCl_4$ induced shifts of ketones.
4. This was prepared according to the procedure of Piskala and Gut[5] beginning with ^{13}C-urea (90%).



Modification involved the use of $NaBH_4CN$ conjugate reduction at pH 5.5 in methanol (room temp., 95% yield) in place of catalytic hydrogenation. The experiments were performed on material diluted to 5% ^{13}C-enrichment.
5. A. Piskala and J. Gut, Coll. Czech. Chem. Commun., 26, 2519 (1961).
6. This fact strongly precludes the possibility of desilylation occurring since the unsilylated triazine precursor exhibits C_2 (37.18) and C_4 (35.66) with 0.6 eq. of $SnCl_4$ and further addition of $SnCl_4$ causes decomposition. Also little change occurs with the TMS-carbons of 1 (not included in Table I or Figure A) during the addition of $SnCl_4$.
7. Acetonitrile is known to weakly complex[9] with $SnCl_4$, a fact which is consistent with a slightly more rapid (within experimental error) attainment of a fully complexed state in $CDCl_3$ than in CD_3CN.
8. Acceptable C,H,N, Cl analysis obtained allowing for approx. 0.5% H_2O (determined by K.F.) accruel during weighing/combustion. Interestingly, if one adds 2 mmole $SnCl_4$ to 1 mmole 1, analysis indicates approx. 1:1 ratio. Coupling this with the observation that two new, minor peaks appear only next to C_6 and NCH_3 in the ^{13}C-NMR spectrum after 0.8 eq. $SnCl_4$ and beyond, suggests a weak, secondary complexation of $SnCl_4$ with an already complexed 1, perhaps in a polymeric, O_h Sn^{IV} array.
9. I.R. Beattie and L. Rule, J. Chem. Soc., 3267 (1964).
10. J.E. Fergusson, W.R. Roper and C.J. Wilkins, ibid., 3716 (1965).
11. S.S. Sandhu and J.C. Bhatia, Ind. J. Chem., 9, 70 (1971).
12. S.A.A. Zaidi and T.A. Khan, ibid, 15A, 313 (1977).
13. J. -M. Dumas and M. Gomel, Bull. Soc. Chim. Fr., 1885 (1974).
14. Since ligand 1 affords two possible binding sites with $SnCl_4$, alternative explanations for intermediate $a_1b_1c_1d_1$ might involve isomerization from N_1 binding to N_3, or vice versa. However, any possible scenario envisioned would appear to require a higher multiplicity of resonances than observed.
15. The *cis*-octahedron has lower symmetry (C_{2v}) than the *trans*, a fact substantiated by a more complex IR spectrum[9,10]; however, the assymetry arises from the equivalency of the four chlorides expanding to two different chlorines (two sets of two chlorines) and thus the introduction of *cis* ligands should still require these two ligands to appear equivalent.
16. F.A. Cotton and G. Wilkinson, Adv. Inorganic Chemistry, p. 175-8, Wiley Interscience, New York, 1967.

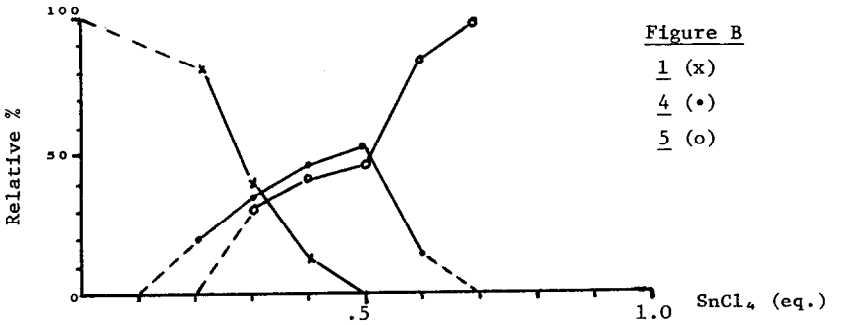


Figure B

1 (x)

4 (•)

5 (o)

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