Table I. Some Thermodynamic and Kinetic Data of Octahedral Co(III)–Amine Complexes

Amine ligand,[a] Am	$\Delta\bar{\nu}$,[b] cm^{-1}	$pK_{(1)}$[c]	$pK_{(2)}$[c]	k_{H_2O}[d] (25°), sec^{-1}	k_{ex}[e] (25°), M^{-1} sec^{-1}	k_{OH}[f] (25°), M^{-1} sec^{-1}
NH_3	8500	5.79[g]	...	1.8×10^{-2}	1.6×10^{6}	1.8×10^{3}
1/2(m-bn)	...	...	...	4.2×10^{-3}	...	9.8×10^{3}
1/2(*dl*-bn)	...	...	...	1.5×10^{-4}	5.0×10^{6}	2.1×10^{3}
1/2(pn)	8200	...	...	6.2×10^{-5}	4.5×10^{6}	2.3×10^{3}
1/2(en)	8100	4.45[h]	7.94[h]	3.2×10^{-5}	2.5×10^{6}	3.0×10^{3}
1/2(N-me·en)	...	...	...	1.7×10^{-5}	3.0×10^{8}	1.1×10^{4}
1/4(cyclam)	8000[i]	2.82[i]	7.22[i]	1.1×10^{-6} [k]	3.0×10^{9} [l]	6.7×10^{4} [k]

[a] m-bn = *meso*-butylenediamine, *dl*-bn = *dl*-butylenediamine, pn = propylenediamine, N-me·en = N-methylethylenediamine. [b] $\Delta\bar{\nu}$ = energy separation between $^1T_{1g}$ and $^1T_{2g}$ of $[Co(Am)_6]^{3+}$ in aqueous solution. In the case of cyclam, $\Delta\bar{\nu}$ is for *trans*-$[Co(cyclam)(NH_3)_2]^{3+}$. Data were taken from M. Linhard and M. Weigel, *Z. Anorg. Allg. Chem.*, **266**, 49 (1951); **271**, 101 (1952), except as indicated. [c] $pK_{(1)}$ and $pK_{(2)}$ are the first and second pK_a, respectively, for *trans*-$[Co(Am)_4(H_2O)_2]^{3+}$ in aqueous solution. Complicated by *cis–trans* isomerization reactions, not many reliable data have been reported. [d] k_{H_2O} = first-order aquation rate constant for *trans*-$[Co(Am)_4Cl_2]^+$. Data were taken from R. G. Pearson, R. E. Meeker, and F. Basolo, *J. Amer. Chem. Soc.*, **78**, 709 (1956), except as indicated. [e] k_{ex} = second-order amine–proton exchange rate constant for $[Co(Am)_6]^{3+}$ in D_2O. In the case of cyclam, k_{ex} is the estimated value for the complex *trans*-$[Co(cyclam)(H_2O)_2]^{3+}$. Data were taken from F. Basolo, J. W. Palmer, and R. G. Pearson, *J. Amer. Chem. Soc.*, **82**, 1073 (1960), except as indicated. [f] k_{OH} = second-order base hydrolysis rate constant for *trans*-$[Co(Am)_4Cl_2]^+$ in aqueous solution. Data were taken from Pearson, *et al.*, footnote *d*, except as indicated. [g] The gross acid dissociation for the *cis–trans* equilibrium. The equilibrium *cis*/*trans* ratio is 0.17; Pearson, *et al.*, footnote *d* and R. G. Yalman and T. Kuwana, *J. Phys. Chem.*, **59**, 298 (1955). [h] Reference 7. [i] B. Bosnich, C. K. Poon, and M. L. Tobe, *Inorg. Chem.*, **4**, 1102 (1965). [j] Reference 6. [k] Reference 2. [l] Estimated from ref 6.

Assuming an SN1cb mechanism,[13,14] the rate constant is directly proportional to the product of k_a and k_{cb}, where k_a is the acid ionization constant of the conjugate acid and k_{cb} is the rate constant for the dissociation of the conjugate base. The greater tendency by Co(III) to attract donor electron density in cyclam complexes, on one hand, indirectly weakens the N–H bond and, therefore, increases the value of k_a while, on the other hand, promotes k_{cb} by enhancing the π-donating ability of the amido group in the conjugate base. Both effects jointly increase the rate of base hydrolysis of the two cyclam complexes. The second-order amine proton exchange rate constant for *trans*-$[Co(cyclam)(H_2O)_2]^{3+}$ could be estimated to be 3×10^9 (M^{-1} sec^{-1}) at 25°.[15] This is very much faster than that of the equally charged $[Co(en)_3]^{3+}$ (Table I).

Similarly, both "thermodynamic" and "kinetic" nephelauxetic effects could also explain satisfactorily the properties of other Co(III)–amine complexes and to correlate them with the cyclam and bisethylenediamine analogs. Some of these properties are collected in Table I.

It is obvious from Table I that as $\Delta\bar{\nu}$ decreases down the amine series $pK_{(1)}$ and k_{H_2O} decrease while k_{ex} and k_{OH} increase. This systematic variation is fully consistent with the above discussion. In the absence of available data on $\Delta\bar{\nu}$ and $pK_{(1)}$ for m-bn, *dl*-bn, and N-me·en, these ligands are inserted into the series according to a decreasing order of k_{H_2O}.

As a conclusion, it seems worthwhile noting that the nephelauxetic effect is still only one of the many factors affecting the thermodynamic and kinetic stability of coordination compounds. Its importance may be relatively more pronounced in octahedral low-spin d^6 systems, such as Co(III)–amine complexes. It is in these systems that there are a maximum number of electrons in the nonbonding or antibonding π orbitals to display the maximum benefit out of this d electron repulsion effect. Even in this Co(III)–amine system, however, other factors, under favorable conditions, may overshadow the nephelauxetic effect. A higher k_{H_2O} and k_{OH} for (m-bn) than for (*dl*-bn) is a good indication of the influence of steric effect in the reactions of these two compounds. The two amine ligands are electronically similar but sterically different. In the *meso* form, the methyl groups are *cis* and very nearly maximally opposed. Consequently, the dissociative rate constants of the complex and of the conjugate base are higher than those in the corresponding *dl* isomers. The steric effect, however, cannot be more important than the nephelauxetic effects in Co(III)–cyclam complexes; otherwise, both k_{H_2O} and k_{OH} of these complexes would be changed in the same direction when compared to those of the bisethylenediamine analogs.

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(15) Estimated from suitable data in ref 6.

Synthesis and Characterization of a Nitrogen-Bridged [12]Annulene

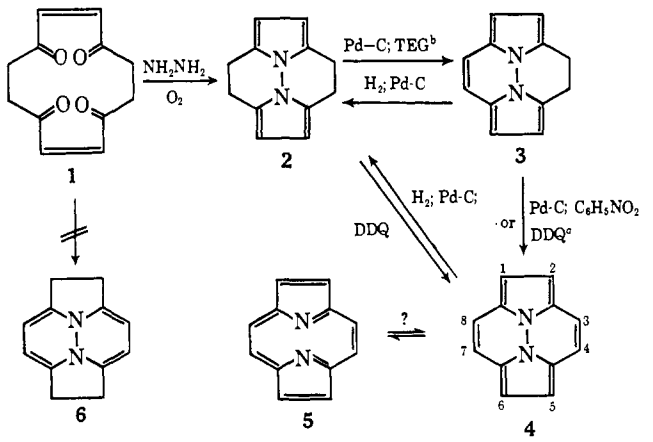
Sir:

Oth and Schröder and coworkers[1a,b] have recently reported the synthesis of [12]annulene in which the *cis* and *trans* double bonds alternate. Farquhar and Leaver[2] have described the preparation of the related cycl[3.3.3]azine. We now wish to report the synthesis of the [12]annulene derivative 8b,8c-diazacyclopent[*fg*]acenaphthylene (**4**) in which, because of the presence of a central N–N bridge, the double bonds are situated *trans–trans–cis–trans–trans–cis*.

Scheme I delineates the reactions which have led to the formation of this compound and its structural interrelationship with the starting compound 3,4,7,8-tetrahydro-8b,8c-diazacyclopent[*fg*]acenaphthylene (**2**).

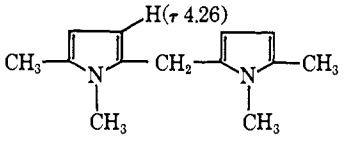
(1) (a) J. F. M. Oth, H. Röttelle, and G. Schröder, *Tetrahedron Lett.*, 61 (1970); (b) Jean F. M. Oth, J. M. Gilles, and G. Schröder, *ibid.*, 67 (1970).
(2) D. Farquhar and D. Leaver, *Chem. Commun.*, 24 (1969).

Scheme I

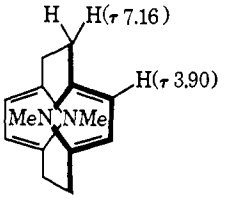


[a] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. [b] TEG = triethylene glycol.

The addition of hydrazine to compound **1**, a known material,[3] in the presence of oxygen, affords compound **2** and nitrogen. The structure of this substance (mp 172–173°, 25% yield) is established by its elemental analysis, mass spectrometric molecular weight, as well as its nmr spectrum (τ 4.15 4 H) and 7.04 (8 H)). The alternate, nonaromatic structure **6** can be excluded since the protons bonded to the sp^2 carbon atoms in this structure would not appear in the deshielded resonance region as is observed. Further structure proof is afforded by a comparison of the nmr spectrum of compound **2** with those of the pyrrole derivatives **7** and **8**.[4]



7



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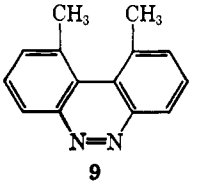
The pyrrolic protons in compound **2** resonate at positions which are intermediate between the chemical shifts of the corresponding protons in compounds **7** and **8**. The similarity of the chemical shifts of the olefinic protons in these substances is noteworthy since it implies a minimum amount of interaction between the two pyrrole rings in compound **2**.

The conversion of the locked metaheterocyclophane **2** to the 14π-electron "aromatic" ring system 3,4-dihydro-8b,8c-diazacyclopent[*fg*]acenaphthylene (**3**) (mp 168–170°, 15% yield by Pd–C dehydrogenation), which is superficially analogous to the dimethylbenzocinnoline **9**, is readily accomplished by the means indicated in Scheme I.



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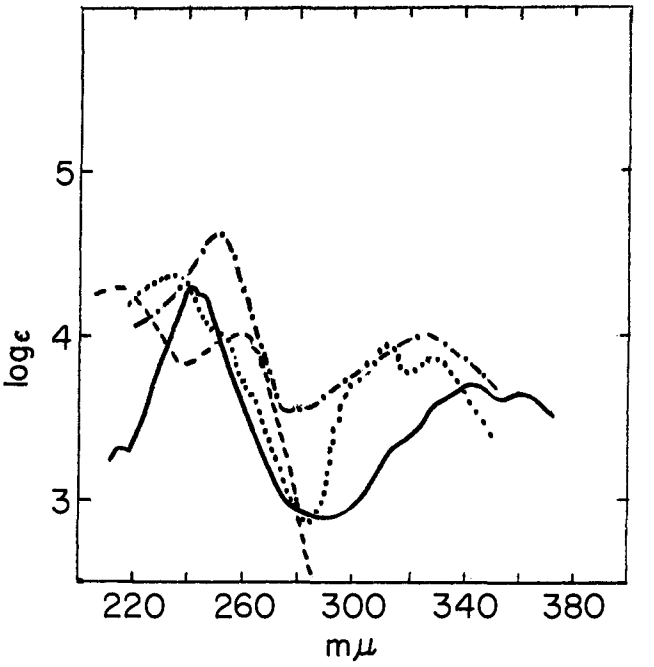


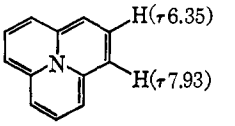
Figure 1. Uv spectral data: **2**, – – –; **3**, ——; **4**, · · · ·; **9**, —·— (G. Wittig and H. Zimmermann, *Chem. Ber.*, **86**, 629 (1953)). Solutions in 95% ethanol. Compound **4** also has a visible spectrum (λ_{max} mμ (log ϵ) 470 sh (1.45), 498 (1.59), 537 (1.64), 586 (1.53), 643 (1.14); λ_{min} mμ (log ϵ) 520 (1.53), 568 (1.40), 623 (1.01)).

The structure of this new heteroaromatic ring system is established by its correct elemental analysis, mass spectrometric molecular weight, and its nmr spectrum (τ 3.18 (2 H), 3.68 (4 H), 6.72 (4 H)), as well as its facile catalytic reduction to compound **2**. The great similarity of the uv spectra of compounds **3** and **9** (see Figure 1) further supports the structure assignment.

The considerably enhanced deshielding experienced by the pyrrolic (τ 4.15 → τ 3.68) as well as the methylenic (τ 7.04 → τ 6.72) protons upon introduction of the double bond (**2** → **3**) attests to the presence of a ring current and thus suggests that 3,4-dihydro-8b,8c-diazacyclopent[*fg*]acenaphthylene[5] is an aromatic compound.

Further dehydrogenation of compound **3** either with Pd–C in nitrobenzene or with DDQ in toluene affords a labile purple material (25% yield) whose elemental analysis, mass spectrometric molecular weight, as well as its facile catalytic reduction to compound **2** establish its structure as 8b,8c-diazacyclopent[*fg*]acenaphthylene (**4**). The nmr spectrum of this compound (τ 4.78 (4 H), 4.87 (4 H)) clearly demonstrates that the introduction of the second double bond into the tetrahydro derivative **2** destroys a considerable amount of the ring current contributing to the deshielding of the protons in compound **3**.

It is most intriguing to note that the proton chemical shifts in cycl[3.3.3]azine (**10**) are vastly more shielded



10

(3) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Amer. Chem. Soc.*, **82**, 1428 (1960).

(4) H. H. Wasserman and D. T. Bailey, *Chem. Commun.*, 107 (1970).

(5) We wish to thank Dr. K. L. Loening of the Chemical Abstracts Service for his help in establishing the name of this ring system.

than the protons in compound **4**. Not until the X-ray crystallographic structure determination is completed so that an answer regarding the planarity of compound **4** is available can any reasonable arguments be offered regarding these chemical-shift differences.

There also exists the possibility that compound **4** might be in rapid equilibrium with the diazaannulene derivative **5**. However, there is no change in the nmr spectrum of compound **4** when a solution of it in $CDCl_3$ is cooled to $-55°$. The compound might also be more properly represented by structure **5**. An alternate possibility to be considered involves the potential valence-bond tautomerization of structure **4** to structure **5**.

Studies in progress are aimed at finding answers to these questions.

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Characterization of Cardenolides by Field Ionization Mass Spectrometry

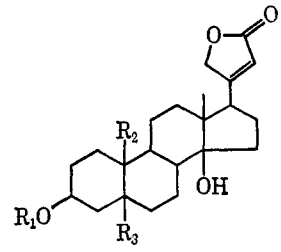
Sir:

Field ionization (FI) mass spectrometry produces molecular ions of low internal energy relative to those generated by electron impact (EI). Fragmentation is consequently reduced, the spectrum is simplified, and higher mass peaks are relatively more prominent in FI spectra.[1,2]

Although the behavior of several groups of simple functionalized organic compounds under FI conditions has been described,[1-4] very few spectra of higher molecular weight compounds (*e.g.*, mol wt > ~150) have been reported. Notable exceptions are those of some pesticides[5] and long-chain fatty acids and their methyl esters.[6] In the area of natural products, FI spectra for 3β-acetoxy-11-oxo-5α-androstane,[1] some mono-[1,7-9] and disaccharides,[1,2,9] nucleosides,[10] amino acids[8] and peptides,[8,11] monoterpenes,[12] abcisin II,[8] and somalin[2,13] have appeared. In almost every case a molecular ion was observed in FI mode even when none appeared in EI mode.

As part of our continuing program[10,11] to evaluate the potential of FI mass spectrometry (relative to and in conjunction with EI) in the structure elucidation of natural products, we report here our preliminary observations concerning cardenolides of the cardiac glycoside[14] type. These physiologically active compounds comprise a steroidal genin (G) (Scheme I; I, II) with a mono- up to pentasaccharide residue attached by a 3β-glycoside linkage.[14] Spectra were secured initially using the underivatized materials.[15] The major objective was characterization of the genin moiety and of the component monosaccharides and their sequence, and if possible the nature of the respective glycoside linkages.

Scheme I



I, $R_1 = R_3 = H$; $R_2 = CH_3$; digitoxigenin
II, $R_1 = H$; $R_2 = CHO$; $R_3 = OH$; strophantidin
for cardiac glycosides, R_1 = sugar residue

As an example, the EI and FI spectra of digitoxin[16,17] (III) are presented in Figure 1, and precise mass measurements of the principal peaks in EI mode are given in Table I. A major decomposition pathway in both ionization modes is α cleavage of a glycoside bond accompanied by H transfer (Scheme II).

Table I. Compositions of Principal Ions in the EI Mass Spectrum of Digitoxin (III)[a]

m/e	Composition	Fragment
634	$C_{35}H_{54}O_{10}$	GS1S2
504	$C_{29}H_{44}O_7$	GS1
374	$C_{23}H_{34}O_4$	G
357	$C_{23}H_{33}O_3$	G-17
339	$C_{23}H_{31}O_2$	G-35
203	$C_{15}H_{23}$	G-171
147	$C_{11}H_{15}$ (40%)	G-227
	$C_6H_{11}O_4$ (60%)	S-1
131	$C_{10}H_{11}$ (5%)	G-243
	$C_6H_{11}O_3$ (95%)	S-17
113	$C_6H_9O_2$	S-35
95	C_7H_{11} (30%)	G-279
	C_6H_7O (65%)	S-53
	$C_5H_3O_2$ (5%)	S-53
73	$C_3H_5O_2$	S-75

[a] G = genin, S = sugar. Accurate mass measurements made on Atlas SM1B, resolution approximately 12,500, probe temperature 250°.

The integral mass difference between this series of peaks (130 amu) when added to the molecular weight of water gives the molecular weight(s) of successive sugars in the glycoside, *i.e.*, 148 in each case for three D-digitoxoses in III. The remaining mass (374) clearly characterizes the genin (404 in the case of II). Analogous "sequence peaks" appear (Table II) in the spectra

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(2) H. D. Beckey, *Angew. Chem., Int. Ed. Engl.*, **8**, 623 (1969).
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(12) H. D. Beckey and H. Hey, *ibid.*, **1**, 47 (1968).
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(14) T. Reichstein, *Naturwissenschaften*, **3**, 53 (1967).
(15) For experimental details, see ref 10.
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(17) M. Spiteller-Friedman and G. Spiteller, *Fortschr. Chem. Forsch.*, **12**, 440 (1969).