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

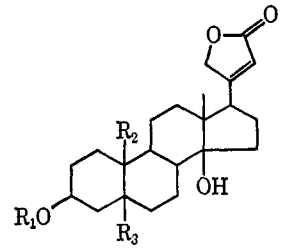
Sir:

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

(1) H. D. Beckey, H. Knöppel, G. Metzinger, and P. Schulze, *Advan. Mass Spectrom.*, **3**, 35, (1966), and references cited therein.
(2) H. D. Beckey, *Angew. Chem., Int. Ed. Engl.*, **8**, 623 (1969).
(3) A. J. B. Robertson and B. W. Viney, *J. Chem. Soc. A*, 1843 (1966).
(4) G. G. Wanless and G. A. Glock, *Anal. Chem.*, **39**, 2 (1967).
(5) J. N. Damico, R. P. Barron, and J. A. Sphon, *Int. J. Mass Spectrom. Ion Phys.*, **2**, 161 (1969).
(6) P. Schulze, B. R. Simoneit, and A. L. Burlingame, *ibid.*, **2**, 181 (1969).
(7) M. F. Grutzmacher, K. Heyns, D. Muller, and H. Scharman, *Fortschr. Chem. Forsch.*, **5**, 448 (1967).
(8) E. M. Chait, T. W. Shannon, W. O. Perry, G. E. Van Lear, and F. W. McLafferty, *Int. J. Mass Spectrom. Ion Phys.*, **2**, 141 (1969).
(9) H. Krone and H. D. Beckey, *Org. Mass Spectrom.*, **2**, 427 (1969).
(10) P. Brown, G. R. Pettit, and R. K. Robins, *ibid.*, **2**, 521 (1969).
(11) P. Brown and G. R. Pettit, *ibid.*, **3**, 67 (1970).
(12) H. D. Beckey and H. Hey, *ibid.*, **1**, 47 (1968).
(13) C. Brunnée, *Z. Naturforsch. B*, **22**, 121 (1967).
(14) T. Reichstein, *Naturwissenschaften*, **3**, 53 (1967).
(15) For experimental details, see ref 10.
(16) D. Satoh and J. Morita, *Chem. Pharm. Bull.*, **17**, 1456 (1969).
(17) M. Spiteller-Friedman and G. Spiteller, *Fortschr. Chem. Forsch.*, **12**, 440 (1969).

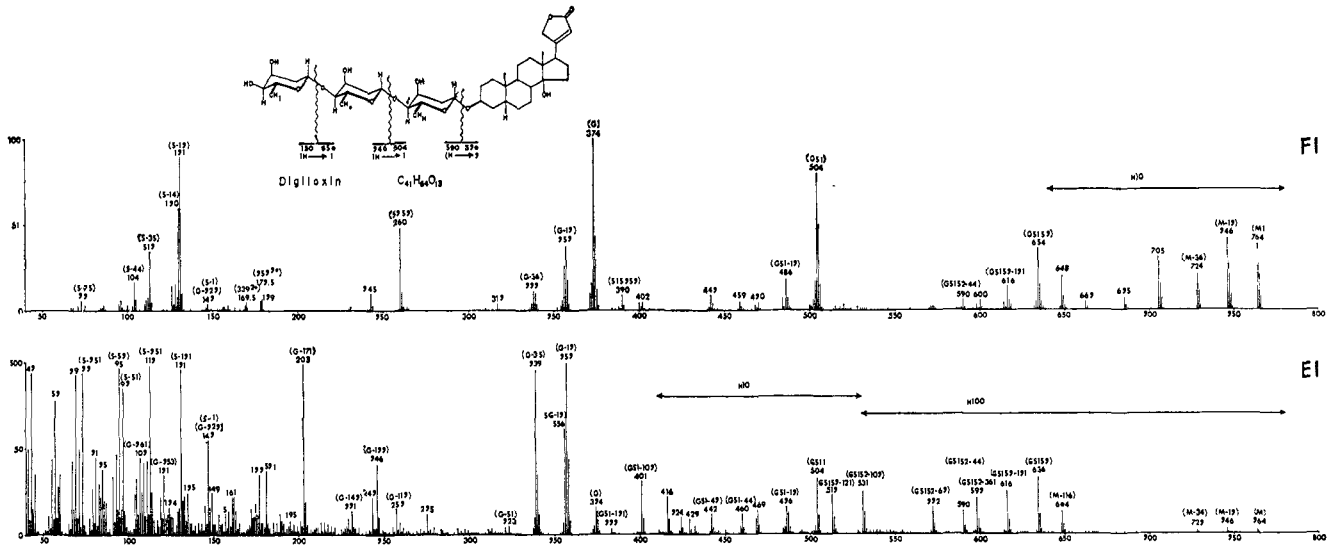
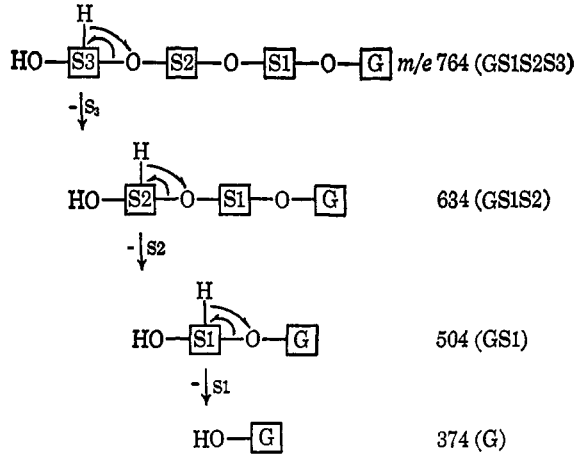


Figure 1. FI and EI (70 eV) mass spectra of digitoxin (III).

Scheme II



of other typical cardenolides based on digitoxigenin (I) and strophantidin (II), *e.g.*, 160 (S1) and 162 (S2) amu differences in thevebioside[18] (V) for L-thevetose (mol wt 178) and D-glucose (mol wt 180), respectively.

Further diagnostic complementary ion peaks are present in the FI spectrum only of III (Figure 1) 130 amu apart at *m/e* 390 (M − 374; S1S2S3), 260 (M − 504; S1S2), 130 (M − 634; S1), and at appropriate *m/e* values in the FI spectra of the other cardenolides.

Thus the molecular weight(s) and sequence of up to three unmodified monosaccharide residues can be readily determined from the FI spectrum under favorable circumstances, *i.e.*, when the total number of free hydroxyl groups in the cardiac glycoside is not too great, as for example in digitoxin (III), and intermolecular H bonding is thereby minimized. Changing to cardenolides containing sugars with more free hydroxyl groups in their glycosides (*e.g.*, L-thevetose, D-glucose) or to the aglycone strophantidin (II) rather than digitoxigenin (I) both lead to loss of higher mass structurally diagnostic peaks (Table II), and derivatization[19] is indicated for such polar materials. Stereochemical details of the glycosidic bonds cannot be assigned as yet from the mass spectra, and must await more comprehensive and sensitive investigations for their elucidation.

Table II. Diagnostic Genin and Sugar Peaks in FI Spectra of Representative Cardenolides

Cardenolide	G	GS1	GS1S2	GS1S2S3
Genin = Digitoxigenin (I), S1 = S2 = S3 = D-Digitoxose (148)				
Digitoxin (III)	374 (100[a])	504 (80)	634 (36)	764 (3.8)
Genin = Digitoxigenin (I), S1 = L-Thevetose (178), S2, S3 = D-Glucose (180)				
Neriifolin (IV)	374 (15)	534 (65)		
Thevebioside (V)	374 (100)	534 (54)	696 (20)	
Cerberoside (VI)	374 (38)	534 (33)	696 (2.0)	858 (0)
Genin = Strophantidin (II), S1 = D-Cymarose (162), S2, S3 = D-Glucose (180)				
Cymarin (VII)	404 (7.0)	548 (10)		
K-Strophantin-β (VIII)	404 (1.2)	548 (1.5)	710 (0)	
K-Strophantoside (IX)	404 (7.0)	548 (0.2)	710 (0)	872 (0)

[a] Per cent relative abundance.

Relatively few isolated examples of EI spectra of intact cardiac glycosides have been published,[17,19,20] and the severe problems associated with obtaining useful spectra of free sugars are well known.[21] The results of our systematic survey described here clearly show the great potential of combined EI–FI mass spectrometry for structure determination in this intriguing class of compounds.

Acknowledgments. The National Science Foundation is gratefully acknowledged for financial aid (Grant No. GP-6979) in acquiring the Varian Atlas SM1B mass spectrometer and the National Cancer Institute (PHS Research Grant CA-11451-01) for generous sup-

(18) (a) J. Helfenberger and T. Reichstein, *Helv. Chim. Acta*, **31**, 1470 (1948); (b) R. Bloch, S. Rangaswami, and O. Schindler, *ibid.*, **43**, 652 (1960).

(19) B. Blessington and I. M. Morton, *Org. Mass Spectrom.*, 3, 95 (1970).

(20) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, Chapter 21.6.

(21) Reference 20, Chapter 27.

port. We are also grateful to Miss Patricia Eyring for drawing the spectra.

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Narcissistic Reactions

Sir:

In this communication a class of reactions is defined and its elementary properties are studied. A reaction is defined as *narcissistic* if reactant(s) and product(s) are mirror images with respect to a fixed plane and if the image of the reactant(s) undergoes the reverse "reaction" to the image of the product(s). (The mirror plane need not be a plane of symmetry for the starting system.)[1] Such reactions include the great majority of automerizations

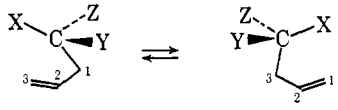
$$A \rightleftarrows A \qquad (1)$$

where A is achiral, and of interconversions

$$F \rightleftarrows \overline{F} \qquad (2)$$

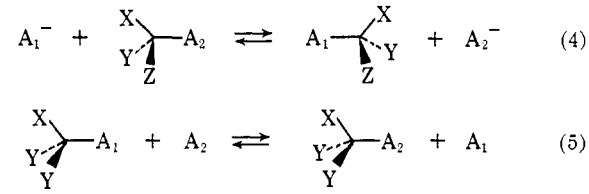
where F is chiral[2] and $\overline{F}$ is its enantiomer. The spontaneous racemization of an optically active species is almost always a narcissistic reaction; however the automerization $F \rightleftarrows F$ is not narcissistic.

There are innumerable examples of narcissistic reactions. Particularly interesting cases for our purposes are (a) the 1–3 suprafacial sigmatropic shift with inversion of configuration at the migrating center[3] (eq 3)



(3)

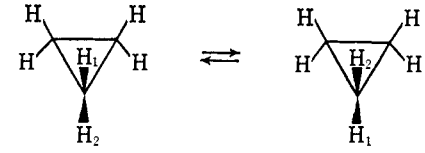
(the 1–5 transposition, with retention of configuration, although also allowed by orbital symmetry,[3] is not narcissistic; however if the asymmetric center is replaced by a hydrogen atom, it becomes narcissistic); (b) the substitution reactions (examples of bimolecular narcissistic reactions) (eq 4 and 5); (c) the geometric



(4)

(5)

isomerization of cyclopropane[4] (eq 6).



(6)

The potential energy surface for narcissistic reactions has the important property of being divided into two enantiomeric moieties. To each point on the surface, which represents a certain structure of the reactant, corresponds a point representing the image structure. There are also a number of points which coincide with their image point and hence possess reflection symmetry—for instance, points where all the atoms are forced into the fixed mirror plane.

Consider now the trajectory which converts the reactant into the image system, and the enantiomeric trajectory which brings the reverse reaction. At halfway these two trajectories might be expected to meet at one of these symmetric points, which would be the reaction midpoint. The two trajectories would then coincide, the first half of one being the second half of the other. However such a property is by no means ensured, because the trajectories can also remain distinct, equivalent, enantiomeric entities throughout. Burwell and Pearson have shown[5] that such a two-path mechanism is perfectly compatible with the principle of microscopic reversibility. The question thus arises as to the conditions under which a narcissistic reaction goes through a symmetric midpoint.

The coordinates which contribute to the reaction coordinate can be divided into two categories according to their symmetry with respect to the mirror plane: (1) "antisymmetric" coordinates, whose value inverts from some value *a*, *e.g.*, to $-a$ with intermediate value 0. Our definition of narcissistic reactions requires that there be at least one coordinate which is antisymmetric with respect to the mirror plane.[1b] A change of sign in all the antisymmetric coordinates is equivalent to reflection in the mirror plane. Configurations in which all antisymmetric coordinates are zero possess reflection symmetry. (2) The second category consists of "symmetric" coordinates which start from a certain value *b* and end up with the same value *b*, with *any* intermediate value *c* (for instance, transient stretching of a bond during the reaction). Now if the reaction coordinate involves only one antisymmetric coordinate, this coordinate

(1) (a) In this definition it should be understood that the reactant and product image are defined relative to a *single* space-fixed set of coordinate axes. This mirror plane is then *uniquely* defined within the reaction process. (It cannot be chosen arbitrarily as is done conventionally to create an image.) Under these conditions, the narcissistic definition covers all reactions which are equivalent to *pure reflection* (and, which therefore, as we shall see, may have a symmetry plane at halfway), while excluding those reactions which are equivalent to *reflection plus rotation*. The second part of the definition (in which reverse "reaction" does not necessarily imply reverse "trajectory") ensures that the reflection is not obtained *via* an overall translation or rotation of the displaced nuclei. (b) A typical nonnarcissistic reaction can be found in K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966, p 93, in which the product system is not related to the reactant *via* a fixed mirror plane. Another case arises if the biphenyl group rotates by 90° (in the positive torsional direction, for example): there is a fixed mirror plane but the image of the reactant undergoes the *forward* (positive torsional direction) rather than the *reverse* (negative torsional direction) reaction. Similar exceptions will occur whenever antisymmetric coordinates are absent. See G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand, Princeton, N. J., 1945, pp 82–83.

(2) For a review, see V. Prelog and R. S. Cahn, *Chem. Brit.*, **4**, 382 (1968).

(3) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965); (b) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 8, 787 (1969).

(4) For recent chemical evidence see J. A. Berson and J. M. Balquist, *J. Amer. Chem. Soc.*, **90**, 7343 (1968); W. L. Carter and R. G. Bergman, *ibid.*, **90**, 7344 (1968).

(5) R. L. Burwell and R. G. Pearson, *J. Phys. Chem.*, **70**, 300 (1966). The two paths are followed equally by 50% of the reactants.