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## Stereochemical Effects on Anion Mass Spectra of Cyclic Diols. Negative Chemical Ionization, Collisional Activation, and Metastable Ion Spectra

*Sir:*

Gaseous alkoxide anions, $(M - H)^-$, can be formed under a variety of ionizing conditions and provide conclusive mass spectrometric molecular weight information in the alcohol series.[1-3] In contrast to the importance of stereochemistry in positive ion mass spectrometry,[4] there are no detailed and systematic investigations on the stereochemistry of gas phase anions.[5] This also applies to the class of cyclic alcohols, especially diols, which are model compounds of natural products. The observations on dimeric $(M_2 - H)^-$ alkoxide ions[2,6] indicated to us that the stereochemical studies, based on intramolecular hydrogen bridge effects in diol type mass spectra,[7-11] might be extended from the cationic species $MH^+$ and $M^+\cdot$ to the anionic species $(M - H)^-$.

We used $OH^-$ negative chemical ionization (NCI)[3] to produce $(M - H)^-$ parent ions for the stereochemical investigations.[12] The NCI mass spectra of the cis and trans isomers of 1,3- and 1,4-cyclohexanediol and 1,2-cyclopentanediol are shown in Figure 1 and Table I. The differences in the spectra of the configurational isomers are substantial and depend strongly on the geometry of the $(M - H)^-$ ions. The only large peaks in the spectra of the cis isomers are the $(M - H)^-$ parent ions; fragment ions are generally below 5% of the total substrate ion current. All of the trans isomers form $(M - H_3)^-$ ion products with high intensity by loss of $H_2$ from $(M - H)^-$,

**Table I.** Partial $OH^-$ NCI Spectra of Cyclic Diols (% $\Sigma_{40}$)[a]

| | 1,4-cyclohexanediol | | | | 1,2-cyclopentanediol | |
|---|---|---|---|---|---|---|
| | 140 °C | | 230 °C | | 240 °C | |
| ion | *p* 0.8 cis | *p* 0.2 trans | *p* 26 cis | *p* 43 trans | *p* 51 cis | *p* 65 trans |
| $(M - H - H_2O)^-$ | 1.7 | 12 | 4.0 | 20 | 2.2 | 1.4 |
| $(M - H_3)^-$ | 7 | 6 | 3.7 | 11 | 3.1 | 56 |
| $(M - H)^-$ | 81 | 61 | 82 | 50 | 82 | 37 |

[a] See Figure 1

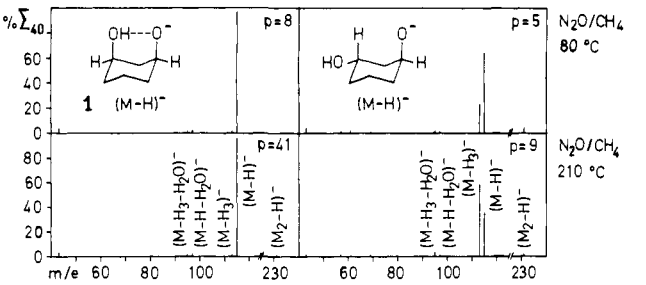



Figure 1. $OH^-$ NCI mass spectra of *cis*- and *trans*-1,3-cyclohexanediols.[12] Intensities in percentage of substrate ions, $\%\Sigma_{40}$. The C-13 isotope peaks are omitted. The "*p*" values represent the percentage of substrate ions relative to total ionization, used as a sample pressure indication.

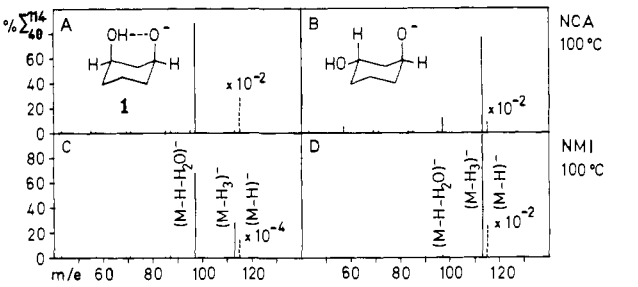
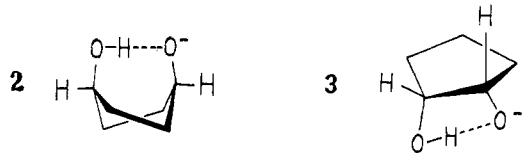



Figure 2. NCA and NMI spectra of $(M - H)^-$ ions from *cis*- and *trans*-1,3-cyclohexanediols.[12] Intensities in percentage of product ions, $\%\Sigma_{40}^{114}$. The NCA spectra, corrected for NMI contributions, were obtained at a helium pressure which reduced the precursor ion intensity to one third of its original value.

a fragmentation known from anion mass spectra of primary and secondary monoalcohols.[1-3] Different from the 1,2- and 1,3-diol constitution, the trans-1,4 derivative preferentially loses $H_2O$ to form $(M - H - H_2O)^-$ ions.

The stabilization of the $(M - H)^-$ ions with cis geometry should arise from the existence of an intramolecular hydrogen bridge as shown for the various cis conformations **1-3**. The




trans configuration of the diols discussed here does not permit any conformation suitable for intramolecular hydrogen bridging. A similar hydrogen bridge stabilization effect is well known for the $MH^+$ species in positive CI spectra of cyclic cis diols[9,10] and cis amino alcohols.[8] Dimeric $(M_2 - H)^-$ peaks in the NCI spectra of the diols (Figure 1) are due to intermolecular H bonding.[2]

The temperature dependence of the NCI spectra was checked for 1,3- and 1,4-cyclohexanediols. High ion source temperatures around 220 °C are more favorable than lower temperatures for assignment of the diol configuration. As NCI generally gives low energy $(M - H)^-$ sample ions,[13] additional thermal energy will increase the intensity of the stereospecific fragmentations. In positive CI spectra appropriate energy conditions are also needed for maximizing stereochemical effects.[9]

Fragmentation of unreactive anions can also be achieved by collisional activation[14] as reported by Bowie.[15] Figure 2A,B gives the negative collisional activation (NCA) spectra of the $(M - H)^-$ ions from *cis*- and *trans*-1,3-cyclohexanediols. The difference for the configurational isomers is increased dramatically regarding the ratio of the $(M - H_3)^-$ product peaks, even compared with the high temperature NCI spectra. Additional structural information is shown by intense (M − H

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$-H_2O)^-$ peaks, which verify the diol nature of the compounds. Collisional activation seems to be most appropriate here to optimize anion spectral information.

The fraction of $(M-H)^-$ parent ions with little excess energy decomposing in the metastable ion region of the mass spectrometer should be highly sensitive to stereochemistry. Grützmacher et al.[16] have successfully applied the metastable ion spectra technique (DADI resp. MIKES)[17] to stereochemical problems of gas phase cations. Our findings on $(M-H)^-$ ions are also in keeping with this reasoning. The negative metastable ion (NMI) spectra of *cis*- and *trans*-1,3-cyclohexanediols (Figure 2C,D) strikingly show the intramolecular hydrogen bridge stabilization effect in the cis isomer.

These examples demonstrate the potential of negative ion mass spectrometry for the identification of stereoisomers. We are applying anion techniques now to a larger variety of cyclic diols and related compounds to obtain more information about the analytical utility of stereochemical effects on anion mass spectra.

**Acknowledgments.** The financial support of the Fonds national suisse pour la recherche scientifique is gratefully acknowledged. F.J.W. is very grateful to Professor T. Gäumann of the EPFL for encouraging support of this work.

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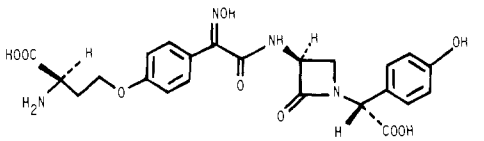
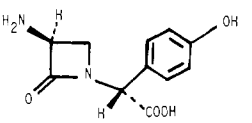
## A Synthesis of (±)-3-Aminonocardicinic Acid (3-ANA)

*Sir:*

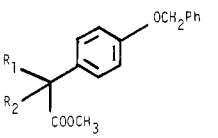
The nocardicins, monocyclic β-lactams recently isolated from the fermentation broth of a strain of actinomycetes,[1] exhibit activity against a broad spectrum of Gram-negative bacteria. The nucleus of this β-lactam system, 3-aminonocardicinic acid (3-ANA) (**2**), is an attractive target for synthesis since its availability permits the preparation of new derivatives of the nocardicins by acylation of the 3-amino group. Two syntheses of nocardicin A (**1**) have been reported,[2,3a] both involving the preparation of 3-ANA followed by a second-stage coupling with the side chain.[2,3b] We now report a novel, efficient synthesis of (±)-3-aminonocardicinic acid (**2**), which has



**1**



**2**



**3**, $R_1=R_2=H$
**4**, $R_1=H$; $R_2=COOCH_3$
**5**, $R_1=N_3$; $R_2=COOCH_3$
**6**, $R_1=NH_2$; $R_2=COOCH_3$

advantages over previous syntheses in that it involves few steps, proceeds in good yields, and utilizes readily available starting materials.

A suitably protected amine (**6**) was prepared from methyl *p*-(benzyloxy)phenylacetate (**3**).[4] Condensation of the ester **3** with dimethyl carbonate (NaH, ether, $CH_3OH$, 25 °C, 24 h) gave the malonate **4** (75%). The amine functionality was introduced by reaction of the malonate anion (NaH, THF, HMPA, 25 °C, 2 h) with *p*-toluenesulfonyl azide[5] (50 °C, 2.5 h) to yield the azido malonate **5** (76%) followed by reduction with zinc in 90% aqueous acetic acid (25 °C, 2 h) giving the amino malonate **6** (85%).

Formation of the β-lactam ring was accomplished by two methods. Initially **6** was added to a solution of cyclopropanone (ether, $CH_2Cl_2$) prepared from ketene and diazomethane at −78 °C.[6] The alkylaminocyclopropanol **7**, formed in quantitative yield, was chlorinated in situ to form **8** (not isolated) ($NaHCO_3$, $ClOC(CH_3)_3$, −10 °C, 40 min) and treated directly with silver nitrate ($CH_3CN$, 25 °C, 1.5 h) to give the β-lactam **9**,[7] mp 103–104 °C (40%). The cyclopropanone route which, in our earlier experience,[6b] generally proceeds in good yield to the β-lactam was complicated in this case by the formation of the chloroamide **10**,[8] mp 151–153 °C, as a side product (30%) (Scheme I).

In a more convenient route to **9**, 3-chloropropionamide (**10**)[9] in $DMF/CH_2Cl_2$ (1:4) (0.1 M) was added slowly (5.5 h) to a suspension (0.1 M) of NaH in $DMF/CH_2Cl_2$ (1:4) at 25 °C. Workup after 1 h yielded the β-lactam **9** (76%). This type of cyclization has previously been used to prepare β-lactams in special cases,[3a,10] but it has not been shown to be general for *N*-alkyl unsubstituted β-halopropionamides.[11] (In more concentrated solutions the reaction gives substantial amounts of the elimination product **11**.) Under the above conditions, a small amount (~5%) of **11** was observed.

The β-lactam malonate **9** was converted to the 3-azido derivative using the procedure of Kuhlein and Jensen[12] (Scheme

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