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Utility of an Inverse-Matrix Technique in the Fast Atom Bombardment Mass Spectrometry-Based Structural Determination of 2-Substituted 1,3-Bis(benzotriazolyl)isoindolines

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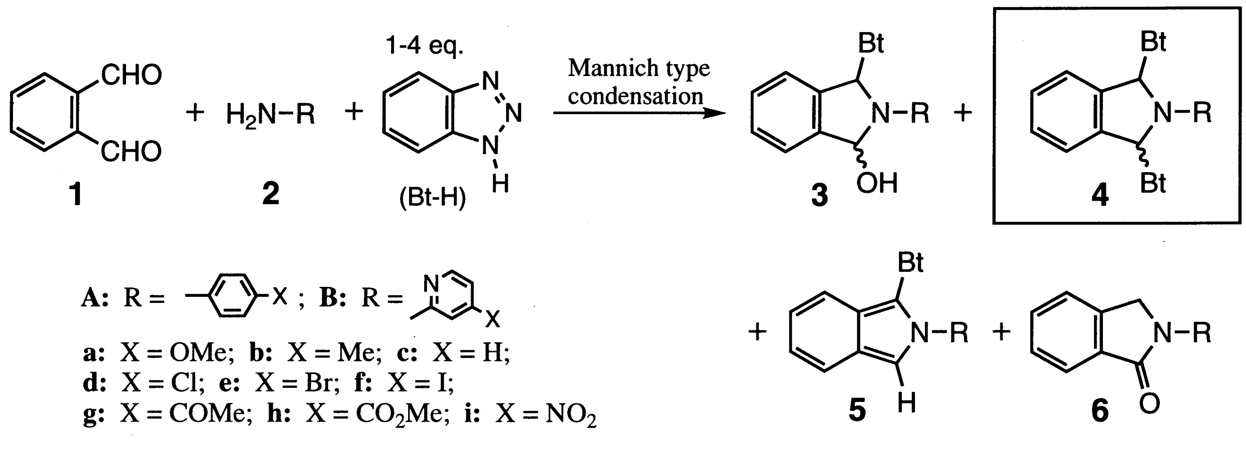
Molecular ions ($M^{+\cdot}$'s) of reactive synthetic intermediates (1,3-bis(benzotriazolyl)-isoindolines) can be monitored with certainty through a new sample-sorting technique in the fast atom bombardment mass spectrometry (FABMS).

The utility of 1*H*-benzotriazole (Bt-H) as the synthetic auxiliary to the Mannich type condensation reaction has attracted a considerable synthetic interest in recent years. Thus, the condensation reaction of monoaldehyde (RCHO), amine (R'R"NH), and Bt-H gives a mixed aminal (RCH(NR'R")Bt), which is readily converted into the corresponding RCH(NR'R")Nu, when attacked by a nucleophile (Nu^-). It is attributed to the dual character of Bt-H, performing first as a nucleophile and second as a leaving group.1) As an extension of this strategy to polyfunctional substrates to produce practically useful materials, we came to investigate on the double Mannich condensation reaction of phthalaldehyde (**1**; a representative dialdehyde) with primary amines (**2**) in the presence of Bt-H to form 2*H*-isoindole derivatives (**3**-**6**),2) of which skeletons have been evaluated as the antihypertensives/antihyperglycemics3) and as the unit compounds for electrically conductive polymers.4)



a: X = OMe; **b:** X = Me; **c:** X = H;
d: X = Cl; **e:** X = Br; **f:** X = I;
g: X = COMe; **h:** X = CO_2Me; **i:** X = NO_2

Scheme 1.

Among them, 1,3-bis(benzotriazolyl)-2-arylisoindolines (**4**),[2c] possessing two reactive centers as mixed aminals, have often been found difficult in determining their identities by combustion analyses. It is because these materials are likely to release Bt-H to give the corresponding 2*H*-isoindoles (**5**) even under mild conditions,[5,6] which undergo polymerization. These characteristics, which are indispensable as reactive synthetic intermediates, have inevitably limited at once the chance of their purification and the determination of purities themselves. For this reason, a series of derivatives, possessing molecular structures different only in substituents, must be determined as a whole by some indirect methods, *i.e.*, the cumulation of circumstantial evidences obtained from spectral measurements. In this paper, we wish to report a new sample-sorting technique to monitor molecular ions (M^{+}'s) with certainty in fast the atom bombardment mass spectrometry (FABMS) on which the successful structural determination of Bt-substituted isoindolines are based.[7]

Isoindolines (**4Aa-i**, **4Bb-c**) were prepared in 7-91% isolated yields through procedures analogous to those reported previously (molar ratio of **1**:**2**:Bt-H = 1:1:3 in CH_3CN at rt for 8 h).[2] Mass spectral measurements were carried out with a JEOL JMS DX-303 mass spectrometer. In the FAB mode, in order to monitor M^{+}'s peaks in appreciable intensities, the following new sample-sorting technique was adopted prior to its introduction to an ion source. Thus, a matrix (*m*-nitrobenzyl alcohol (MNBA) in the present work)[8] was put on a target (8 mm x 1 mm) as its surface tension allowed. Then an appropriate sample was immersed on it as much as possible, so as to adsorb the matrix in. The result of this sample-sorting is that an appropriate amount of a matrix is capsuled by a *sample-matrix* (Fig. 1, Type A), which we name *inverse-matrix*, instead of a matrix solution of a sample (Type B) as usual. Results of FABMS measurements of isoindolines (**4Aa-i**, **4Bb-c**) are summarized in Table 1. A typical spectrum of **4Ae** is shown in Fig. 2.

In the electron ionization (EI) mode measurements, M^{+}'s have scarcely been found. On the contrary, in the FAB mode measurements using our new technique, all 2-phenylisoindoline derivatives (**4A**) are found to exhibit their M^{+}'s with certain reproducibility, and even $(M+3)^{+}$'s[9] are found for some of them. In addition, fragment ions corresponding to $(M\text{-}BtH)^{+}$ and $(M\text{-}BtH\text{-}N_2)^{+}$ (trends of intensities of these fragment ions are inverse of those in EIMS), characteristic of benzotriazole-containing compounds,[1,10] are observed to assure original structures of Bt-substituted isoindolines.

On the other hand, spectra of 2-pyridylisoindoline derivatives (**4B**) exhibit far lower ionic intensities than those in 2-phenylisoindoline derivatives (**4A**). Spectrum of **4Bc** is by far different from those of other compounds, since M^{+} is trace and a fragment ion corresponding to $(M\text{-}220)^{+}$ is observed as the base peak. $(M\text{-}220)^{+}$ corresponds to the structure of phthalimidine (**6**), which are more or less observed in all other measurements, too. These evidences indicate the existence of the reversal reaction **4** → **3** induced by the attack of water (emerged by the dehydration of MNBA in the ion source of mass spectrometer, may be), followed by the elimination of Bt-H from **3** to give **6**, which we have previously reported as a liquid phase reaction.[2b] The reason why this conversion is by far effectively done in case of **4Bc** is not made clear at the present stage.

Combining these results with other spectral data,[11] a series of isoindolines are proven as substituent isomers. However, with use of ordinary *in-matrix* techniques, M^{+}'s are not found, and spectra are not reproducible, either. It is attributed to the release of Bt-H from isoindolines in matrices (MNBA, DMSO, ethylene glycol, *etc.*), which are proven as the rapid colorization of sample solution.[5,6] Therefore, our new sample-sorting technique possesses an advantage in some elongation of the lifetime of samples as isoindoline format.

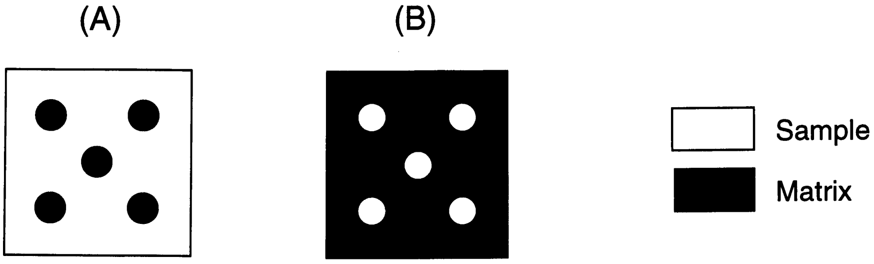


Fig. 1. Conceptional Sample-Matrix Relationships.
(A) Inverse-matrix. (B) Usual in-matrix (solution).

Table 1. Results of the FABMS of isoindolines with use of the inverse-matrix technique$^{a)}$.

Compounds			Mass Numbers$^{b)}$						
No.	X	M.N.	$(M+3)^+$		M^+	$(M-119)^+$		$(M-147)^+$	$(M-220)^+$
4Aa	OMe	459	462(13)	>	459(6)	$\overline{341}$(45)	<	312(100)	239(14)
4Ab	Me	443	446(9)	=	443(9)	$\overline{325}$(100)	=	296(99)	$\underline{222}$(18)
4Ac	H	429	432(8)	>	429(3)	$\overline{311}$(47)	>	$\overline{283}$(34)	$\overline{210}$(51)
4Ad	Cl	463	466(1)	<	463(7)$^{c)}$	$\overline{345}$(100)	>	316(54)	$\underline{242}$(28)
4Ae	Br	507	--------	<	507(15)$^{c)}$	$\overline{389}$(88)	>	$\overline{361}$(53)	$\overline{288}$(21)$^{c)}$
4Af	I	555	--------	<	555(9)	$\overline{437}$(34)	<	408(39)	$\underline{334}$(17)
4Ag	COMe	471	--------	<	471(5)	$\overline{353}$(31)	>	$\overline{325}$(9)	$\overline{252}$(7)
4Ah	CO_2Me	487	490(3)	>	487(2)	$\overline{369}$(27)	>	340(12)	$\underline{266}$(7)
4Ai	NO_2	474	--------	<	474(5)	$\overline{356}$(100)	>	$\overline{328}$(13)	$\overline{255}$(10)
4Bb	Me	444	--------	<	444(3)	$\overline{326}$(9)	=	$\overline{298}$(8)	224(4)
4Bc	H	430	--------		--------	$\overline{312}$(81)	>	$\overline{284}$(12)	$\overline{211}$(100)

a) Measured with MNBA as a matrix. The gas for the fast atom gun is argon. The energy of the fast atoms is 4 keV and the tube current is 20 mA.

b) Those of local maxima (relative intensities in parentheses) are recorded. In order to make things clear, those ions such as $(M-119+1)^+$ and $(M-147-1)^+$ are abbreviated as $\overline{311}$ and $\underline{283}$, respectively. In measurements of **4Ac**, **4Ae**, **4Af**, **4Ag**, **4Ah**, and **4Bb**, m/z 154 (protonated MNBA) are base peaks.

c) Following isotopic peaks are also found: **4Ad**, 465 (6); **4Ae**, 509 (10), 289 (31).

Our results would provide a tacit device in determining/identifying some naturally occurring active synthetic intermediates. Further investigations on the interpretation of this dramatic *inverse-matrix* effect are now in progress in our laboratories.

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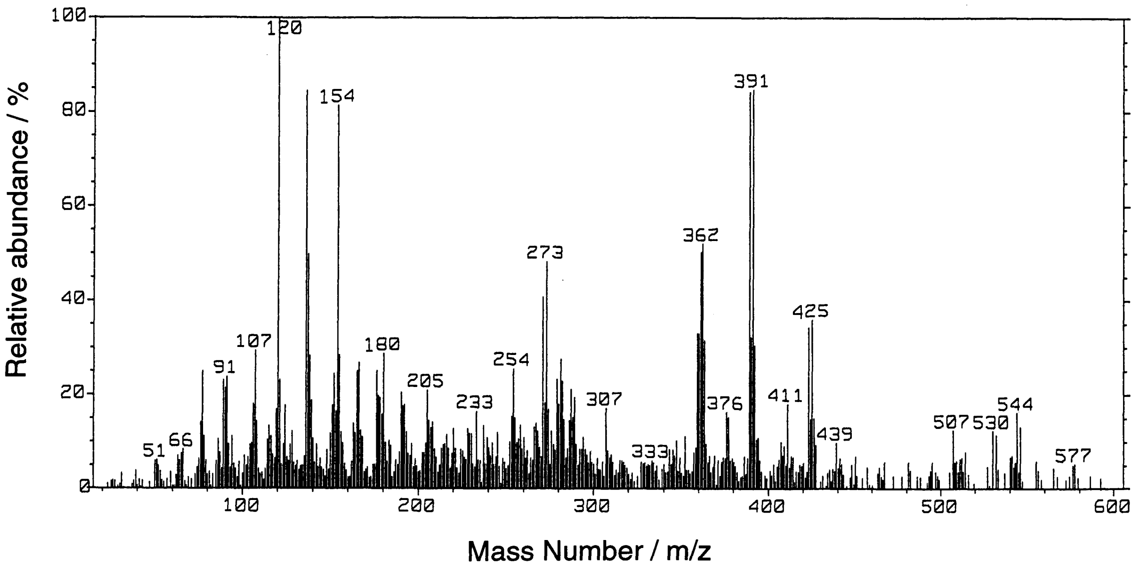

Fig. 2. FABMS of isoindoline **4Ae** (R = p-BrC_6H_4) with use of the inverse-matrix technique.

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11) In combustion analyses (CHN), except for **4Ac**, **4Af**, and **4Ai**, satisfactory results (<0.4%) are obtained. In HRMS (EI mode), satisfactory molecular formulas are obtained for fragment ions ($(M\text{-}BtH)^+$ and $(M\text{-}BtH\text{-}N_2)^+$) of **4Ac**, **4Af**, and **4Ai**. In ^1H and ^{13}C NMR spectra, chemical shifts vary only in 2-substituents. For examples of complete sets of spectra for **4Ab** and **4Ah**, see Ref. 2c.

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