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# Chiral recognition by proton transfer reactions with optically active amines and alcohols

**Habib Bagheri,† Hao Chen and R. Graham Cooks***
*Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette IN 47907, USA.*
*E-mail: cooks@purdue.edu; Fax: +1 765 494 9421; Tel: +1 765 494 5262*

***Received (in Corvallis, OR, USA) 15th July 2004, Accepted 1st September 2004***
***First published as an Advance Article on the web 15th October 2004***

**A simple, rapid tandem mass spectrometric method for recognition of chiral molecules by proton transfer reactions with chiral *sec*-butylamines and *sec*-butanols is reported.**

Chirality remains a major topic in the chemical and biological sciences. Enantiomers can be distinguished in an asymmetric environment and this forms the basis for analysis using chiral chromatography or NMR shift reagents.[1,2] However, enantiomers have identical mass spectra, so mass spectrometry (MS) has often been thought of as a "chirally blind" technique. In fact, MS, especially tandem MS, has unique features that allow rapid chiral analysis, including the ready creation of intrinsic chiral interactions in the absence of solvent and measurable effects of small energy differences between diastereomers. In addition, MS has great intrinsic sensitivity, molecular specificity, tolerance to impurities, and is capable of rapid qualitative and quantitative analyses.

Tandem MS procedures based on cluster ion dissociation[3–7] especially metal-centered clusters, have proven especially useful for chiral analysis. The majority of mass spectrometry-based chiral recognition experiments divide into four types: (i) Diastereomeric adducts are generated using chiral reference compounds and investigated in single-stage MS experiments;[8,9] one enantiomer is isotopically labeled, allowing the corresponding mixture of diastereomeric adducts to be mass resolved. (ii) Chiral recognition is based on gas-phase ion/molecule reactions, often *exchange reactions*; a diastereomeric adduct, typically generated from a chiral ligand and a chiral host like cyclodextrin, is mass-selected and allowed to exchange the chiral ligand in a reaction with a neutral gas.[10–12] Chiral distinction is achieved because the exchange rate varies with the chirality of the analyte incorporated into the adduct ion. (iii) Dissociation of diastereomeric adducts formed from the enantiomers of an analyte and a chiral reference give distinctive MS-MS spectra.[13] (iv) The *kinetic method* is used to quantify chiral effects occurring in MS-MS.[2,14]

This communication presents a simple and rapid method of the second type for the recognition of chiral molecules by deprotonation of their protonated ions $[M + H]^+$ with chiral amines or by deprotonation of the neutral molecules using chiral alkoxide anions to give their $[M - H]^-$ ions. Both experiments are based on the dependence of ion/molecule reaction efficiency on analyte chirality. Chiral amines have been used previously for chiral recognition in charge reduction reactions of multiply-charged cytochrome c ions, by equilibrium measurements.[3,15]

Experiments were carried out in a triple quadrupole TSQ-70 mass spectrometer, using chemical ionization (CI) at 150 °C source temperature. Positive ion/molecule reactions were performed by mass selection of the precursor ion, (protonated camphor, *m/z* 153), using quadrupole Q1, reaction with neutral reagent in Q2, and mass analysis using Q3 to monitor product ions. Either (*R*)-(−)-*sec*- or (*S*)-(+)-*sec*-butylamine was used as the collision gas. The kinetic energy (corrected voltage difference between the ion source and collision quadrupole), was varied from nominal −1 to 12 eV (negative values are due to the distribution of initial ion kinetic energies). Ion/molecule reactions of negative ions used deprotonated (*S*)-(+)-2-butanol or (*R*)-(−)-2-butanol as the reactant ion and employed D-camphor as the collision gas. Otherwise conditions were analogous to those for the positive ion experiments.

Proton transfer from protonated (D)- and (L)-camphor ($MH^+$ *m/z* 153), selected as model analytes, to (*R*)-(−)-*sec*- and (*S*)-(+)-*sec*-butylamine (MW = 73), showed chirally distinctive abundances of the products ions at *m/z* 74 (Fig. 1). The ratio of relative abundance ratios is 1.3. The other major ions are due to fragmentation and have similar intensities when comparing L- and D-camphor (*m/z* 135 is assigned to loss of water from protonated camphor and *m/z* 109 to further loss of acetylene). The proton-bound butylamine dimer is at *m/z* 147. The ratio of ion abundances, [74]/[109] was employed (Fig. 2) to measure the efficiency of deprotonation of camphor in the presence of chiral butylamine. (The ratios [74]/[153] and [74]/[135] gave similar but somewhat poorer results; the use of the abundance of a fragment ion ([109] or [135]) in the quotient instead of the residual precursor ion abundance ([153]) has the advantage of being blind to contributions from ions other than protonated camphor at *m/z* 153.) Measurements were made in triplicate and the abundance of the ion at *m/z* 74 clearly distinguishes the camphor enantiomers. Fig. 2 shows that proton transfer from D- and L-camphor occurs with (*S*)-(−)-*sec*-butylamine to different extents and also how the relative rates vary with collision energy. These results indicate that (i) steric effects in the transition state for proton transfer play a major role in the reaction efficiency and (ii) the ion/molecule

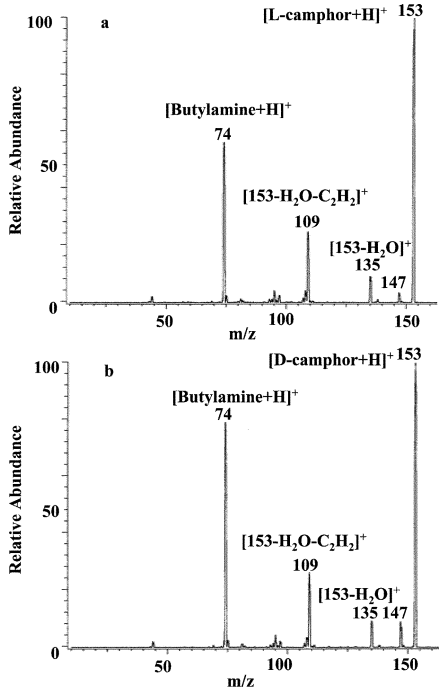


**Fig. 1** Product ion MS-MS spectra (1 eV, 1 mTorr) showing proton transfer from protonated (a) L-camphor and (b) D-camphor to (*R*)-(−)-*sec*-butylamine.

† On leave from Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Iran. E-mail: bagheri@sharif.edu; Fax: +98 21 6012983; Tel: +98 21 6005718.

DOI: 10.1039/b410882e

 

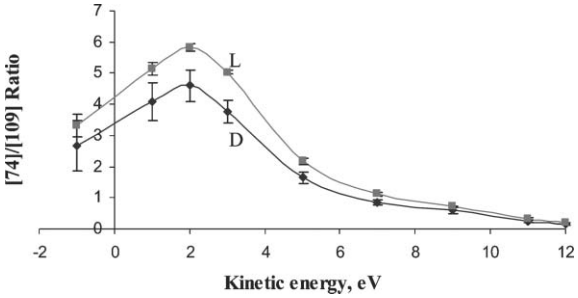


**Fig. 2** Proton transfer efficiency of D- and L-camphor with (*S*)-(−)-*sec*-butylamine at a pressure of 0.2 mTorr *versus* the laboratory collision energy (eV) (negative values are due to the distribution of initial ion kinetic energies).

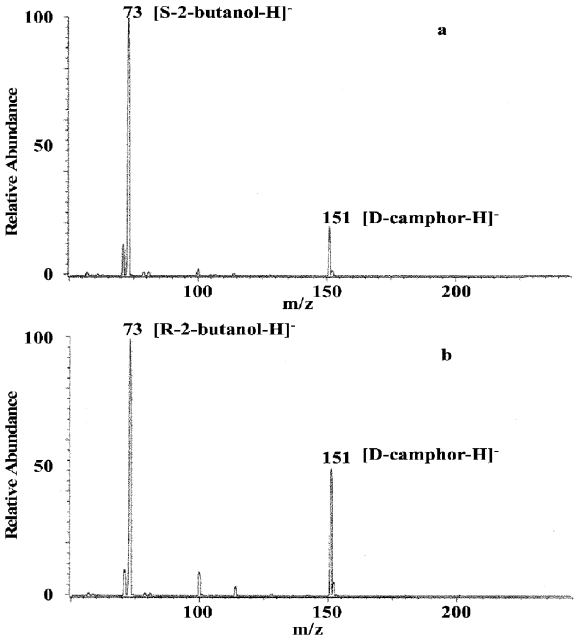


**Fig. 3** Product ion MS-MS spectra (6 eV, 0.7 mTorr) showing proton transfer from D-camphor to deprotonated (a) (*S*)-(+)-2-butanol and (b) (*R*)-(−)-2-butanol.

reaction rate is strongly velocity dependent. Ion intensities obtained for D- and L-camphor for the (*S*)-(−)-*sec*-butylamine reagent were reversed when (*R*)-(+)-*sec*-butylamine was employed, as expected.

Ion/molecule reactions in the negative ion mode can in general be expected to produce closer interactions between the chiral centers in the complexes involving two chiral reagents. (The negatively charged complex will have one proton fewer than the neutral complex, and the positively-charged complex one proton more.) This effect should enhance the differences in steric interactions associated with enantiomeric analytes. This expectation is confirmed by the data shown in Fig. 3 on proton transfer reactions of deprotonated (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol, ($[M - H]^-$, *m*/*z* 73) with (D)-camphor (MW = 152). Comparison between the alcohol and amine systems is qualitative only but the product ion MS-MS spectra show that the abundance of

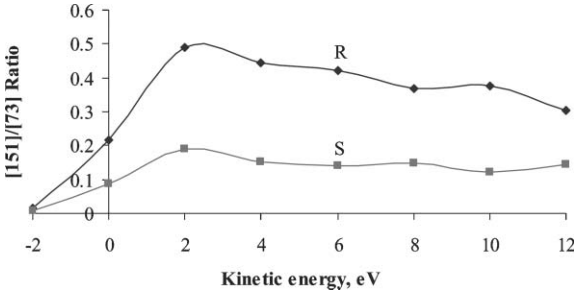


**Fig. 4** Proton transfer efficiency of deprotonated (*R*)- and (*S*)-2-butanol with D-camphor at 0.7 mTorr *versus* the collision energy (eV) (negative values are due to the distribution of initial ion kinetic energies).

deprotonated camphor (*m*/*z* 151) depends much more strongly on chirality in the negative than in the positive ion system.

The negative ion data have the advantage that the neutral analyte itself is probed in the ion/molecule reaction, rather than a modified (ionic) form. Although the two systems (butylamine and butyl alcohol) do not permit precise comparison, the magnitude of the chiral discrimination is much greater in the negative ion system. This is shown further by comparison of Fig. 2 with Fig. 4, which shows that over a wide range of collision energies the enantiomeric alcohols react at very different rates with camphor.

Proton transfer is the most common reaction in the gas-phase making this approach a promising one for simple, rapid, and sensitive chiral recognition.

Support from the US DOE (DE-FG02-94ER 14470A8) is gratefully acknowledged.

## Notes and references

1 D. Seebach, A. Beck and A. Heckel, *Angew. Chem., Int. Ed.*, 2001, **40**, 92.
2 W. A. Tao and R. G. Cooks, *Anal. Chem.*, 2003, **75**, 25A.
3 E. Camara, M. K. Green, S. G. Penn and C. B. Lebrilla, *J. Am. Chem. Soc.*, 1996, **118**, 8751.
4 Y. Liang, J. S. Bradshaw, R. M. Izatt, R. M. Pope and D. V. Dearden, *Int. J. Mass Spectrom.*, 1999, **185–187**, 977.
5 D. V. Dearden, Y. Liang, J. B. Nicoll and K. A. Kellersberger, *J. Mass Spectrom.*, 2001, **36**, 989.
6 G. Grigorean, S. Gronert and C. B. Lebrilla, *Int. J. Mass Spectrom.*, 2002, **219**, 79.
7 T. T. Dang, S. F. Pedersen and J. A. Leary, *J. Am. Soc. Mass Spectrom.*, 1994, **5**, 452.
8 M. Sawada, Y. Takai, H. Yamada, J. Nishida, T. Kaneda, R. Arakawa, M. Okamoto, K. Hirose, T. Tanaka and K. Naemura, *J. Chem. Soc., Perkin Trans. 2*, 1998, **3**, 701.
9 M. P. So, T. S. M. Wan and T. W. D. Chan, *Rapid Commun. Mass Spectrom.*, 2000, **14**, 692.
10 E. N. Nikolaev, G. T. Goginashvili, V. L. Tal'Rose and R. G. Kostyanovsky, *Int. J. Mass Spectrom. Ion Processes*, 1988, **86**, 249.
11 D. V. Dearden, C. Dejsupa, Y. J. Liang, J. S. Bradshaw and R. M. Izatt, *J. Am. Chem. Soc.*, 1997, **119**, 353.
12 J. Ramirez, F. He and C. B. Lebrilla, *J. Am. Chem. Soc.*, 1998, **120**, 7387.
13 G. Smith and J. A. Leary, *J. Am. Chem. Soc.*, 1996, **118**, 3293.
14 W. Y. Shen, P. S. H. Wong and R. G. Cooks, *Rapid Commun. Mass Spectrom.*, 1997, **11**, 71.
15 S. N. Gong, E. Camara, F. He, M. K. Green and C. B. Lebrilla, *Int. J. Mass Spectrom.*, 1999, **187**, 401.