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Novel Parallel Reaction between a [1,5] Sigmatropic Alkylthio Shift and a [1,5] Sigmatropic Hydrogen Shift Observed in a 2*H*-Azepine Ring

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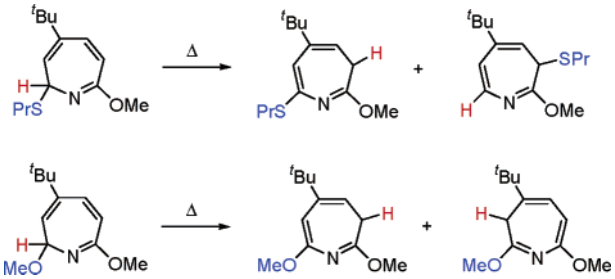
ABSTRACT



Although heating 2-methoxy-2*H*-azepine results in a [1,5] sigmatropic hydrogen shift, heating 2-propylthio-2*H*-azepine results in not only a [1,5] sigmatropic hydrogen shift but also a [1,5] sigmatropic propylthio shift. Kinetic measurements reveal that migratory aptitudes increase in the order of MeO < H, PrS. These [1,5] sigmatropic shifts are discussed on the basis of ab initio DFT calculations.

Interest in the study of concerted processes in organic chemistry has significantly increased since the development of the general theory of the principles of orbital symmetry by Woodward and Hoffmann (W−H).[1] According to the W−H rule, suprafacial [1,5] sigmatropic shifts in polyenes are thermally allowed. Many studies have reported the thermal [1,5] sigmatropic hydrogen shift.[2] Not only the hydrogen shift but also the [1,5] shift of other functionalities[2] (alkyl,[3] aryl,[4] boron,[5] chlorine,[6] amine,[7] silicon,[8] tin,[9] and germanium[10]) have been documented. Meanwhile, only two examples of a formal [1,5] sulfur shift via an ionic process have been reported so far. One is a base-catalyzed [1,5] alkylthio shift,[11] and the other is an acid-promoted [1,5] phenylthio shift.[12] Cavazza et al. have reported a rapid [1,7] migration[13] of 1,7-dialkylthiocycloheptatrienes at room temperature. This may result from the successive occurrence of

(1) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511−2513. (b) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22. (c) Frey, H. M.; Walsh, R. *Chem. Rev.* **1969**, *69*, 103−124. (d) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853. (e) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie GmbH/Academic Press: Weinheim/Bergstr., 1970.

(2) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187−217.

(3) (a) Spangler, C. W.; Boles, D. L. *J. Org. Chem.* **1972**, *37*, 1020−1023. (b) Herndon, W. C.; Manion, J. M. *J. Org. Chem.* **1968**, *33*, 4504−4507.

(4) Youssef, A. K.; Ogliaruso, M. A. *J. Org. Chem.* **1972**, *37*, 2601−2604.

(5) Gridnev, I. D.; Tok, O. L.; Gridneva, N. A.; Bubnov, Y. N.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 1034−1043.

(6) (a) Okajima, T.; Imafuku, K. *J. Org. Chem.* **2002**, *67*, 625−632. (b) van Eis, M. J.; van der Linde, B. S. E.; de Kanter, F. J. J.; de Wolf, W. H.; Bickelhaupt, F. *J. Org. Chem.* **2002**, *65*, 4348−4354.

(7) Yamaguchi, K.; Kai, C.; Yoshitake, Y.; Harano, K. *Eur. J. Org. Chem.* **2004**, 826−834.

(8) (a) Sergeyev, N. M.; Avramenko, G. I.; Kisin, A. V.; Korenevsky, V. A.; Ustynyuk, Y. A. *J. Organomet. Chem.* **1971**, *32*, 55−77. (b) Green, J. R.; Majewski, M.; Alo, B. I.; Snieckus, V. *Tetrahedron Let.* **1986**, *27*, 535−538.

(9) (a) Larrabee, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 1510−1512. (b) Gridnev, I. D.; Tok, O. L. *J. Am. Chem. Soc.* **2003**, *125*, 14700−14701.

(10) Luzlkov, Y. N.; Sergeyev, N. M.; Ustynyuk, Y. A. *J. Organomet. Chem.* **1974**, *65*, 303−310.

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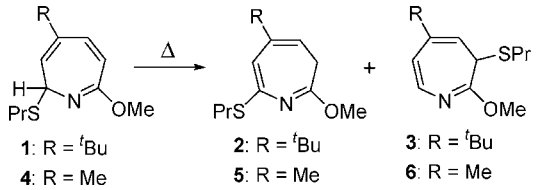
the [1,5] alkylthio shift. Although Mikhailov et al. have reported circumambulatory rearrangements[14] based on [1,5] migration in arylthio-substituted cyclopentadienes,[15] it was not shown whether the observed [1,5] migration was a concerted process.

It is known that 2*H*-azepines isomerize easily to more thermodynamically stable 3*H*-derivatives by the [1,5] sigmatropic hydrogen shift.[16] Therefore, 2*H*-azepine is considered to be a suitable system for the study of a thermal [1,5] sigmatropic rearrangement. Here, we present an unusual competitive reaction between a genuine [1,5] sigmatropic alkylthio shift and a [1,5] sigmatropic hydrogen shift observed in a 2*H*-azepine ring.

When a $CDCl_3$ solution of 2-propylthio-2*H*-azepine **1**[17] was heated at a reflux temperature, a parallel reaction between the [1,5] sigmatropic hydrogen shift and the [1,5] propylthio shift occurred quantitatively to yield a mixture of **2** and **3** in the ratio of 1:1 (Scheme 1).

Scheme 1. Thermal Parallel Reaction between a [1,5] Hydrogen Shift and a [1,5] Propylthio Shift in 2-Propylthio-2*H*-azepines **1** and **4**



1: R = ^{t}Bu
4: R = Me
2: R = ^{t}Bu
5: R = Me
3: R = ^{t}Bu
6: R = Me

It is important to establish whether the observed [1,5] propylthio shift occurs via an orbital-symmetry-allowed [1,5] sigmatropic shift (concerted mechanism) or via an ionic pathway (dissociative mechanism). Recently, we reported the formation of azepinium ions by the reactions of 2-methoxy-2*H*-azepines with $TiCl_4$.[18] The azepinium ion resulting from 2-methoxy-2*H*-azepine **7** reacted with PrSH to predominantly yield **1** rather than **3**,[19] suggesting that the rearrangement of **1** to **3** did not proceed by the dissociative mechanism. To reveal the mechanism, the rates of the [1,5] propylthio and [1,5] hydrogen shifts in various solvents such as cyclohexane-d_{12}, $CDCl_3$, and DMSO-d_6 were compared at 62 °C (Table 1). To estimate the rate of the parallel reaction of 2*H*-azepine **1**, the decrease in the intensity of peaks attributed to azepine ring protons in the ^{1}H NMR spectrum was measured.[19] Consequently, kinetically estimated rates of the [1,5] propylthio and [1,5] hydrogen shifts were effected very slightly by the polarity of the solvent (Table 1). These experimental data show that the mechanism of the observed [1,5] propylthio shift is considered to be a concerted process.

Table 1. Rates of the [1,5] Propylthio and [1,5] Hydrogen Shifts of **1** in Various Solvents at 62 °C

solvent	k_H[a] (10^{-6} s^{-1})	$k_{1/2-H}$[b] (10^2 s)	k_{PrS}[c] (10^{-6} s^{-1})	$k_{1/2-PrS}$[d] (10^2 s)
DMSO-d_6	32.1	216	27.2	255
$CDCl_3$	26.8	258	18.5	375
cyclohexane-d_{12}	23.8	290	21.3	325

[a] Rate constants for the [1,5] hydrogen shift. [b] Half-lives for the [1,5] hydrogen shift. [c] Rate constants for the [1,5] propylthio shift. [d] Half-lives for the [1,5] propylthio shift.

The kinetic parameters for the [1,5] hydrogen shift and [1,5] propylthio shift of **1** are shown in Table 2. The negative activation entropy of the [1,5] propylthio shift and the [1,5] hydrogen shift corresponds to a rigid transition state, indicating that the observed [1,5] shifts are not radical processes. The parameters of the [1,5] propylthio shift correlate well with those of the [1,5] hydrogen shift. Furthermore, heating 4-methyl-2-propylthio-2*H*-azepine **4**[19] also results in a parallel reaction of a [1,5] hydrogen shift and a [1,5] propylthio shift (Scheme 1, Table 2). The

Table 2. Experimental Activation Parameters of a [1,5] Sigmatropic Hydrogen Shift and a [1,5] Sigmatropic Propylthio Shift

2*H*-azepines	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/Kmol)	$\Delta G^{\ddagger}_{298}$ (kJ/mol)
1[a]	95.7	−47.7	110
1[b]	99.4	−39.9	111
4[a]	96.0	−44.5	109
4[b]	99.4	−34.7	110
7[a]	92.8	−66.2	113

[a] [1,5] hydrogen shift. [b] [1,5] propylthio shift.

(11) Apparao, S.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 641−645.
(12) Iwama, T.; Matsumoto, H.; Ila, H.; Kataoka, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 835−843.
(13) Cavazza, M.; Morganti, G. *J. Chem. Soc., Chem. Commun.* **1978**, 945−946.
(14) (a) Childs, R. F. *Tetrahedron* **1982**, *38*, 567−608. (b) Buo, R. E.; Jansen, H.; Ehlers, A. W.; de Kanter, F. J. J.; Schakel, M.; Lutz, M.; Spek, A. L.; Lammertsma, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 714−717. (c) Jarzecki, A. A.; Gajewski, J.; Davidson, E. R. *J. Am. Chem. Soc.* **1999**, *121*, 6928−6935. (d) Minkin, V. I.; Minyaev, R. M.; Yudilevich, J. A. *J. Mol. Struct.* (*Theochem.*) **1989**, *186*, 293−303.
(15) (a) Mikhailov, I. E.; Klenkin, A. A.; Minkin, V. I.; Olekhnovich, L. P. *Zh. Org. Khim.* **1986**, *22*, 865−867. (b) Mikhailov, I. E.; Minkin, V. I.; Klenkin, A. A.; Dushenko, G. A.; Kompan, O. E.; Struchkov, Yu. T.; Yanovskii, A. I.; Olekhnovich, L. P.; Borisenko, N. I. *Zh. Org. Khim.* **1988**, *24*, 2301−2309. (c) Mikhailov, I. E.; Minkin, V. I.; Klenkin, A. A.; Dushenko, G. A.; Kompan, O. E.; Yanovskii, A. I.; Struchkov, Yu. T. *Zh. Org. Khim.* **1990**, *26*, 28−40. (d) Mikhailov, I. E.; Dushenko, G. A.; Sadekov, I. D.; Zschunke, A.; Minkin, V. I. *Phosphorus Sulfur Silicon* **1998**, *136*−*138*, 541−544.
(16) (a) Hamprecht, D.; Josten, J.; Steglich, W. *Tetrahedron* **1996**, *52*, 10883−10902. (b) Satake, K.; Tawada, Y.; Okamoto, H.; Kimura, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2015−2017. (c) Nitta, M.; Shibata, K.; Miyano, H. *Heterocycles* **1989**, *29*, 253−256.
(17) (a) Cordonier, C. E. J.; Satake, K.; Atarashi, M.; Kawamoto, Y.; Okamoto, H.; Kimura, M. *J. Org. Chem.* **2005**, *70*, 3425−3436. (b) Satake, K.; Cordonier, C. E. J; Kubota, Y.; Jin, Y.; Kimura, M. *Heterocycles* **2003**, *60*, 2211−2215.
(18) (a) Satake, K.; Kubota, Y.; Cordonier, C. E. J.; Okamoto, H.; Kimura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 736−738. (b) Kubota, Y.; Satake, K.; Okamoto, H.; Kimura, M. *Org. Lett.* **2005**, *7*, 5215−5218.
(19) Details are described in Supporting Information.

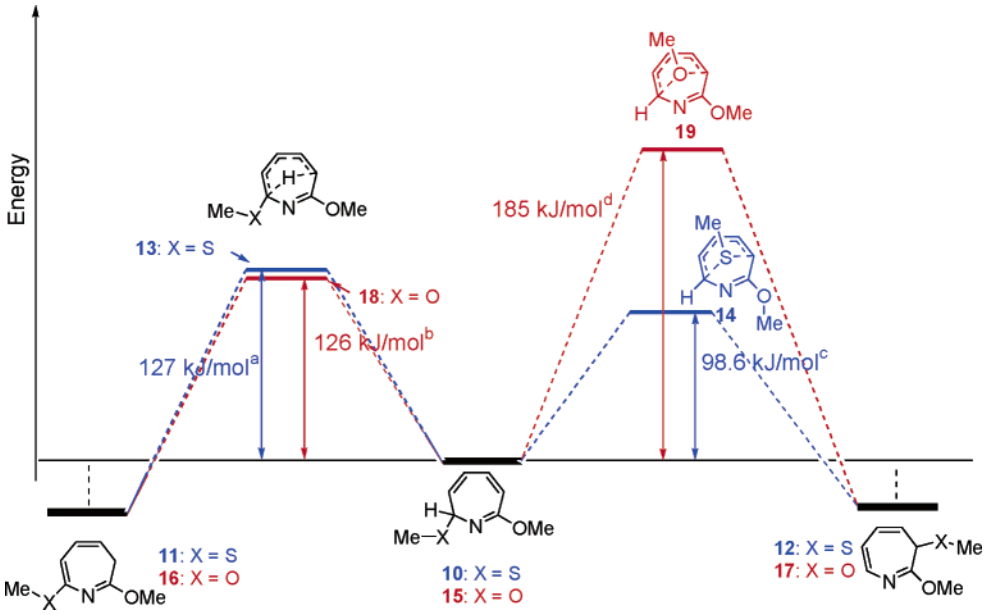
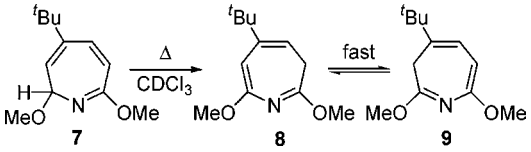


Figure 1. Calculated energy profile of a [1,5] sigmatropic reaction. [a]Calculated barrier for the [1,5] hydrogen shift between **10** and **11**. [b]Calculated barrier for the [1,5] hydrogen shift between **15** and **16**. [c]Calculated barrier for the [1,5] methylthio shift between **10** and **12**. [d]Calculated barrier for the [1,5] methoxy shift between **15** and **17**.

exchange of the *tert*-butyl group for the methyl group in the 4-position on the azepine ring shows no effect on the rate of the [1,5] hydrogen shift and the [1,5] propylthio shift.

On the other hand, when 2-methoxy-2*H*-azepine **7**[17] was heated in $CDCl_3$, an exclusive hydrogen shift was observed to yield an azepine mixture of 5-*tert*-butyl-2,7-dimethoxy-3*H*-azepine (**8**) and 4-*tert*-butyl-2,7-dimethoxy-3*H*-azepine (**9**) in the ratio of 1:8 (Scheme 2). Efforts to separate the

Scheme 2. Thermal [1,5] Sigmatropic Hydrogen Shift of 2-Methoxy-2*H*-azepine **7**



two isomeric azepines, **8** and **9**, by utilizing column chromatography were unsuccessful. The mixture already attained equilibrium because when a benzene solution was heated for 10 days the 1:8 mixture of the 3*H*-azepines **8** and **9** was maintained. In the time-dependent ^{1}H NMR spectrum of isomerization of **7** in $CDCl_3$, **8** and **9** were formed in a ratio of 1:8 simultaneously with a decrease in **7**, suggesting that the [1,5] hydrogen shift from **8** to **9** is very fast. These results indicate that rapid equilibrium between **8** and **9** is reached as soon as the isomerization of **7** occurs. It is considered that **8** is formed by an exclusive [1,5] hydrogen shift of **7** followed by **9**, which is produced by successive [1,5] hydrogen shifts of **8**. The [1,5] methoxy shift was not observed in the thermal isomerization of **7**.

To obtain a theoretical background for the difference between the [1,5] alkoxy shift and the [1,5] alkylthio shift, calculations were performed using simple model compounds such as 7-methoxy-2-methylthio-2*H*-azepine (**10**) and 2,7-dimethoxy-2*H*-azepine (**15**) by using the GAUSSIAN03 program package.[20] The density functional method was employed using the B3LYP[21] and 6-31G(d,p) basis sets. Transition-state structures were characterized by an imaginary frequency. Two optimized structures were found by calculating the transition state of the [1,5] methylthio shift between **10** and **12**. The structure in which the methyl group is on the opposite side of the nitrogen atom is a more stable transition structure than the structure in which the methyl group is on the same side.[19] The calculated activation energy of the respective [1,5] shifts is shown in Figure 1.

Because it is preferable that the calculated barrier of the suggested [1,5] methylthio shift is smaller than that of the [1,5] methoxy shift, isomerization of 2-alkylthio-2*H*-azepine

(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(21) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

proceeds via competitive alkylthio and hydrogen shifts. Conversely, the high activation energy indicates that a [1,5] alkoxy shift cannot proceed easily in the case of 2-methoxy-2*H*-azepine. Thermally allowed [1,5] sigmatropic rearrangement on heating has a close connection with the frontier orbital interaction between the σ^* orbital of the moving group and the π_{HOMO} of a conjugated diene system (Figure 2).[22]

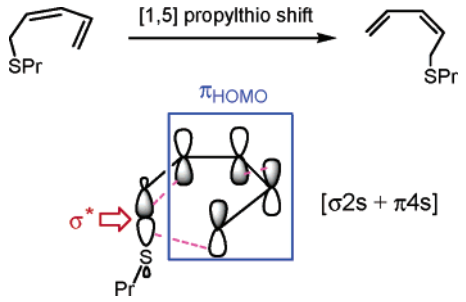


Figure 2. Frontier orbital interaction between the σ^* orbital of the moving group and the π_{HOMO} of a conjugated diene system.

According to AM1 calculations, the σ^* energy of the C−O bond is considerably higher than that of the C−S bond. The AM1 calculated σ^* energy of CH_3SCH_3 is 0.94 eV, and that of CH_3OCH_3 is 3.25 eV. It is considered that the low-energy level for the σ^* orbital of the C−S bond stabilizes the transition state for the [1,5] alkylthio shift compared to that of the [1,5] alkoxy shift.

These calculations agree with experimental observations. Although the calculated activation energy of the [1,5] hydrogen shift (127 kJ/mol) is larger than that of the [1,5] methylthio shift (98.6 kJ/mol), the experimental activation parameter of the former (96 kJ/mol) is slightly smaller than that of the latter (99 kJ/mol) (Table 2, Figure 1). This contradiction may be ascribed to the solvent effect. Therefore, calculations including the Onsager reaction field approximation[23] with the dielectric constant 5.05 ($CHCl_3$)[24] were performed to improve the discrepancy between experimental and calculated results. Unfortunately, there is a slight change in the activation energy of the [1,5] hydrogen shift (127 kJ/mol) and that of the [1,5] methylthio shift (98.0 kJ/mol).[19]

Generally, B3LYP calculations tend to underestimate the activation energy of some proton and hydrogen shift reactions.[25] In this regard, the present overestimated activation energy of the [1,5] hydrogen shift is inexplicable. A similar overestimation of [1,5] hydrogen shifts on cyclopentadiene and cycloheptatriene systems is reported.[6a] Recently, Yamabe et al. have proposed that such an overestimation should be ascribed to a bimolecular multistep reaction.[26] The scheme occurs successively as follows: [6 + 4] cycloaddition → a hydrogen shift in the cycloadduct → Cope rearrangement → retro hydrogen shift → retro [6 + 4] cycloaddition. Therefore, an overestimation of the [1,5] hydrogen shift may suggest the possibility that the observed hydrogen shift on 2*H*-azepine occurs via a bimolecular multistep process.

In conclusion, heating 2-propylthio-2*H*-azepine results in a parallel reaction between the [1,5] sigmatropic hydrogen shift and the [1,5] sigmatropic propylthio shift to yield 7-propylthio-3*H*-azepine and 3-propylthio-3*H*-azepine. Kinetic measurements have revealed that the observed [1,5] propylthio shift proceeds via a concerted mechanism (i.e., sigmatropic rearrangement). DFT calculations of simple model compounds have shown that the [1,5] shift of an alkylthio group occurs easily, whereas the [1,5] alkoxy shift occurs with difficulty.

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Supporting Information Available: Experimental procedures and physical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57−64.
(23) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486−1493.
(24) Wyman, J., Jr. *J. Am. Chem. Soc.* **1936**, *58*, 1482−1486.
(25) Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811−4815.
(26) Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Chem. Theory Comput.* **2005**, *1*, 944−952.