DOI: 10.1002/cjoc.201100455

Water-Promoted Kinetic Separation of *trans*- and *cis*-Limonene Oxides

Xu, Zhao-Bing(徐招兵)　　Qu, Jin*(渠瑾)

State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

The efficient hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(＋)-limonene oxides was realized in a 1∶1 mixed solvent of water and 1,4-dioxane without additional catalyst. Optically pure *trans*-(*R*)-(＋)-limonene oxide was recovered in high yield (77%).

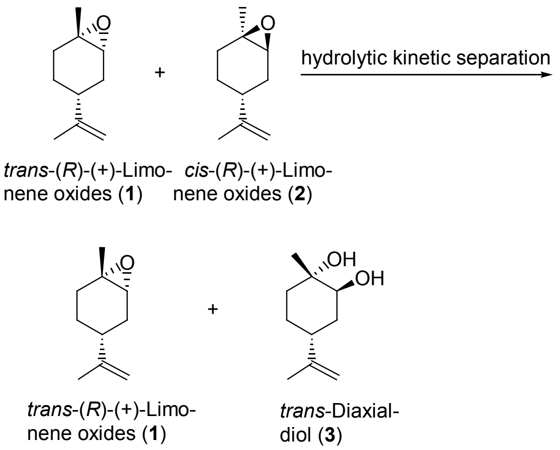
Keywords *trans*/*cis*-(*R*)-(＋)-limonene oxides, kinetic separation, water, 1,4-dioxane

Introduction

Monoterpene epoxides, in particular limonene oxide, serve either as starting material in synthesis of natural products or as the chiral core of chiral auxiliaries in asymmetric synthesis.[1] The direct epoxidation of (*R*)-(＋)-limonene gave a diastereomeric mixture of *trans*- and *cis*-(*R*)-(＋)-limonene oxides (**1**∶**2**＝1∶1) which were difficult to separate by fractional distillation.[2] The chemical method employed to separate these diastereomeric isomers is based on their different reaction rates in epoxide ring-opening reactions. In the nucleophilic ring opening of *trans*- and *cis*-limonene oxides by secondary amines, the ring opening of the *trans*-isomer **1** is more facile and the unreacted *cis*-isomer **2** can be recovered after the complete consumption of *trans*-isomer.[3] However, in acidic condition, the hydrolysis of *trans*- and *cis*-(*R*)-(＋)-limonene oxides leads to the same *trans*-diaxial diol **3** but in different reaction rate. The selective axial nucleophilic attack to *cis*-isomer **2** is faster due to steric hindrance and electronic effects that can be rationalized by the Fürst-Plattner rule (Scheme 1).[4] It was reported that Lewis acids (*e.g.* lanthanoid benzoate,[5] *β*-ketophosphonate complexes of molybdenum (VI)),[6] photo-assisted Lewis acids,[7] Brønsted acids (*e.g.* $HClO_4$,[8] 1 mol/L aq. $NaHSO_3$,[9] acidic buffer solutions[10]), or non-nucleophilic amines (triazole and pyrazole[3]) could catalyze the hydrolytic kinetic separation of **1** and **2**. Some of the existing methods either suffered from hazardous reagents used,[6-8] long reaction time needed,[6,9] or low efficiency[9] of separation.

In recent years, green chemistry has become a growing research area and much attention has been focused on finding more environmentally friendly chemical processes.[11] The use of water as solvent or co-solvent in organic reactions has attracted great attentions from the organic community and a number of reports have emerged.[12] Since Breslow *et al.*[13] observed an exceptional acceleration of the Diels-Alder reaction in water in 1980, the rate-enhancing effect is widely observed in organic reactions operated in water without additional catalyst.[14] In our previous study, hot water was found to exhibit similar property to that of near-critical water, and it could act as a mild Brønsted acid catalyst in epoxide-opening reactions.[15] Here we reported that the hydrolytic kinetic separation of *trans*- and *cis*-(*R*)-(＋)-limonene oxides could be accomplished in refluxing mixed solvent of water and 1,4-dioxane without additional catalyst.

Scheme 1 Hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(＋)-limonene oxides under acidic condition



---

* E-mail: qujin@nankai.edu.cn; Tel.: 0086-(22)-23499247

Received October 6, 2011; accepted October 25, 2011; published online March 7, 2012.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201100455 or from the author.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in $CDCl_3$. Chemical shifts were reported down field from internal TMS. GC analysis was recorded using SHIMADZU GC-2014 model equipped with an rtx-5 column. Phenyl *n*-butyl ether was used as an internal standard. Organic solvents used were purified by standard methods. *trans*/*cis*-(*R*)-(+)-Limonene oxides were synthesized from (*R*)-(+)-limonene with a 1∶1 mixture of two diastereomeric isomers.[16]

General procedure for preparation of *trans*-(*R*)-(+)-limonene oxide in gram scale

trans/*cis*-(*R*)-(+)-Limonene oxides (5.8 g, 38 mmol), distilled water (30 mL) and 1,4-dioxane (30 mL) were added to a 100 mL of round-bottom flask equipped with a magnetic stir bar and a reflux condenser. The reaction mixture was heated to reflux and ceased until total consumption of the *cis*-(*R*)-(+)-limonene oxide occurred as detected by GC analysis (1.5 h). The mixture was extracted by diethyl ether, washed with brine and then dried over anhydrous sodium sulfate. The crude product was purified by column chromatography to give *trans*-(*R*)-(+)-limonene oxide **1** (hexane ∶ diethyl ether =95 ∶ 5, R_f=0.5) as a colorless oil (2.2 g, 74% yield, >99% *de*, recovered yield was based on the initial amount of *trans*-(*R*)-(+)-limonene oxide in the *trans*/*cis*-(*R*)-(+)-limonene oxides) and *trans*-diaxial diol **3** (hexane ∶ EtOAc=70 ∶ 30, R_f=0.25) as a white solid (3.9 g, 95% yield, >99% *de*, this yield was calculated based on the recovered *trans*-limonene oxide).

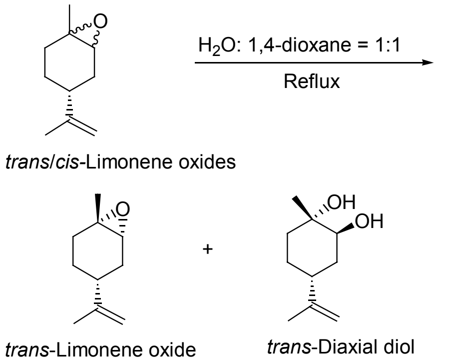
***trans*-(*R*)-(+)-Limonene oxide 1**[9] Colorless oil; $[\alpha]_D^{20}$ +76 (*c* 0.98, $CHCl_3$) [lit.[9] $[\alpha]_D^{25}$ +76 (*c* 0.98, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.67 (s, 2H), 2.99 (d, *J* = 5.2 Hz, 1H), 2.05—2.00 (m, 2H), 1.88—1.85 (m, 1H), 1.74—1.62 (m, 2 H), 1.67 (s, 3 H), 1.39—1.36 (m, 2H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.15, 109.03, 59.20, 57.44, 40.67, 30.68, 29.81, 24.27, 23.04, 20.16.

***trans*-Diaxial diol 3**[3] White solid, m.p. 70—71 ℃; $[\alpha]_D^{20}$ +25.6 (*c* 1, $CHCl_3$) [lit.[10] $[\alpha]_D^{20}$ +18.1 (*c* 0.01, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.74 (s, 2H), 3.65 (m, 1H), 2.31—2.23 (m, 1H), 1.97—1.90 (m, 1H), 1.81—1.75 (m, 1H), 1.74 (s, 3H), 1.71—1.65 (m, 1H), 1.60—1.52 (m, 5H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 149.13, 108.97, 73.72, 71.43, 37.39, 33.84, 33.61, 26.35, 26.05, 21.06.

Results and Discussion

The hydrolysis of *trans*/*cis*-(*R*)-(+)-limonene oxides was firstly tried in water. In pure water, the hydrolysis of both *trans*- and *cis*-limonene oxides proceeded slowly under refluxing condition. *cis*-Limonene oxide **2** reacted a little faster than *trans*-limonene oxide **1** which was identical with that found in acid catalyzed hydrolytic separations. After *cis*-limonene oxide was totally consumed, *trans*-limonene oxide was recovered in 8% yield (recovered yield was based on the initial amount of *trans*-limonene oxide in the mixture, Entry 1, Table 1). We assumed that extremely hydrophobic epoxides such as limonene oxide should reacted faster when a suitable organic co-solvent was added as the dissolution of the substrate was needed for their hydrolysis. Thus several water soluble organic co-solvents were tested in the reaction system and the results of the hydrolytic separations were summarized in Table 1. In all cases, the reaction was ceased after the total consumption of the *cis*-limonene oxide monitored by GC analysis. When polar solvent like acetone, CH_3OH, CH_3CN, or DMF was used as the co-solvent, the rate of the reaction was similar compared with that performed in pure water and the yield of the recovered *trans*-limonene oxide was low (Entries 2—5, Table 1). The reaction rate was largely increased in the 1∶1 mixture of water and ethylene glycol and 58% of *trans*-limonene oxide was recovered (Entry 6). In the 1∶1 mixed solvent of 1,4-dioxane and water, the hydrolysis of *cis*-limonene oxide was completed in 2 h and *trans*-limonene oxide was recovered in 71% yield (Entry 7). With another two etheric solvent THF or DME, 2% or 38% of *trans*-limonene oxide was recovered respectively (En-

Table 1 Hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(+)-limonene oxides in water or a mixed solvent of water and organic co-solvent under refluxing condition[a]



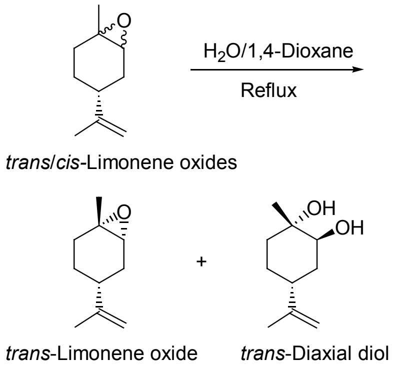
Entry	Organic solvent	*t*/h	*trans*-Limonene oxide recovered[b]/%
1	None	16	8
2	Acetone	25	5
3	CH_3OH	16	14
4	CH_3CN	17	10
5	DMF	15	12
6	Ethylene glycol	2.5	58
7	1,4-Dioxane	2	71
8	THF	17	2
9	DME	3.5	38

[a] Reaction condition: 0.2 mmol of *trans*/*cis*-(*R*)-(+)-limonene oxides were refluxed in 2 mL of water and 2 mL of organic co-solvent for indicated time. [b] The yield was determined by GC with phenyl *n*-butyl ether as an internal standard.

tries 8 and 9). Overall, the fastest reaction led to the highest recovered yield of *trans*-limonene oxide, and 1,4-dioxane was the most suitable organic co-solvent.

Then the ratio of water to 1,4-dioxane in the mixed solvent and the concentration of the substrate were further studied (Table 2). The amount of the recovered *trans*-limonene oxide increased when a small amount of 1,4-dioxane was added initially, reaching a maximum at 50% volume ratio of 1,4-dioxane, then the reaction rate decreased sharply with further addition of 1,4-dioxane (Entries 1—4, Table 2). This suggested that suitable amounts of 1,4-dioxane made the reaction faster as the dissolution of the substrate increased, but excessive amount of 1,4-dioxane was harmful to the reaction since 1,4-dioxane could disturb the ionization of water and the reaction system became less acidic.[17] It seemed that the concentration of the substrate was not crucial in the reaction (Entries 3, 5—7). The highest recovery of *trans*-limonene oxide was obtained at the concentration of 0.025 mol/L in which *trans*-isomer **1** (purity>99%) was recovered in 77% yield (Entry 6, Table 2). Furthermore, when this reaction was scaled-up to gram level, *trans*-limonene oxide could also be recovered in high yield (>70%). The amounts of *trans*-limonene oxide **1**, *cis*-limonene oxide **2**, and *trans*-diaxial diol **3** in the reaction process plotted as functions of time were shown in Figure 1.

Table 2 Hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(+)-limonene oxides in mixed solvent of water and 1,4-dioxane under reflux condition[a]



Entry	*cis*/*trans*-Limonene oxides concentration/(mol•L^{-1})	H_2O : 1,4-Dioxane	*t*/h	*trans*-Limonene oxide recovered[b]/%
1	0.05	5 : 1	70	56
2	0.05	2 : 1	75	68
3	0.05	1 : 1	75	71
4	0.05	1 : 2	420	58
5	0.033	1 : 1	105	70
6	0.025	1 : 1	120	77
7	0.02	1 : 1	60	69

[a] Reaction condition: 0.2 mmol of *trans*/*cis*-(*R*)-(+)-limonene oxides were refluxed in a mixed solvent of water and 1,4-dioxane for indicated time. [b] The yield was determined by GC with phenyl *n*-butyl ether as the internal standard.

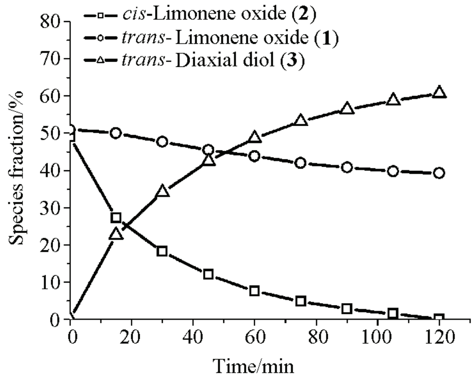
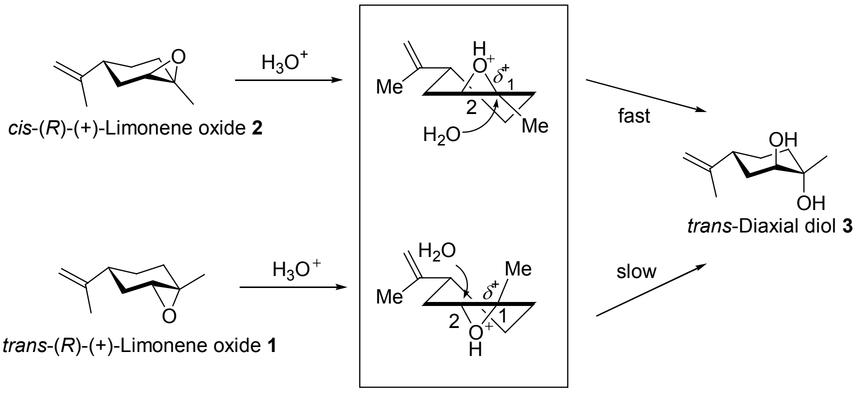


Figure 1 Reaction profile of the hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(+)-limonene oxides **1** and **2** (0.2 mmol) in equal volume of water (4 mL) and 1,4-dioxane (4 mL).

The hydrolysis of *trans/cis*-(*R*)-(+)-limonene oxides was consistent with the Fürst-Plattner rule.[4] The epoxide was activated with proton from the ionization of water. The axial nucleophilic attack of water at the C-1-carbon atom of a chair-like transition state of *cis*-(*R*)-(+)-limonene oxide led to the *trans*-diaxial diol **3** rapidly. In contrast, the axial nucleophilic attack of water at the C-1-carbon atom of *trans*-(*R*)-(+)-limonene oxide **1** was stereo-hindered, water can only attack the C-2-carbon atom, affording the same product

Scheme 2 Selective opening of *cis*-(*R*)-(+)-limonene oxide



trans-diaxial diol **3**, but with very low reaction rate.

Conclusions

In summary, we reported a simple and less hazardous way to operate the hydrolytic kinetic separation of *trans*/*cis*-(*R*)-(+)-limonene oxides. This discovery again suggested that hot water can act as a mild acid catalyst to promote organic reactions. The roles water played during the separation were solvent, reactant, and Brønsted acid catalyst. This method was superior to the existing methods for not using additional catalysts, high yield and high purity of *trans*-(*R*)-(+)-limonene oxide recovered and relatively fast reaction rate.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China (Nos. 20772065 and 21072098), Program for New Century Excellent Talents in University. We thank Mr. Liang Yan-Liang at Nankai University for helpful discussions.

References

[1] For example, see: (a) Ho, T.; Chein, R. *Helv. Chim. Acta* **2006**, *89*, 231; (b) Byrne, C. M.; Allen, S. D.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2004**, *126*, 11404; (c) Grimm, E. L.; Methot, J.; Shamji, M. *Pure Appl. Chem.* **2002**, *75*, 231; (d) Chrisman, W.; Camara, J. N.; Marcellini, K.; Singaram, B.; Goralski, C. T.; Hasha, D. L.; Rudolf, P. R.; Nicholson, L. W.; Borodychuk, K. K. *Tetrahedron Lett.* **2001**, *42*, 5805; (e) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807; (f) Kido, F.; Abiko, T.; Kato, M. *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 2989; (g) Ho, T.; Lee, K. *Tetrahedron Lett.* **1995**, *36*, 947; (h) Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 16; (i) Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 414; (j) Yamasaki, M. *J. Chem. Soc.*, *Chem. Commun.* **1972**, *10*, 606a.

[2] Newhall, W. F. *J. Org. Chem.* **1959**, *24*, 1673.

[3] Steiner, D.; Ivison, L.; Goralski, C. T.; Appel, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron*: *Asymmetry* **2002**, *13*, 2359.

[4] Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.

[5] Andrews, P. C.; Blair, M.; Fraser, B. H.; Junk, P. C.; Massi, M.; Tuck, K. L. *Tetrahedron*: *Asymmetry* **2006**, *17*, 2833.

[6] Salles, L.; Nixon, A. F.; Russell, N. C.; Clarke, R.; Pogorzelec, P.; Cole-Hamilton, D. J. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1471.

[7] Bettadaiah, B. K.; Srinivas, P. *J. Photochem. Photobiol.*, *A* **2004**, *167*, 137.

[8] Leffingwell, J. C.; Shackelford, R. E. (R. J. Reynolds Tobacco Co.) *FR 2002595*, **1969**.

[9] dos Santos, A. G.; de Lima Castro, F.; Jones, J. *Synth. Commun.* **1996**, *26*, 2651.

[10] Blair, M.; Andrews, P. C.; Fraser, B. H.; Forsyth, C. M.; Junk, P. C.; Massi, M.; Tuck, K. L. *Synthesis* **2007**, 1523.

[11] For example, see: (a) Horvàth, I. T. *Green Chem.* **2008**, *10*, 1024; (b) Lancester, M. *Green Chemistry*: *An Introductory Text*, Royal Society of Chemistry, Cambridge, **2002**; (c) Clark, J. H.; Macquarrie, D. *Handbook of Green Chemistry & Technology*, Blackwell, Oxford, **2002**; (d) Matlack, A. S. *Introduction to Green Chemistry*, Marcel Dekker, New York, **2001**; (e) Anastas, P. T.; Heine, L. G. *Green Chemical Syntheses and Processes*, Eds.: Williamson, T. C., American Chemical Society, Washington, DC, **2000**; (f) Anastas, P. T.; Williamson, T. C. *Green Chemistry*: *Frontiers in Benign Chemical Syntheses and Processes*, Oxford University Press, Oxford, **1998**; (g) Anastas, P. T.; Warner, J. C. *Green Chemistry*: *Theory and Practice*, Oxford University, New York, NY, **1988**; (h) Liu, Y.; Zeng, Q.-L.; Tang, H.-Y.; Gao, S.; Yang, Z.-R.; Zhang, S.; Liu, J.-C. *Chin J. Org. Chem.* **2011**, *31*, 986 (in Chinese).

[12] For example, see: (a) *Organic Reactions in Water*, Ed.: Lindström, U. M., Blackwell, Oxford, UK, **2007**; (b) Grieco, P. A. *Organic Synthesis in Water*, Blackie Academic and Professional, London, **1998**; (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*, Wiley, New York, **1997**; (d) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010,** *110*, 6302; (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725; (f) Chen, L.; Li, C.-J. *Chem. Soc. Rev.* **2006**, *35*, 68; (g) Lindström, U. M.; Andersson, F. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 548; (h) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (i) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751; (j) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159; (k) Zhang, Y.; Cheng, M.-Y.; Shang, Z.-C. *Chin J. Org. Chem.* **2011**, *31*, 814 (in Chinese); (l) Zhang, M.-M.; Li, Q.; Wu, J.-R.; Wang, X.-S. *Chin J. Org. Chem.* **2009**, *29*, 1811 (in Chinese); (m) Yang, M.; Yang, Q.; Chen, P.-Q.; Peng, Y.-Y. *Chin. J. Chem.* **2011**, *29*, 499.

[13] Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc*. **1980**, *102*, 7816.

[14] For representative work, see: (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189; (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383; (c) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem.*, *Int. Ed.* **2009**, *48*, 4430; (d) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 3275; (e) Tiwari, S.; Kumar, A. *J. Phys. Chem. A* **2009**, *113*, 13685; (f) Shapiro, N.; Vigalok, A. *Angew. Chem.*, *Int. Ed.* **2008**, *47*, 2849; (g) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492; (h) Zhang, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Eur. J. Org. Chem.* **2006**, 869.

[15] (a) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem*. **2008**, *73*, 2270; (b) Xu, Z.-B.; Qu, J. *Sci. China Chem*. **2011**, *54*, 1718; (c) Li, G.-X.; Qu, J. *Chem. Commun.* **2010**, 2653; (d) Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Commun.* **2009**, 5144.

[16] Leffingwell, J. C.; Royals, E. E. *Tetrahedron Lett.* **1965**, 3829.

[17] Woolley, E. M.; Hurkot, D. G.; Hepler, L. G. *J. Phys. Chem.* **1970**, *74*, 3908.

(Lu, Y.)