Pergamon

Tetrahedron 56 (2000) 6651–6655

TETRAHEDRON

Effect of a Substituent on an Aromatic Group in Diastereomeric Resolution

Kazushi Kinbara,[a] Koji Oishi,[b] Yoshiko Harada[b] and Kazuhiko Saigo[a,*]

[a]*Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan*

[b]*Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan*

Received 27 December 1999; accepted 11 February 2000

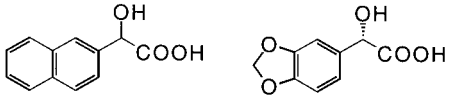
Abstract—The diastereomeric resolution of *p*-substituted 1-arylethylamines by enantiopure (*S*)-3′,4′-methylenedioxymandelic acid ((*S*)-**2**) was carried out in order to know how an electron-donating or -withdrawing group on the aromatic group of the racemic amines would affect the efficiency of resolution. As a result, it was found that 1-arylethylamines having an electron-withdrawing substituent could be efficiently resolved by (*S*)-**2**, while the amines having an electron-donating group could not. The crystal structures of the less- and more-soluble salts, and the molecular orbital calculations of the ammonium cations indicated that the *p*-substituted electron-withdrawing group enhanced the positive charge on the *meta*-hydrogen of the aromatic group of the ammonium cations, which is favorable for the formation of a CH···π interaction in crystal.

Introduction

Although the diastereomeric salt method[1] is the most practically important method for the preparation of enantiopure compounds, the mechanism of chiral discrimination upon crystallization of the diastereomers has not been understood fully up to the present due to its high complexity. Even a simple trend, such as a substituent effect on the efficiency of resolution, has not been studied thoroughly.

In the course of our studies concerning the diastereomeric resolution of racemic 1-arylethylamines by enantiopure mandelic acid and its related compounds,[2] we recently found that a resolving agent, which has a naphthyl group (**1**), had an excellent resolution ability for a variety of 1-arylethylamines.[3] On the basis of the crystallographic studies, one of the most important effects of the naphthyl group of **1** in the chiral discrimination of 1-arylethylamines was suggested to come from the formation of an effective CH···π interaction between the naphthyl group of **1** and the aromatic group of the target racemate. This result indicates that the efficiency of the diastereomeric resolution would be influenced by an electron-withdrawing or -donating substituent on the aromatic group of the racemate. However, since the resolving ability of **1** for 1-arylethylamines was too high, it was difficult to estimate how largely such a substituent would affect the efficiency of the resolution.

In the present study, we carried out the resolution of racemic 1-arylethylamines by enantiopure, substituted mandelic acid **2**, which has a fundamentally similar shape to but a largely different electronic structure from those of **1**, in order to know the importance of the electronic characteristic of the substituent in the racemates and the role of a CH···π interaction in chiral discrimination.



1 (*S*)-**2**

Results and Discussion

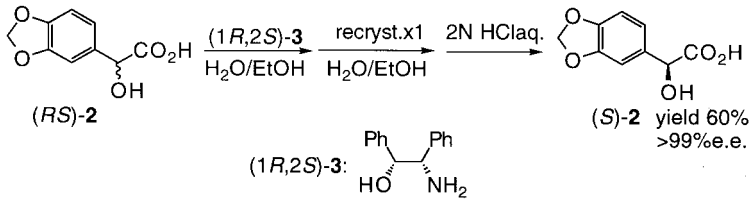
Preparation of the resolving agent

Racemic **2** was prepared from piperonal by following the method reported for the preparation of substituted mandelic acids.[4]

Although the preparation of enantiopure (*R*)-**2** by (−)-ephedrine had been already reported,[5] the method was not convenient in practical use because of the toxicity of the resolving agent and because of inavailability of (+)-ephedrine in a large scale. Hence, we re-investigated other resolving agents for **2** more suitable than ephedrine. The resolution of racemic **2** was examined by using some artificial resolving agents, such as 1-phenylethylamine,

Keywords: diastereomer method; chiral discrimination; crystal engineering.
* Corresponding author. Tel.: +81-3-5841-7266; fax: +81-3-5802-3348; e-mail: saigo@chiral.t.u-tokyo.ac.jp

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00472-5



Scheme 1.

1-*p*-tolylethylamine, 1-(1-naphthyl)ethylamine. As a result, among them, *erythro*-2-amino-1,2-diphenylethanol (**3**)[6] was found to have the highest resolution ability for **2** to give enantiopure **2** in high yield (Scheme 1); enantiopure (*S*)-**2** could be obtained by single recrystallization of a diastereomeric salt mixture, deposited from an aqueous ethanol solution of equimolar amounts of racemic **2** and (1*R*,2*S*)-**3**.

Resolution of 1-arylethylamines by (*S*)-2

The resolution of various *p*-substituted 1-arylethylamines having an electron-donating or -withdrawing group on the aromatic ring was performed using (*S*)-**2** as a resolving agent. The results are summarized in Table 1. In order to compare the results as objectively as possible, the crystallization conditions were arranged as described in our previous papers.[2,3]

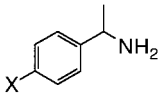
As is shown in Table 1, there is a remarkable trend in the results that the efficiency of resolution depends on the electronic characteristic of the substituent on the aromatic group of 1-arylethylamines; (*S*)-**2** showed a high resolution ability for the racemic amines having an electron-withdrawing substituent on the aromatic group (entries 6–10), while a low resolution ability for the racemic amines having an electron-donating substituent on the aromatic ring (entries 2, and 4–5) and for 1-phenylethylamine itself (entry 1). These results suggest that an interaction between the aromatic group of (*S*)-**2** and the electron-deficient aromatic group of 1-arylethylamines would play some role in the process of chiral discrimination.

Crystal structures of the less- and more-soluble salts

The crystal structures of the less-soluble (*S*)-**2**·(*S*)-**4g** and more-soluble (*S*)-**2**·(*R*)-**4g** could be determined, which are shown in Fig. 1.[7] A characteristic supramolecular hydrogen-bonded sheet, similar to that found previously in the crystals of 1-arylethylammonium mandelates,[2] was formed in each crystal. The carboxylate and the ammonium group formed a columnar hydrogen-bond network (Fig. 1A), and the hydroxy group of (*S*)-**2** interlinked the columns by strong hydrogen bonds (Fig. 1B) to form a supramolecular sheet. No significant difference was found in the hydrogen-bonding pattern between the less- and more-soluble salts.[8]

The most evident difference in crystal structure between the less-soluble (*S*)-**2**·(*S*)-**4g** and more-soluble (*S*)-**2**·(*R*)-**4g** was found in the orientation of the aromatic groups in the supramolecular hydrogen-bond sheet. Fig. 2 shows the packing of the aromatic groups at the hydrophobic surface region of the supramolecular sheet. In less-soluble (*S*)-**2**·(*S*)-**4g**, the

Table 1. Resolution of 1-arylethylamines **4a**–**j** with (*S*)-**2** (the resolution was carried out in a 1–3 mmol scale)



4a: X = H
4b: X = Me
4c: X = Et
4d: X = Pr
4e: X = OMe
4f: X = F
4g: X = Cl
4h: X = Br
4i: X = CN
4j: X = NO_2

Entry	Racemic amine	Solvent ratio (EtOH/H_2O)[a]	Yield (%)[b]	ee (%)[c]	Yield×ee
1	4a	2.7/0	99	11	0.11
2	4b	1.9/0.5	83	14	0.11
3	4c	1.6/0	70	78	0.55
4	4d	0.8/0	76	39	0.30
5	4e	3.2/0.5	70	26	0.18
6	4f	2.05/0.6	51	97	0.49
7	4g	2.5/0.4	80	>99	0.79
8	4h	2.5/0.5	91	85	0.77
9	4i	1.6/1.4	67	99	0.66
10	4j	1.6/0.4	66	>99	0.66

[a] The weight (g) of the solvent normalized to a 1 mmol-scale.
[b] Yield of the crystallized diastereomeric salt based on a half amount of the racemic amine.
[c] Enantiomeric excess (ee) of the liberated amine, which was determined by an HPLC analysis [Daicel CrownPak CR(+)].

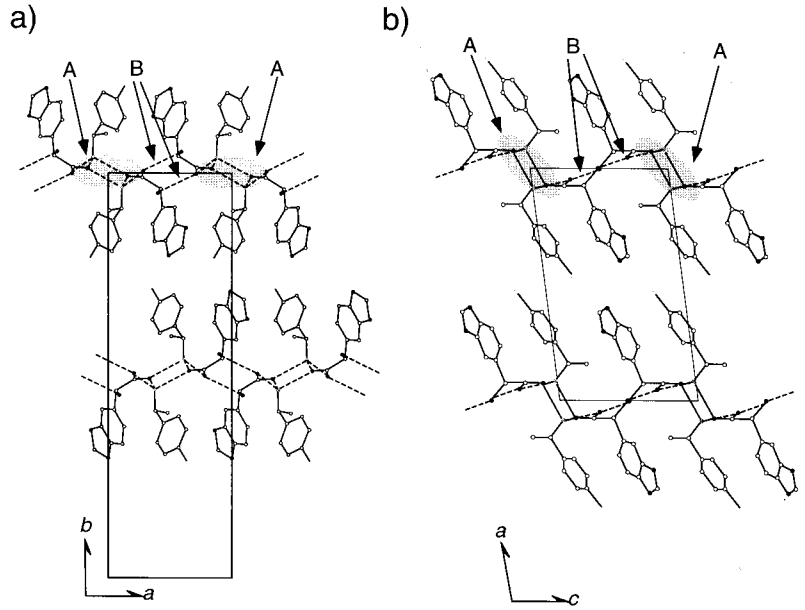


Figure 1. Crystal structures of: (a) less-soluble (*S*)-**2**·(*S*)-**4g** viewed down the *c*-axis; and (b) more-soluble (*S*)-**2**·(*R*)-**4g** viewed down the *b*-axis. The dotted lines represent the hydrogen bonds. The shadowed ellipses show the columnar hydrogen-bond networks formed by the carboxylate and the ammonium group (viewed down the columnar axis).

aromatic groups are almost vertical to the supramolecular sheet to realize an efficient herringbone packing. On the other hand, in the case of more-soluble (*S*)-**2**·(*R*)-**4g**, the aromatic groups are inclined against the supramolecular sheet, resulting in the less-efficient herringbone packing (see: Fig. 2, schematic representations at lower). Since it is known that a T-shape geometry is the most favorable one for an effective CH···π interaction,[9] the efficiency of a CH···π interaction would be higher in the less-soluble salt than in the corresponding more-soluble salt.

Thus, in the present system, the CH···π interaction would be one of the important factors, which differentiate the stability between the less- and more-soluble diastereomeric salts.

Effect of an electron-donating or -withdrawing group on chiral discrimination

In the present system, a possible CH···π interaction would occur between a rather positively charged hydrogen and sp^2-carbons. Therefore, the atomic charge of the hydrogen would be important in order to understand the strength of the CH···π interaction. The results in Table 1 suggest that the efficiency for the resolution of 1-arylethylamines by (*S*)-**2** is influenced by the electronic characteristic of the substituent on the aromatic group of the racemic amines. One possible explanation for this phenomenon is that the atomic charge on the aromatic hydrogen was affected by the substituent, resulting in the change in the stability of the CH···π interaction.

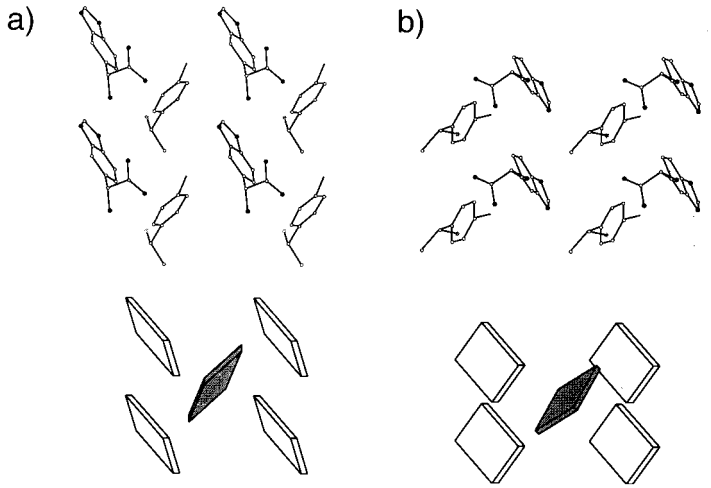
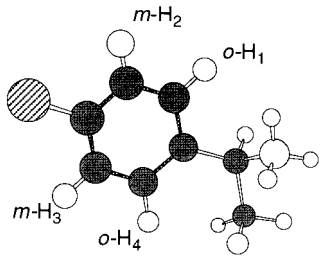


Figure 2. Packings of the aromatic groups at the hydrophobic surface region of the supramolecular sheet (upper) and their schematic representations (lower): (a) less-soluble (*S*)-**2**·(*S*)-**4g** and (b) more-soluble (*S*)-**2**·(*R*)-**4g**. The white and shadowed plates represent the aromatic groups of (*S*)-**2** and **4g**, respectively.

Table 2. Atomic charge of the aromatic hydrogen in **4·H**$^+$ calculated at B3LYP/6-311+G(d,p) level



Ammonium	*o*-H_1[a]	***m*-H_2**[a]	***m*-H_3**[a]	*o*-H_4a
4a·H$^+$	0.140214	**0.160860**	**0.159846**	0.133408
4b·H$^+$	0.136798	**0.149791**	**0.148997**	0.130550
4e·H$^+$	0.133090	**0.156671**	**0.149387**	0.136876
4f·H$^+$	0.147149	**0.170933**	**0.169793**	0.141163
4g·H$^+$	0.145084	**0.179220**	**0.177874**	0.138789
4h·H$^+$	0.144829	**0.175599**	**0.174372**	0.138518
4i·H$^+$	0.149604	**0.172670**	**0.171240**	0.142331
4j·H$^+$	0.151921	**0.192329**	**0.191100**	0.143622

[a] For definition of the hydrogen names: see the figure above.

Thus, in order to estimate the charge of the hydrogen, ab initio molecular orbital calculations[10] were performed for the ammonium cations of **4·H**$^+$ (Table 2). The optimized structures showed that **4f–j·H**$^+$, which were efficiently resolved by (*S*)-**2**, had more positively charged aromatic hydrogens than those of **4a·H**$^+$, **4b·H**$^+$ and **4e·H**$^+$. Particularly, the difference in charge was larger for the *meta*-hydrogens than the *ortho*-hydrogens. On the other hand, the crystal structure of (*S*)-**2**·(*S*)-**4g** indicated that the most probable CH···π interaction occurred between the *meta*-hydrogen of the ammonium part and the aromatic carbons of the carboxylate part, as shown in Fig. 3. Therefore, it is suggested that the increase in the positive charge of the *meta*-hydrogen, which is caused by the electron-withdrawing substituent, can induce a significant effect on the stability of the CH···π interaction in the hydrophobic region.

Conclusion

The present results suggested that the efficiency of resolution for the diastereomeric resolution was affected by a substituent on the aromatic group of the racemates to a considerable extent. As a result, racemic amines, which have an electron-withdrawing group on the aromatic group, could be resolved by (*S*)-**2** with high efficiency; such a trend has not been detected in the examples studied previously. The crystallographic analyses of the less- and more-soluble diastereomeric salts, and the molecular orbital calculations of the ammonium cations indicated that this effect of the substituent came from the enhancement of the positive charge of the aromatic proton, which increased the stability of the CH···π interaction in the less-soluble salt.

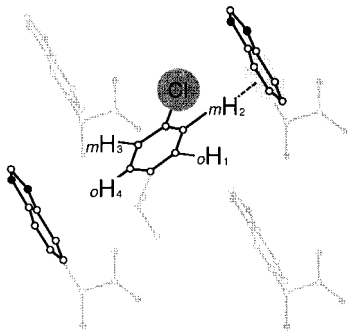


Figure 3. Possible geometry for a CH···π interaction in less-soluble (*S*)-**2**·(*S*)-**4g**.

Experimental

General methods

The IR spectra were recorded on a JASCO IR-810 spectrophotometer, and the ^{1}H NMR spectra were measured on a Varian MERCURY 300 instrument using tetramethylsilane as an internal standard. Analytical HPLC was performed using a Daicel Chiralcel OD (eluent: hexane/2-propanol=19/1, detected at 254 nm) or CrownPak CR(+) (eluent: pH 2 $HClO_4$ or 5% MeOH/pH 2 $HClO_4$, detected at 200 nm) column. The melting points were measured using a Laboratory Devices Mel-Temp and are uncorrected. Racemic amines were prepared according to the procedures described in the literatures.[3,12]

Preparation of racemic 2

To a mixture of lithium chloride (6.78 g, 0.16 mol), potassium hydroxide (17.93 g, 0.32 mol), and piperonal (10.07 g, 0.067 mol) in water (65 mL), which was cooled with an ice bath, was added bromoform (20.19 g, 0.08 mol) at once. After stirring was continued for 24 h, the reaction mixture was washed with ether (2×30 mL). The aqueous layer was acidified with concentrated hydrochloric acid (30 mL), and the liberated solid was extracted with ether (5×30 mL). The combined ethereal solutions were dried over magnesium sulfate. Removal of the solvent under reduced pressure gave crude racemic **2** (12.1 g), which was purified by recrystallization from chloroform/ethanol (50/11 mL) to afford pure racemic **2** (7.62 g, 0.039 mol, 49% yield). Racemic **2**: mp 159–161°C (lit.[5] 158–160°C); IR (KBr) ν=3250–2500, 1730, 1510, 1110, 810 cm^{-1}; ^{1}H NMR (300 MHz, [D_6] DMSO/$CDCl_3$): δ=5.04 (s, 1H), 5.95 (s, 2H), 6.76 (d, *J*=8.4 Hz, 1H), and 6.95 (m, 2H).

Optical resolution of 2

To a solution of racemic **2** (4.08 g, 20 mmol) in ethanol/water (90/6.4 mL) was added (1*R*,2*S*)-2-amino-1,2-diphenylethanol ((1*R*,2*S*)-**3**) (4.46 g, 20 mmol), and the mixture was refluxed for 30 min. After being slowly cooled to room temperature, the mixture was left standing for one day, and the precipitated crystalline salt was collected by filtration (3.45 g). The salt was recrystallized from ethanol/water (45/5.9 mL) to afford pure (*S*)-**2**·(1*R*,2*S*)-**3** (2.81 g, 28%). This salt was dissolved in hydrochloric acid (2 M, 30 mL), and the liberated solid was extracted with ether (3×20 mL). The combined organic extracts were dried over magnesium sulfate. Upon removal of the solvent under reduced

pressure, the crude acid was obtained as a white solid (1.20 g), which was purified by recrystallization from ethanol/chloroform (0.9/10 mL) to afford pure (*S*)-**2** (0.74 g, 55% yield). Enantiomeric excess of (*S*)-**2** was determined by an HPLC analysis on Daicel Chiralcel OD (eluent: hexane/2-propanol=19/1), after (*S*)-**2** was converted into the corresponding methyl ester with diazomethane. (*S*)-**2**: mp 129.5–131.0°C (lit.[5] 129–131°C for (*R*)-**2**); IR (KBr) ν=3440, 3250–2460, 1725, 1505, 1120, 810 cm^{-1}; ^1H NMR (300 MHz, [D_6] DMSO/$CDCl_3$): δ=5.04 (s, 1H), 5.95 (s, 2H), 6.76 (d, J=8.4 Hz, 1H), and 6.95 (m, 2H); $[\alpha]_D^{18}$=+120.5 (c=1.0 in EtOH) (lit.[5] $[\alpha]$=−128.5 (in EtOH) for (*R*)-**2**).

Optical resolution of racemic amines with (*S*)-2

To a solution of a racemic amine in aqueous ethanol (the amount and ratio are listed in Table 1) was added an equimolar amount of (*S*)-**2**, and the mixture was heated to reflux. The solution was then slowly cooled to 30°C and left standing for 12 h in a water bath kept at 30°C. The precipitated crystalline salt was collected by filtration. The salt was dissolved in water, and basified to pH=10 with potassium hydroxide. The liberated oil was extracted with dichloromethane for a few times, and the combined organic extracts were dried over anhydrous magnesium sulfate. Upon removal of the solvent under reduced pressure, the amine was obtained as a colorless oil, of which the enantiomeric excess was determined by HPLC on Daicel CrownPak CR(+).

Crystal-structure determination and refinement

The X-ray intensities were measured up to 2θ=130° with graphite-monochromated CuKα radiation (λ=1.5418 Å) on a Mac Science MXC18 four-circle diffractometer by a $2\theta-\omega$ scan. All of the data were collected at 293 K. The cell dimensions were obtained by least-square analyses of the setting angles of 20 reflections (50°<2θ<60°). The intensities and orientation of the crystals were checked by three standard reflections every 100 reflections.

The structures were solved and refined by applying the CRYSTAN-GM package;[13] the direct method (SIR92[14]) followed by normal heavy-atom procedures, and full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens in calculated positions with thermal parameters equal to those of the atom to which they were bonded. Atomic coordinates, thermal parameters, bond lengths and angles for all diastereomeric salts have been deposited at the Cambridge Crystallographic Data Centre.

(*S*)-2·(S)-4g. Mp 203.0–209.5°C; ν_{max}/cm^{-1} 3200–2400, 1570, 1530, 1500, 1485, 930 and 810.

(*S*)-2·(*R*)-4g. Mp 177.0–181.5°C; ν_{max}/cm^{-1} 3200–2400, 1560, 1540, 1495, 930 and 820.

Acknowledgements

The present work was supported by Grants-in-Aid for Scientific Research (Nos. 09450330 and 10750618) from the Ministry of Education, Science, Sports and Culture of Japan, and the Kawakami Memorial Foundation.

References

1. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, Krieger: Malabar, Florida, 1994.
2. (a) Kinbara, K.; Sakai, K.; Hashimoto Y.; Nohira, H.; Saigo, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1539. (b) Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2615.
3. (a) Kinbara, K.; Harada, Y.; Saigo, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2219. (b) Kinbara, K.; Harada, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans 2*, **2000**, 1339.
4. Compere Jr., L. E. *J. Org. Chem.* **1968**, *33*, 2565.
5. Neilson, D. G.; Zakir, U.; Scrimgeour, C. M. *J. Chem. Soc., C* **1971**, 898.
6. (a) Saigo, K.; Ozawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H. *Bull. Chem. Soc. Jpn* **1982**, *55*, 1568. (b) Saigo, K.; Sugiura, I.; Shida, I.; Tachibana, K.; Hasegawa, M. *Bull. Chem. Soc. Jpn* **1986**, *59*, 2915. (c) Kinbara, K.; Kobayashi, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1767.
7. Crystallographic data: (*S*)-**2**·(*S*)-**4g**: orthorhombic, $P2_12_12_1$, a=8.453(2), b=27.926(9), c=7.005(2) Å, V=1653.7(8) $Å^3$, Z=4, ρ=1.413 g cm^{-1}, μ=2.299 cm^{-1}, 1560 unique reflections, 1486 observed, R=0.079, Rw=0.102. (*S*)-**2**·(*R*)-**4g**: monoclinic, $P2_1$, a=15.586(4), b=6.048(2), c=9.148(2) Å, β=97.26 (2)°, V=855.3(4) $Å^3$, Z=2, ρ=1.366 g cm^{-1}, μ=2.222 cm^{-1}, 1541 unique reflections, 1479 observed, R=0.086, Rw=0.117.
8. The melting points of (*S*)-**2**·(*S*)-**4g** and (*S*)-**2**·(*R*)-**4g** were 198.0–204.5°C and 167.0–170.5°C, respectively. These results suggests that less-soluble (*S*)-**2**·(*S*)-**4g** is thermodynamically more stable than the corresponding more-soluble (*S*)-**2**·(*R*)-**4g**. However, we could not detect a clear evidence in the IR spectra that the hydrogen-bonding interaction is stronger in (*S*)-**2**·(*S*)-**4g** than in (*S*)-**2**·(*R*)-**4g**.
9. Nishio, M.; Hirota, M.; Umezawa, Y. *CH···π Interaction: Evidence, Nature, and Consequences*, Wiley-VCH: Weinheim, Berlin, 1998.
10. The calculations were performed at B3LYP/6-311+G(d,p) level using GAUSSIAN 94[11] program.
11. Frisch, M. J; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. GAUSSIAN 94, Revision D.3; Gaussian: Pittsburgh, PA, 1995.
12. Borch, R. F.; Bernstein, M. D.; Drust, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
13. CRYSTAN GM, A Computer Program for the Solution and Refinement of Crystal Structures for X-ray Diffraction Data (MAC Science Corporation).
14. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343.