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Stereoselectivity of Superacid-Catalyzed Pictet–Spengler Cyclization Reactions

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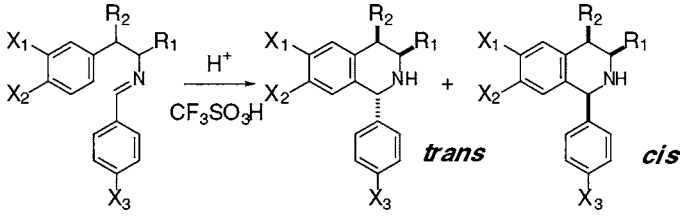
ABSTRACT



High stereoselectivities were found in a wide range of superacid-catalyzed Pictet–Spengler cyclization reactions. Particularly in the cases of 2-alkyl-*N*-benzylidene-2-phenethylamines, an enhanced stereoselectivity was observed under the superacid conditions as compared with the corresponding weak acid (TFA)-catalyzed (monocationic) cyclization reaction of the *N*-benzylidene-2-(3′,4′-dimethoxy)phenethylamines that bear electron-donating groups on the cyclizing aromatic ring. The computational study also supported the energetic favorability of the cyclization of the *N*,*N*-diprotonated imine and revealed a significantly early transition-state structure.

The Pictet−Spengler reaction is an acid-catalyzed intramolecular cyclization of the intermediate imine of 2-arylethylamine, formed by condensation with a carbonyl compound, to give 1,2,3,4-tetrahydroisoquinoline derivatives.[1−3] The Pictet−Spengler reaction, like the Bischler−Napieralski reaction, is one of the key reactions for construction of the isoquinoline skeleton, which constitutes an important motif of naturally occurring bioactive compounds.[4,5] Although the Pictet−Spengler reaction has long been believed to require electron-rich aromatics such as indoles and benzenes substituted with strongly electron-donating groups such as a hydroxy or alkoxy group, superacid catalysts enabled the cyclization reactions of imines (e.g., **1**, $X_1 = X_2 = H$) of 2-phenethylamine to give 1-substituted 1,2,3,4-tetrahydroisoquinoline (e.g., **2**, $X_1 = X_2 = H$) in moderate to high yields (Scheme 1).[6] In the ^1H NMR spectrum of a related imine

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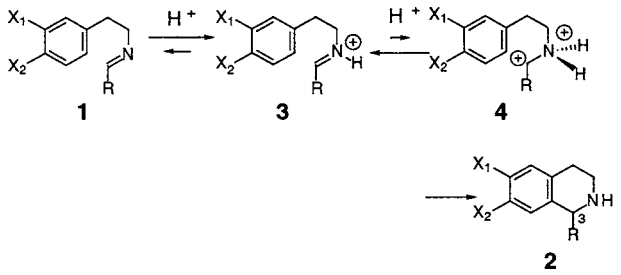
Scheme 1. Cationic Reactive Species Involved in the Pictet−Spengler Reaction



(**1**, $X_1 = X_2 = R = H$), *N*-methylene-2-phenethylamine, prepared from 2-phenethylamine and paraformaldehyde in TFA at −18 °C, an NH proton was observed at 12.29 ppm, and two methylene signals were coupled with the NH signals.[6] This supported practically complete *N*-protonation of the imine nitrogen atom to form the monocation **3** in TFA. However, the cyclization of **1** ($X_1 = X_2 = H$, and, e.g., R = Ph, **1a**, see Table 1) did not proceed in TFA. Superelectrophiles,[7] *N*,*N*-diprotonated imines (**4**), were proposed to be involved in this cyclization on the basis of kinetic measurements of the acidity-dependence of the reaction (Scheme 1).[8]

Table 1. Stereoselection in the Pictet−Spengler Reaction

imines					conditions (T (°C),	yield	
X_1 =	X_2	X_3	R_2	R_1	acid[a]	time (h))	(%)	trans/cis[b]
1a[c]	H	H	H	H	TFSA	120, 15	90	
1a[c]	H	H	H	H	TFA	90, 14	0	
1b	H	H	Me	H	TFSA	120, 20	76	88:12
1c	H	H	Et	H	TFSA	120, 17	81	81:19
1d	H	H	*n*-Bu	H	TFSA	120, 19	95	82:18
1e	H	H	H	Et	TFSA	120, 16	77	8:92
1f	H	H	H	*n*-Bu	TFSA	120, 16	74	5:95
5a[c]	OMe	H	H	H	TFA	120, 12	89	
5b	OMe	H	Me	H	TFA	90, 3	91	80:20
5c	OMe	H	Et	H	TFA	90, 3	100	61:39
5d	OMe	H	n-Bu	H	TFA	90, 3	96	60:40
5e	OMe	H	H	Et	TFA	90, 3	79	6:94
5f	OMe	H	H	*n*-Bu	TFA	90, 3	73	6:94
8a[c]	H	Cl	H	H	TFSA	120, 15	94	
8b	H	Cl	Me	H	TFSA	120, 20	81	85:15
8c	H	Cl	Et	H	TFSA	120, 6	67	80:20

[a] 100 equiv. [b] Ratios of trans/cis isomers were determined in terms of ^{1}H NMR signals. [c] Reference 6.

In this paper, we characterized the differences of the monocationic and dicationic cyclizations of the imines theoretically and experimentally. First we evaluated theoretically the dicationic cyclization catalyzed by the superacid with the aid of ab initio calculation. We also compared the experimental stereoselectivity of the superacid-catalyzed cyclization reaction of 1-substituted and 2-substituted *N*-benzylidene-2-phenethylamines **1b−f** with that found in the TFA-catalyzed cyclization reaction of the corresponding *N*-benzylidene-2-(3′,4′-dimethoxy)phenethylamines **5b−f** (see Scheme 2). The different stereoselectivity was consistent with the postulate that the activation mechanism and the transition-state structures are different in the dicationic cyclization from those in the monocationic cyclization.

The transition-state (TS) structures for the monocationic (through **3a**) and the dicationic (through **4a**) cyclization of the *N*-benzylidene-2-phenethylamine (**1a**, see Scheme 2) were optimized at the RHF/6-31G* level of calculation (**TS1** and **TS2**, Figure 1).[9] The enthalpy of activation of the cyclization of the monocation **3a** is 32.0 kcal/mol.[10] This high activation barrier strongly indicates that the monocationic imine (**3a**) is not the reactive species in the Pictet−Spengler reaction of *N*-benzylidene-2-phenethylamine (**1a**). The enthalpy of activation of the corresponding cyclization

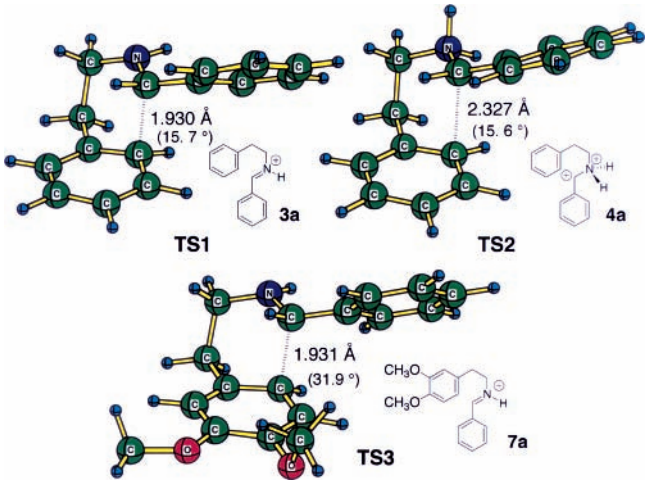


Figure 1. Calculated transition structures for cationic cyclization of imines (the out-of-plane angle between the bending aromatic C−H bond and the aromatic plane is shown in parentheses).

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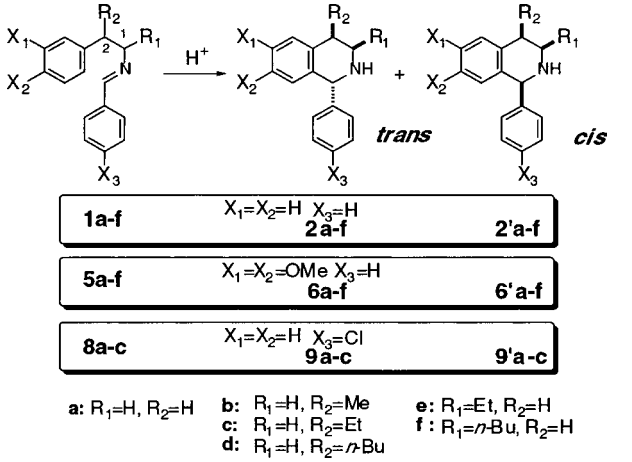
of the monocation **7a**, derived from the electron-rich substrate (**5a**) bearing dimethoxy groups on the benzene ring, through the transition state **TS3** (Figure 1) is 25.8 kcal/mol,[10] much smaller than that of the monocationic cyclization of the inactivated case (**TS1**).[11] The enthalpy of activation of the cyclization of the dication **4a**, the *N*-protonated form of the monocation **3a**, is calculated to be 9.2 kcal/mol (**TS2**).[12] These differences of activation barriers are consistent with the observation that the cyclization of *N*-benzylidene-2-phenethylamine (**1a**) requires a strong acid (TFSA) while the corresponding cyclization of *N*-benzylidene-2-(3′,4′-dimethoxy)phenethylamine (**5a**) is catalyzed by TFA.

The activation energy for the cyclization of **1a** in TFSA was evaluated experimentally from the rate constants of the cyclization at three different temperatures. The enthalpy of activation ($\Delta H^{\ddagger}$) of the cyclization of **1a** in TFSA was found to be 17.7 kcal/mol.[6] Other experimentally evaluated enthalpies of activation ($\Delta H^{\ddagger}$) are 11.5 kcal/mol (*N*-*p*-methylbenzylidene-2-phenethylamine) and 18.0 kcal/mol (*N*-*p*-chlorobenzylidene-2-phenethylamine **8a**), respectively. Thus, these values are consistent with the calculated enthalpy of activation of the dicationic cyclization of **4a** (9.2 kcal/mol), rather than that of the monocationic cyclization of **3a** (32.0 kcal/mol). The transition-state structures of the monocationic and dicationic cyclizations are significantly different, particularly in the distances of the forming C−C bond: **TS1**, 1.930 Å; **TS2**, 2.327 Å; **TS3**, 1.931 Å. Thus, the structural distortion in the dicationic cyclization (**TS2**) is less progressed than in the monocationic cyclization (**TS1**). The transition structure (**TS3**) of the monocationic cyclization of the electron-rich substrate is more distorted as compared with that (**TS1**) of the unreactive substrate. The magnitudes of the out-of-plane angle of the aromatic hydrogen atoms at the reaction center, i.e., the angle between the C−H bond and the aromatic plane, supported this trend (Figure 1).[13] The out-of-plane angle of the aromatic bending hydrogen atom of **TS3** is 31.9° and that of **TS1** is 15.7°, which is comparable to that of dicationic **TS2** (15.6°). However, generally the magnitudes of the structural changes, particularly the forming C−C bond lengths in the TSs, are consistent with the height of the activation barriers: the earlier a transition structure is, the less endothermic the activation barrier is.

The present computational results are consistent with the postulated involvement of the dicationic reactive species (**4a**) in the superacid-catalyzed reactions of the *N*-benzylidene-2-phenethylamine (**1a**).

Scheme 2. Stereoselectivity of the Cyclization



Our interest focus was next directed to the experimental differences between the dicationic and monocationic mechanisms, apart from substituent effects of the cyclizing aromatic rings, which may be reflected in the magnitude of the stereoselectivity at the stereogenic center of the cyclization. There is little knowledge about the stereoselectivity of superacid-catalyzed Pictet−Spengler reactions. Thus, we studied here the stereoselectivity of the superacid-catalyzed cyclizations of 1-substituted and 2-substituted *N*-benzylidene-2-arylethylamines (Scheme 2).

While the cyclization of 2-alkyl-substituted *N*-benzylidene-2-phenethylamine **1b**−**d** (as well as **1a**) did not proceed at all in TFA, the cyclization proceeded in TFSA and gave a mixture of trans and cis isomers of the tetrahydroisoquinolines. These cyclization reactions were stereoselective, and the trans isomer (**2b**−**d**) is predominant over the cis isomer (**2′b**−**d**). The ratios are consistent among methyl (**1b**; trans/cis 88:12), ethyl **(1c**; 81:19) and *n*-butyl (**1d**; 82:18) groups as the R_2 substituent (Table 1). Acid-catalyzed isomerization of cis-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines to the trans isomers has been studied.[14] The stereoselectivity of the cyclization was, however, determined kinetically in the present cases because a fraction of the minor product did not isomerize to the corresponding major isomer upon heating in the presence of TFSA (Supporting Information, Table 1S). A similar magnitude of the trans selectivity was also found in the imines **8b**,**c** where the substituent on the 1-phenyl group of the *N*-benzylidene moiety (X_3) was a chloro group.

(10) This value is the sum of electronic and thermal enthalpies (at 298.15 K) with a scaled thermal correction (a scale factor 0.8929, on the basis of the RHF/6-31G* frequency calculation): (a) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345. (b) Scott, A.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502. (c) Foresman, J. B.; Frish, *Æ. Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, 1996.

(11) The most stable conformer with respect to the conformations of the dimethoxy groups of **5a** was used. Another structure, e.g., with anti and all-in-plane conformation of the methoxy groups of **5a**, is higher in energy than the present conformer (in Figure 1) by 2.2 kcal/mol (RHF/6-31G*, after scaled ZPE correction).

(12) Single-point energy calculations with B3LYP/6-31G* levels on the basis of the RHF/6-31G*-optimized geometries were carried out. The enthalpies of activation (at 298.15 K, after the scaled thermal correction, based on RHF/6-31G* frequency calculations) are as follows: **TS1** (monocationic cyclization), 21.1 kcal/mol; **TS2** (dicationic cyclization), −0.3 kcal/mol; **TS3** (monocationic cyclization), 16.0 kcal/mol, respectively. The energy differences of the enthalpies of activation through these relevant TS structures are of similar magnitude as in the RHF calculations, while the dicationic cyclizton through **TS2** became a nonactivation barrier process. This might be partially because of the incomplete estimation of electron correlations in this type of reactions (see ref 10c).

(13) The dihedral angle between the bending aromatic C−H bond and the neighoring aromatic C−H bond is also a descriptor of the strurural distortion (in the reactant cations, these values are less than 0.9°): **TS1**, 23.3°; **TS2**, 13.5°; **TS3**, 28.1°.

(14) Cox, E. D.; Li, J.; Hamaker, L. K.; Yu, P.; Cook, J. M. *Chem. Commun* **1996** 2477−2478.

The stereoselectivity of the TFA-catalyzed reaction of the electron-rich substrates was also studied (Table 1). The imine **5b**, bearing a methyl substituent as the R_2 substituent, showed stereoselectivity (trans/cis 80:20) as high as that observed in the case of superacid-catalyzed cyclization of **1b**. The magnitude of the selectivity of **5b** was slightly decreased as compared with that of **1b**. In the cases of the sterically demanding ethyl (**5c**) and *n*-butyl (**5d**) groups, the stereoselectivity decreased significantly under similar reaction conditions (**5c**: trans/cis 61:39; **5d**: trans/cis 60:40) (see Table 1). Because the two methoxy groups on the benzene ring are remote from the cyclizing reaction centers, the stereoselection should be free from the steric effect of these groups. Therefore, the results support the postulate that a higher stereoselectivity can be realized under superacid conditions. These differences in stereoselectivity presumably arise from the different transition state (TS) structures of the cyclization, although the relevance of this is not clear at present.[15] In all cases of cyclization of 2-alkyl-substituted imines, the trans-cyclization was favored because of the 1,4-diequatorial positions of the substituents (an alkyl and phenyl group) in the transition state of a chairlike conformation (see Figure 1).

On the other hand, in the cases of the cyclizations of 1-alkyl-*N*-benzylidene-2-phenethylamines, the stereoselectivities in the superacid-catalyzed reactions of **1e** (R_1 = ethyl) and **1f** (R_1 = *n*-butyl) are as high as trans/cis 8:92 and 5:95, respectively (Table 1). In the cases of the cyclization reaction of the corresponding electron-rich substrates (**5e** and **5f**), catalyzed by TFA, the stereoselectivities are as high as those observed in the superacid-catalyzed cases (**1e** and **1f**) (Table 1). The minor trans isomers do not isomerize to the corresponding cis isomer under these reaction conditions (Supporting Information, Table 1S).[16] The present high cis preferences in the reactions of **1e**,**f** and **5e**,**f** can be rationalized in terms of the overwhelmingly more stable cis-1,2-diequatorial positions of the substituents of the TSs in a chairlike conformation.

In summary, high stereoselectivities were found in a wide range of superacid-catalyzed Pictet−Spengler cyclization reactions. Particularly in the cases of 2-alkyl-*N*-benzylidene-2-phenethylamines, an enhanced stereoselectivity was observed as compared with the corresponding monocationic cyclization. The present computational study also supported the energetic favorability of the cyclization of the *N*,*N*-diprotonated imine (**4**) and revealed a significantly early TS structure. Further investigation of stereoselectivity in superacid media and a detailed computational study are under way.

Acknowledgment. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports, Culture and Technology, Japan, Uehara Memorial Foundation, and Tokuyama Science Foundation. Part of the calculations were carried out at the Computer Center, the Institute for Molecular Science, and the Computer Center of the University of Tokyo. We thank these computational facilities for generous allotments of computer time.

Supporting Information Available: Experimental procedures and characterizations, Table 1S, and Scheme 1S. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Our preliminary calculations suggested that the enhanced stereoselectivity in the cases of 2-alkyl-substituted imines under superacid conditions can be rationalized in terms of the difference in the structures and energies of the TSs of the cyclizations. The TSs for trans and cis cyclization of the *N*-monoprotonated cation (**7c**) of 2-ethyl-*N*-benzylidene-2-(3′,4′-dimethoxy)phenethylamine (**5c**) were obtained (**TS4** and **TS5**, Scheme S1, Supporting Information). The structural features are similar to those of **TS3**. The TSs for the trans and cis cyclization of the *N*,*N*-diprotonated imine (**4c**) of 2-ethyl-*N*-benzylidene-2-phenethylamine (**1c**) were also obtained (**TS6** and **TS7**, Scheme S1, Supporting Information). The structural features are similar to those of **TS2**. The activation energies for cyclization are 25.6 kcal/mol (for trans cyclization through **TS4**) and 25.8 kcal/mol (for cis cyclization through **TS5**), respectively. The TS for the trans cyclization of the monocation **3c** is lower in energy than that for the cis cyclization by 0.25 kcal/mol. The energy difference between the TSs for trans (**TS5**) and cis (**TS6**) cyclizations of the dication **4c** is increased 0.37 kcal/mol. Thus, the gap is larger than that of the monocationic cyclization of the dimethoxyphenyl substrate (**5c**). This increased gap between the energies of the TSs for the trans and cis cyclizations seems to be consistent with the enhanced stereoselection.

(16) The trans preference was observed in the Pictet−Spengler cyclization product of the indole imines, 1,3-disubstituted N_a-methyl-N_b-benzyltryptophan methyl ester. See ref 14.