Volume demanding geometric isomerization of *cis*-4-stilbazole.HCl salts in the crystalline state: Probing the role of a metastable dimer

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Graphical Abstract

Abstract

Cis-trans isomerization is one of the most common and well-investigated photoreaction of olefins in solution. This occurs via 180° rotation of one of the substituents on C=C bond requiring large space around the double bond. One would expect that in crystals the neighboring molecules would prohibit such a process. In spite of this in early 1960s Schmidt and co-workers reported occurrence of such a process in crystals via 2+2 'meta cyclobutane' formation. In this study by examining the photochemistry of four *cis*-stilbazolium salts we show that the photoconversion to the corresponding *trans* isomers does not occur via 2+2 addition. Large separation that ensures considerable space between neighboring olefins favors *cis-trans* isomerization in crystals. An aspect that is puzzling is that the product *trans* isomer phase separates and recrystallizes within the parent *cis* crystals and photodimerizes to the cyclobutane dimer. Details of this phenomenon are to be understood.

Key words: solid state photochemistry, *cis-trans* isomerization, metastable dimer, free space, stilbazolium salts

Introduction

The sporadic interest for over a century on the photochemistry of organic molecules in the solid state and as host-guest assemblies in solution have intensified during the last five decades.[1] Early studies on light induced reactions performed in the solid state focused mostly on synthesis of new molecules. Recent availability of X-ray diffractometers and powerful computing programs for structure solution has enabled chemists to connect a molecule's crystal packing with their reactivity and probe molecular transformation mechanisms in solids. The topochemical postulate formulated by Schmidt for solid-state photodimerization of *trans*-cinnamic acids, having stood the test of time, has served as the foundation for the development of solid-state photochemistry;[2] the few exceptions to the postulate have helped fine-tune it.[3]

Olefins in general undergo two main reactions in solution: unimolecular geometric isomerization and bimolecular dimerization.[4] Schmidt's attempt to extend the topochemical postulate to *cis*-cinnamic acids led to the observation of geometric isomerization in crystals.[5] Unlike photodimerization, Schmidt's views on light induced geometric isomerization of cinnamic acids in crystals have not been widely accepted with no clear understanding till date of how the *cis-trans* isomerization requiring large molecular motion at least at one end of the C=C bond occurs in the crystalline state. As indicated above *cis-trans* isomerization in crystals was a serendipitous discovery. The dimers from excitation of *cis*-cinnamic acids examined by Schmidt and co-workers could only be understood by dimerization of two *trans*-cinnamic acids and not two *cis*-cinnamic acids. To accommodate this anomalous phenomenon Schmidt proposed a *cis*- to *trans* isomer conversion, prompted by interaction of an excited *cis* isomer with an adjacent ground state molecule within a distance of 4.2 Å, to precede dimerization.[5] The 'metastable dimer' thus formed is presumed to be the intermediate that facilitates *cis* to *trans* isomerization. This proposal implied the requirement of <4.2 Å separation of adjacent molecules for *cis-trans* isomerization. The proposed mechanism by Schmidt and co-workers illustrated in **Scheme 1** involves several steps: the initial formation of a metastable dimer leading to the *trans*-isomer as a solid solution within the *cis* lattice followed by the separation of the *trans*-isomers in a thermally controlled recrystallization

step into their own lattice. In the final step the excited *trans* isomer yields the lattice controlled stable dimer.

Scheme 1 Proposed consolidated mechanism for the *cis-trans* isomerization of *cis*-cinnamic acids in crystals.

After almost four decades following the early (1902 and 1923) reports on solid-state photoisomerization of olefins from the laboratories of Paal, Schulze and Rice on dibenzoylethylene and benzoylacrylic acid esters,[6, 7] Schmidt and co-workers reported their results on the geometric isomerization of *cis*-cinnamic acids.[5, 8] This report prompted several studies focusing on the mechanism of *cis-trans* isomerization in crystals.[9-16] Currently four mechanisms exist, including the original suggestion by Schmidt, to rationalize the *cis-trans* isomerization in crystals: (a) isomerization via a metastable dimer intermediate, (b) conventional one bond (C=C) rotation,[17, 18] (c) two bond rotation of adjacent single and double bonds (Hula twist),[19-22] and (d) bicycle pedal mechanism involving concurrent isomerization of more than one double bond.[23-26]

A few examples of *cis-trans* isomerization where the adjacent C=C bonds are separated by more than 4.2 Å have also been reported since Schmidt and co-workers' report casting doubt on the role of a metastable dimer during *cis-trans* isomerization.[17, 18, 27-29] This prompted us to ponder the importance of metastable dimer and probe the generality of it as an intermediate during *cis-trans* isomerization. In this context we have currently examined the excited state behavior of four *cis*-stilbazole.HCl salts **1b-4b** (**Scheme 2**) where the adjacent C=C bonds were separated by > 5.5 Å (see discussion below). Such a long distance of separation should prevent metastable dimer formation. To examine the second part of the reaction namely the *trans* isomer, formed from the *cis* isomer, yielding the dimer by recrystallizing in the lattice of the *cis*-isomer we turned to our recent finding that excitation of hydrated *trans*-stilbazole.HCl salts (**5b-8b**) resulted in [2+2] cycloaddition to yield a *anti*-head-tail dimer.[30, 31] Thus, *cis*-stilbazole.HCl salts **1b-4b** seemed ideal to test whether the corresponding *trans*-stilbazole.HCl salts formed in the *cis* lattice would dimerize. Finally, if metastable intermediate is not involved, identification of a pre-requisite condition for *cis-trans* isomerization in crystals is important. With these in mind we carried out a combined X-ray crystallographic and photochemical study of four *cis*-stilbazole.HCl salts (**1b-4b**) shown in **Scheme 2** whose results are presented below.

Scheme 2 Structures of *cis* and *trans*-stilbazoles and their HCl salts discussed in this manuscript.

Experimental section

Synthesis of cis-stilbazole derivatives: The *cis*-stilbazoles were prepared by irradiation of the *trans* compounds in a CHCl_3 solution in Pyrex test tubes ($\lambda \geq 290$ nm), to afford a mixture of *cis* and *trans* and preparative TLC used to separate the liquid *cis* compound. The purity of *cis* compound was verified by ^1H NMR and UV-Vis spectrum (**Figure 1**). The *cis* stilbazole.HCl salt formed on addition of 3 equivalents HCl (37%) was air dried overnight to give powder.. These salts were vacuum dried for 12 h prior to irradiation.

Figure 1 Absorption spectra in methanol solution of (a) *cis/trans* 4-Br stilbazole, (b) *cis/trans* 4- Cl stilbazole

Irradiation technique: About 8-10 mg of stilbazole.HCl salts were spread uniformly between two Pyrex glass plates, sealed with parafilm and irradiated. The plates were turned around every 1 h, the samples thoroughly mixed and spread on the glass plate and irradiation continued. Irradiations were performed using a 450 W medium pressure mercury arc lamp placed in a water-cooled Pyrex immersion jacket. The progress of the reaction was monitored up to a maximum of 30 h. After a given duration of irradiation, a small portion of the irradiated solid material was dissolved in H_2O and neutralized with 1N NaOH. This neutral solution was extracted with CHCl_3 four times and the combined organic layer was dried over anhydrous Na_2SO_4 . After evaporation of the solvent the product was characterized by ^1H NMR in CDCl_3 .

Crystallographic analysis: Each data crystal was glued onto the end of a thin glass fiber. X-ray intensity data were measured by using a Bruker SMART APEX2 CCD-based diffractometer using Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$).[32] The raw data frames were integrated with the SAINT+ program by using a narrow-frame integration algorithm. Corrections for Lorentz and polarization effects were also applied with SAINT+.[32] An empirical absorption correction based on the multiple measurement of equivalent reflections was applied using the program SADABS. All structures were solved by a combination of direct methods and difference Fourier syntheses, and refined by full-matrix least squares on F^2 , by using the SHELXTL software package.[33, 34] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in geometrically idealized positions and included as standard riding atoms during the least-squares refinements. Crystal data, data collection parameters, and results of the analyses are listed in **Table 1**. Data for HCl salt of **4a** is already published.

Crystals for X-ray diffraction analyses, were obtained by evaporation of solution in chloroform/ethyl acetate solvent mixture at 25 °C. All compounds crystallized in the monoclinic crystal system.

With **1b** the systematic absences in the intensity data were consistent with the unique space groups $P2_1/c$.

With **2b** the systematic absences in the intensity data were consistent with the unique space group $P2_1/c$. With $Z = 8$, there are two formula equivalents of the *cis* 4Cl-stilbazol.HCl present in the asymmetric crystal unit.

With **3b** the systematic absences in the intensity data were consistent with either of the space groups $P2_1/m$ or $P2_1$. The structure could only be solved in the latter space group. With $Z = 4$, there are two formula equivalents of the *cis* 4Br-stilbazol.HCl present in the asymmetric crystal unit.

Crystal structure co-ordinates for the three new structures have been deposited at the Cambridge Crystallographic Data Centre. Their CCDC numbers are CCDC 1405334, CCDC 1405335 and CCDC 1405336 for **1a**, **1b** and **1c** respectively.

Table 1 Crystallographic data for HCl salts of compounds **1b**, **2b**, and **3b**.

	<i>cis</i> 4-F stilbazole. HCl	<i>cis</i> 4-Cl stilbazole. HCl	<i>cis</i> 4-Br stilbazole. HCl
Empirical formula	C ₁₃ H ₁₁ NF•Cl	C ₁₃ H ₁₁ NCl•Cl	C ₁₃ H ₁₁ NBr•Cl
Formula weight	235.68	252.13	296.59
Crystal system	Monoclinic	Monoclinic	Monoclinic
Lattice parameters			
<i>a</i> (Å)	9.2263(6)	16.8596(7)	6.1667(3)
<i>b</i> (Å)	13.4939(9)	8.2441(3)	27.7948(15)
<i>c</i> (Å)	10.3239(7)	18.9795(8)	7.7559(4)
β (deg)	105.584(1)	104.970(1)	101.651(1)
V (Å ³)	1238.06(14)	2548.47(18)	1.99(12)
Space group	<i>P</i> 2 ₁ / <i>c</i> (# 14)	<i>P</i> 2 ₁ / <i>c</i> (# 14)	<i>P</i> 2 ₁ (# 4)
Z value	4	8	4
ρ _{calc} (g / cm ³)	1.264	1.314	1.513
μ (Mo Kα) (mm ⁻¹)	0.293	0.481	3.335
Temperature (K)	296	296	296
2Θ _{max} (°)	56.0	55.0	56.0
No. Obs. (I > 2σ(I))	2390	4693	5095
No. Parameters	146	289	290
Goodness of fit	1.028	1.029	1.085
Max. shift in cycle	0.002	0.001	0.001
Residuals*:R1; wR2	0.0363; 0.1011	0.0397; 0.1038	0.0343; 0.0809
Absorption Correction, Max/min	Multi-scan 0.7461/0.6713	Multi-scan 0.7461/0.6568	Multi-scan 0.7457/0.5244
Largest peak in Final Diff. Map (e ⁻ / Å ³)	0.220	0.198	0.359

$$*R = \sum_{hkl} (| | F_{obs} | - | F_{calc} | |) / \sum_{hkl} | F_{obs} | ; R_w = [\sum_{hkl} w (| F_{obs} | - | F_{calc} |)^2 / \sum_{hkl} w F_{obs}^2]^{1/2},$$

$$w = 1/\sigma^2(F_{obs}); GOF = [\sum_{hkl} w (| F_{obs} | - | F_{calc} |)^2 / (n_{data} - n_{vari})]^{1/2}.$$

Results

Although most *cis*-stilbazoles **1a-4a** were liquid, their HCl salts **1b-4b** were solids. Results of X-ray structural investigation are presented first followed by those of photochemical studies. All structures were solved satisfactorily yielding final refined R factors less than 4%. Crystallographic data for **1b-3b** are presented in **Table 1**. The crystal data for **4b** has been published previously. The packing arrangements of *cis*-stilbazole.HCl salts **1b-4b** are presented in **Figures 2** and **3**. We have previously reported the X-ray crystal structures of hydrated **5b-8b** and dry **6b-8b**, and packing arrangements of these are reproduced in **Figures 4** to **6**. First, one should note that while *trans*-stilbazole.HCl salts **5b-8b** could be crystallized with and without water molecules, *cis*-stilbazole.HCl salts **1b-4b** could only be crystallized without water molecules. In two of these crystals the solvent of crystallization methanol was included in the lattice. Analyses of the packing arrangements provided in **Figures 2-6** reveal the following: (a) The distance between adjacent C=C bonds in hydrated *trans*-stilbazole.HCl salts **6b-8b** was less than 4 Å (**Figures 4** and **5**). (b) The distance between adjacent C=C bonds in dry *trans*-stilbazole.HCl salts **6b-8b** was more than 4.7 Å (**Figure 6**). (c) Most importantly, the distance between adjacent C=C bonds in *cis*-stilbazole.HCl salts **1b-4b** was more than 6.0 Å (**Figures 2** and **3**). Clearly of the three types of crystals, the *trans* isomers in hydrated crystals were most tightly packed (<4.2 Å) and would be expected to dimerize to yield *anti-head-tail* dimers. Consistent with this reasoning we had reported earlier that hydrated crystals **5b-8b** upon exposure to light dimerized while the ‘dry’ crystals were photostable.

Figure 2 Packing arrangement of (a) *cis*-4-F stilbazole.HCl (**1b**) (b) *cis*-4-Cl stilbazole.HCl (**2b**). Cl[−] is represented as green sphere.

Figure 3 Packing arrangement of (a) *cis*-4-Br stilbazole.HCl (**3b**) (b) *cis*-4-I stilbazole.HCl (**4b**). Cl⁻ is represented as green sphere.

Figure 4 Packing arrangement of (a) *trans*-4-F stilbazole.HCl (**5b**.3H₂O) (b) *trans*-4-Cl stilbazole.HCl (**6b**.2H₂O). Oxygen of H₂O represented as red sphere and Cl⁻ as green sphere.

Figure 5 Packing arrangement of (a) *trans*-4-Br stilbazole.HCl (**7b**.3H₂O) (b) *trans*-4-I stilbazole.HCl (**8b**.2H₂O). Oxygen of H₂O represented as red sphere and Cl⁻ as green sphere.

Figure 6 Packing arrangement of anhydrous (a) *trans*-4-Cl stilbazole.HCl (**6b**.MeOH) (b) *trans*-4-Br stilbazole.HCl (**7b**.MeOH) (c) *trans*-4-I stilbazole.HCl (**8b**). Oxygen of methanol represented as red sphere and Cl⁻ as green sphere.

Inspection of the packing in **Figures 2** and **3** reveals loose packing with considerable free space in crystals of **1b-4b**. To estimate the available free space surrounding the olefin molecule we generated a cavity plot using the PLATON program. From **Figures 7** and **8** showing the packing of the four olefins with the cavity generated using radius (r) varying between 1.00 to 1.11 Å we conclude that the three cavities in **1b** have volumes of 5.73, 5.58, and 4.19 Å³; **2b** has two cavities with volumes 5.27, and 4.71 Å³; and **3b** and **4b** have single cavity each with volumes of 4.99 Å³ and 5.13 Å³, respectively. It is important to note that the free space is adjacent to the C=C bond and the aryl substituent in the crystals of **1b-4b**. Based on the loose packing (distance of C=C separation >6 Å) and the location of free space in the crystals of **1b-4b** one would predict no dimerization but likely isomerization to corresponding *trans* isomer of these molecules upon excitation.

Figure 7 Cavity plot of (a) *cis*-4-F stilbazole. HCl (**1b**) (b) *cis*-4-Cl stilbazole. HCl (**2b**) using PLATON program. Cl^- is represented as green sphere. The silvery sphere represents the available free space near $\text{C}=\text{C}$. Note that there is more than one sphere with different volumes.

Figure 8 Cavity plot of (a) *cis*-4-Br stilbazole. HCl (**3b**) (b) *cis*-4-I stilbazole. HCl (**4b**) using PLATON program. Cl⁻ is represented as green sphere. The silvery sphere represents the available free space near C=C.

With the X-ray structures of **1b-4b** on hand photochemical studies of these crystals were performed. The products were identified to be the corresponding *trans* isomer and the *anti-head-tail* dimer of the *trans*-isomer. The *cis* and *trans* isomer products present at shorter times of irradiation (~2 h) were accompanied by *anti-head-tail* dimer at longer times. ¹H NMR spectra taken at various time intervals are presented in **Figures S1-S4** in the Supporting Information section (SI) and the yields of the various products of irradiation estimated from the ¹H NMR spectra tabulated in **Tables S1-S4** in SI are presented in a graphical format in **Figure 9**. The product dimer isolated in each

case upon complete conversion was identified to have *anti-head-tail* stereochemistry by comparing with authentic sample prepared previously by irradiating *trans*-**5b-9b**. ^1H NMR spectra of the product and the X-ray structure of 4-chlorostilbazole and 4-bromostilbazole are presented in **Figures S5** and **S6** in **SI**. Examination of **Figure 9**, **Tables S1-S4** (SI) and **Figures S1-S4** (SI) clearly shows that irradiation of **1b-4b** as crystals leads to the corresponding *trans* isomer as the primary product is clear from examination of **Figure 9**, **Figures S1-S4** (SI) and **Tables S1-S4** (SI). Interestingly, no dimer is generated till at least 25% of the *trans* isomer accumulates in the *cis* isomer lattice.

Figure 9 Graphical presentation of % conversion vs time, upon irradiation of (a) *cis*-4-F stilbazole. HCl (**1b**), (b) *cis*-4-Cl stilbazole. HCl (**2b**), (c) *cis*-4-Br stilbazole. HCl (**3b**), (d) *cis*-4-I stilbazole. HCl (**4b**). In the figures, the red line represents formation of *trans*, blue line represents depletion of *cis* and green line represents formation of dimer.

Discussion

From the results presented above it is clear that *cis*-stilbazole.HCl salts **1b-4b** upon excitation resulted in the corresponding *trans* isomer as the primary product. The metastable dimer can be ruled out as an intermediate during the conversion of these salts **1b-4b** to the corresponding *trans* isomer where adjacent C=C bonds are separated by more than 6 Å as deduced from their crystal packing. These examples do not conform to Schmidt's original proposal of lattice controlled *cis-trans* isomerization (*i.e.*, the olefins have to be within a bonding distance of <4.2 Å) occurring via the metastable cyclobutane intermediate.[5] These *cis*-stilbazole.HCl salts **1b-4b** are however not the first such examples. Schmidt himself noted that *trans*-dibenzoyl ethylene isomerized to the *cis* although adjacent C=C bonds were separated by 5 Å and claimed it to be a single crystal-single crystal process.[27, 28, 35] In the case of 2-ethoxy-*cis*-cinnamic acid whose photochemistry was earlier examined by Schmidt and co-workers and said to isomerize via the metastable dimer intermediate was reported by Bryan and Hartley to have adjacent C=C bonds separated by 5.18 Å from X-ray structural studies.[29] We reported about a decade ago several examples of diarylethylenes isomerizing in the crystalline state where adjacent C=C bonds were separated by > 5.2 Å.[17] Based on the above examples, one can confidently state that crystal packing does not have to be tight and metastable dimers need not be involved for the *cis-trans* isomerization to occur in the crystalline state. The adjacent C=C bond separation distance also may not play a role in this process.

Having ruled out a metastable dimer pathway we needed to identify how exactly the isomerization proceeded in crystals. We believed that conventional one bond rotation is the likely pathway. The conventional one bond rotation pathway requires no steric compression between the rotating group and the surroundings necessitating ample free space in the lattice around the rotating group. Using PLATON program[36] we have estimated the free space within the crystal lattice of **1b-4b** represented in the form of spherical cavity with their location as provided in **Figures 7 and 8**. In all four examples the free space present near the rotating aryl group were estimated to be at least 5 Å³ and favorable for *cis-trans* isomerization. Using similar data, such arguments have

been made earlier for diaryl olefins by one of our groups.[37, 17] A similar approach was utilized by the groups of Moorthy[18] and Saltiel[24] later to understand *cis-trans* isomerization of styrylcoumarins and 1,4-diaryl-1,3-butadienes. Kinbara and Saigo who investigated the *cis-trans* isomerization of α,β -unsaturated amides and thioamides independently came to a similar conclusion regarding the role of free space by estimating the packing co-efficient in the crystal using OPEC program by Gavezzotti and pointed out that looser packing in the crystal favored *cis-trans* isomerization.[16] It is important to note that looser packing would not assure free space where the rotation occurs. Cavity sizes near the C=C bond for the two examples were calculated and they are represented in Figure 10. Interestingly, in both reactive and unreactive crystals there were cavities. Careful analysis of the cavity size and location and other weak interactions between the molecules in crystals is needed to understand the reactivity of molecules in the crystalline state. Obviously, the packing co-efficient (loose or dense packing) is not a direct reflection of the location of the cavity in the crystal.

Based on examples of others and ours in the literature and the current ones we conclude that the most important criterion albeit not the only one for *cis-trans* isomerization is the presence of free space at an appropriate site. While the presence of free space assures initiation of the isomerization, continued rotation and completion of the reaction requires the crystal packing be soft and passive, the former ensuring the surroundings accommodate the change and allow a complete 180° rotation of the C=C substituent, and the latter indicating the absence of strong intermolecular interactions (*e.g.*, hydrogen bond, cation- π interaction, ionic interaction etc.) that could resist any rotational motion. In the past, several groups recognizing the importance of free space in various reactions in crystals have developed their own method to estimate the energy involved in molecular motion within a crystal lattice. Amongst these contributions of Gavezzotti,[38] McBride,[39] Ohashi,[40] Scheffer,[41] Venkatesan and Ramamurthy[3] and Zimmerman[42] should be noted.

Figure 10 Cavity plot estimated using PLATON program of α, β unsaturated amides (a) photostable racemic amide and (b) photoreactive reactive *R*- amide; for details on the photochemistry refer to ref. 16. The silvery sphere represents the available free space. The red arrow indicates the C=C bond.

The last point we address concerns the formation of *anti-head-tail* dimers as the final product. We have previously shown formation of these dimers from hydrated crystals of *trans* **5b-8b**. As shown in **Figures 4 and 5** *trans* **5b-8b** are packed such that the adjacent pairs are within $4.0 \text{ \AA}$ and centrosymmetrically related favoring the formation of *anti-head-tail* dimers. However, in the crystals of **6b-8b** without water molecules the adjacent pairs are separated by more than $4.5 \text{ \AA}$, the C=C bonds displaced

with pseudo mirror symmetry. Thus, crystals that do not contain water molecules are not expected to dimerize. Although the crystals of *cis* isomers **1b-4b** we irradiated did not contain water molecules the final products obtained, and only after about 25% accumulation of *trans* isomers in the *cis* crystals, were *anti-head-tail* dimers. The absence of dimer at earlier stages suggested that the precursor for *anti-head-tail* dimer was the excited *trans* isomer and not the excited *cis* isomer. This begs the question of how the *trans* isomer recrystallized itself in the anhydrous *cis* lattice with a packing arrangement suitable for dimerization but was not explored in this study. For the present we go with Schmidt's mechanism assuming *cis* and *trans* isomers form a solid solution leading to phase separation after which the *trans* isomer recrystallizes itself in its own packing arrangement. The formation of *anti-head-tail* dimers in our case during this process could be resulting from the *trans* isomer absorbing moisture from the atmosphere to pack in a manner as in **Figures 4 and 5**. The details of phase rebuilding and phase separation related to organic solid-state reactions as investigated by Kaupp and co-workers using AFM has not been performed by us at this stage.[43] We believe powder X-ray photographs recorded at various stages of irradiation would throw light on this process and plan to pursue them in the future.

Conclusion

We have explored the photochemistry of four *cis*-stilbazole salts in the crystalline state. To understand their photochemical behavior X-ray crystal structures were obtained. Based on the packing arrangements we claim that *cis-trans* isomerization in the crystalline state does not involve a metastable dimer. Ideally for the *cis-trans* isomerization to occur the molecule in question must be well separated from its neighbors and there be 'free space' around the substituent that undergoes 180° rotation. In addition this isomerization is complicated by the formation of a secondary product (cyclobutane dimer) from the primary product the *trans* isomer. This process requires phase separation and recrystallization of the product in the lattice of the reactant. We have not made any attempt to understand this important aspect of solid-state photochemistry. We plan to focus on this aspect in the near future.

Acknowledgements

VR is grateful to the National Science Foundation for continued financial support that enabled us to keep our interest in solid-state photochemistry. VR dedicates this article to Professor Yoshihisa Inoue, Osaka University, a dear friend, esteemed colleague, dedicated researcher, and a gracious and generous host during VR's multiple visits to Japan.

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