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Design and synthesis of *N*-vinylacetamide derivative with bulky group by nucleophilic substitution reaction

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ABSTRACT

Cyclohexyl, adamantyl, and triphenylmethyl groups were employed for the nucleophilic substitution reaction with *N*-vinylacetamide (NVA), in order to investigate the bulky substituents effects on molecular structures in *N*-vinyl monomers. Although normal alkyl halides were known to produce *N*-substituted NVA, alkyl halides with secondary and tertiary carbons did not occur nucleophilic substitution reaction. On the contrary, triphenylmethyl group was introduced into β-position on NVA, accompanied with hydrogen transfer. The refined crystal structure of β-triphenylmethyl-*N*-vinylacetamide revealed intermolecular linear hydrogen bonds and aromatic bulky triphenylmethyl group supported the structure.

1. Introduction

N-Vinylamides have been studied as vinyl monomers in which the vinyl group is directly connected to a nitrogen atom. The unique features of *N*-vinylamides are that they provide thermosensitive polymers [1,2] and poly(vinylamine) [3,4] as a polycation, by tuning substituents and hydrolysis. Among them, *N*-vinylacetamide (NVA) [5,6] is one of the most investigated functional vinyl monomers, which produces an amphiphilic and nonionic polymer. The aforementioned chemical and physical characters were determined which functional substituent was introduced into nitrogen atom on *N*-vinylamide. However, the detailed molecular structures of *N*-vinylamides, such as conformations have not been discussed.

Bulky substituents in vinyl monomers play important role to construct stereoregularities and higher order structures of polymers, such as one-handed helical polymers [7]. Some of them were applied as the stationary phase in column chromatography for chiral separation of racemates [8], because they maintain the conformation even in solution state, such as triphenylmethyl methacrylate (TrMA) [9,10] and triphenylmethylmethacrylamide (TrMAM) [11,12]. The configurations of their polymers were highly controlled along polymer backbone (isotactic triad: mm >99%), because the bulkiness of triphenylmethyl (Tr) groups regulate the direction of the growing reaction during polymerization. Similarly, hydrogen bondings of amide groups could also contribute the structural control [13]. Thus, it is meaningful to design and characterize bulky substituents of *N*-vinylamides.

In this study, we compared the substituents bulkiness of *N*-(4-methoxyphenyl)-*N*-vinylacetamide and *N*-(3-phenylpropyl)-*N*-vinylacetamide [14], which produce vinyl polymers, to the other bulky substituents, such as cyclohexyl group, adamantyl group, and Tr group (Scheme 1). The single crystal structure of TrNVA was also discussed.

2. Experimental

N-Vinylacetamide (NVA) (Showa Denko, Co. Ltd.), sodium hydride 60% in oil (Wako Co. Ltd.), and triphenylmethylchloride (Tokyo Chemical, Co. Ltd.) were purchased and used without further purification. Tetrahydrofuran (THF) (Kanto Kagaku, Co. Ltd.) and dimethylformaide (DMF) (Aldrich, Co. Ltd.) were used after dehydrated with molecular sieves 4A.

The syntheses of *N*-vinylacetamide derivatives were shown in Scheme 1. Typical procedure is described for β-TrNVA. In round bottom glass flask attached three-way cock, sodium hydride (336 mg, 8.4 mmol) was placed. Under nitrogen atmosphere, it was washed three times by dry THF. After cooling down to 0 °C, 0.60 g of NVA in DMF (0.2 g/mL), which was dehydrated by molecular sieve 4A, was slowly added. Triphenylmethylchloride was introduced into the solution with slight heat generation. Then, temperature increased to 45 °C to keep stirring for 24 h. The reaction was terminated by several drops of water, and washed by 10 mL of ethyl acetate for three times with NaClaq. The organic layer was combined to dry with $MgSO_4$ overnight. The residue

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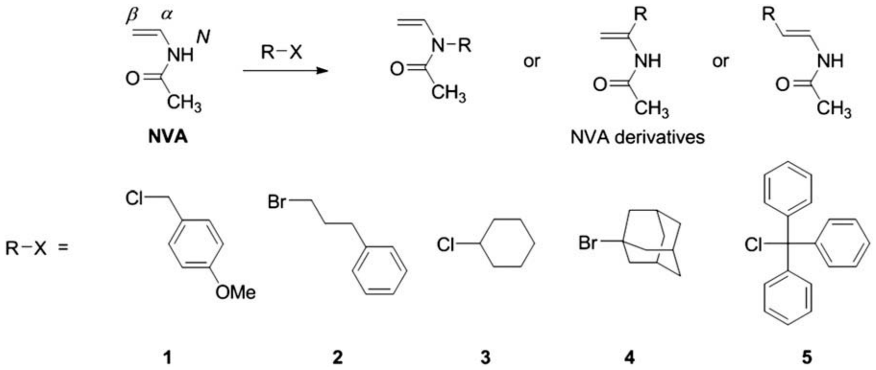

Scheme 1. Nucleophilic substitution reaction with NVA.

was chromatographed on a column of silica gel with hexane–ethyl acetate (90:10–50:50, v/v) to give the fractions containing β-TrNVA (R_f = 0.64, hexane:ethyl acetate = 1:1). The fractions were collected and evaporated under reduced pressure to give β-TrNVA (245 mg, 11%): ^{1}H NMR (CD_3CN, r.t.) δ 1.89 (s, 3H, $C\mathbf{H}_3$—C═O), 6.26 (s, 1H, —C**H**═CH—), 6.28 (s, 1H, —CH═C**H**—), 7.08–7.11(m, 6H, aromatic), 7.22–7.33 (m, 9H, aromatic), 8.31 (br, 1H, N—**H**); IR (cm^{-1}) 1646, 1550, 1528, 1488, 1368, 1291, 698; MS (FAB) m/z = (M+H) calcd for $C_{23}H_{21}NO$ 328.17, found 328.2. Elemental analysis was calcd C: 84.37, H: 6.46, N: 4.28, found C: 83.94, H: 6.37, N: 4.21.

Crystallization was achieved with ethyl acetate evaporating slowly over weeks. Transparent cube crystal was obtained after washed with ethyl acetate. Details of data, data collection and structure solution and refinement are available (Table S1 in Supplementary Material). A colorless chunk crystal of $C_{23}H_{21}ON$ having approximate dimensions of 0.1 × 0.1 × 0.1 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated MoKα radiation. Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with a = 8.7612 (4), b = 22.7026 (8), c = 9.4513 (3) Å, Z = 4, D_{calcd} = 1.157 g cm^{-1}. Based on the systematic absences of: 0kl, $k + l = 2n$; h0l, $h = 2n$, packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $Pna2_1$.

Table 1
Yields of NVA derivatives.[a]

R—X	N-Isomer (%)	β-Isomer (%)
1 [14]	85	0
2 [14]	98	0
3	0	0
4	0	0
5	0	11

[a] Isolated yields.

The data were collected at a temperature 296 K to a maximum 2θ value of 55.0°. Data were processed by the PROCESS-AUTO program package. Of the 30149 reflections which were collected, 2287 were unique (R_{int} = 0.025). An absorption correction was not applied. The data were corrected for Lorentz and polarization effects. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. (1985 and 1999). The structures were all solved by direct methods SIR92 [15] and expanded using Fourier techniques DIRDIF94. The

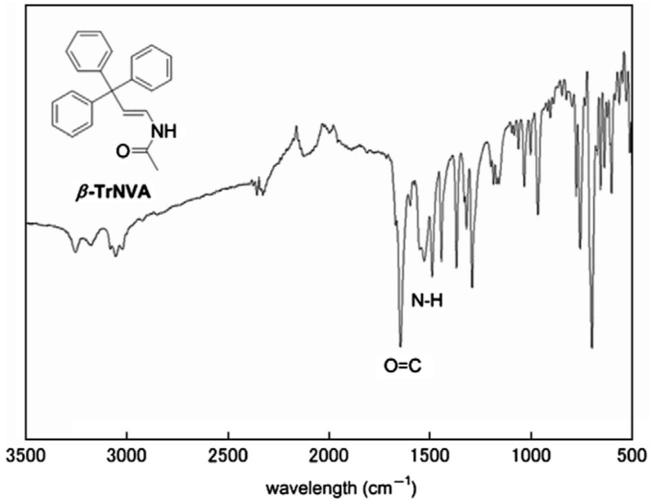

Fig. 1. IR spectrum of β-TrNVA.

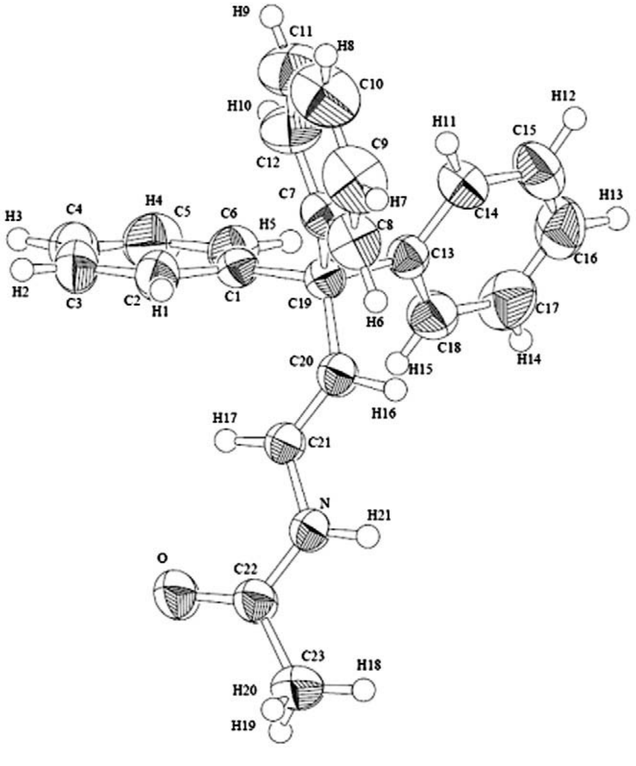

Fig. 2. Molecular structure of β-TrNVA (50% probability).

Table 2
Selected torsion angles.

				Angle (°)
N	C21	C20	C19	172.9 (2)
C20	C21	N	C22	172.5 (2)
O	C22	N	C21	−2.9 (3)
C21	N	C22	C23	178.4 (2)

Table 3
Hydrogen-bonding geometry (Å, °).

	D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
α-NaphNVA[a] [18]	N—H1···O	0.93	1.87	2.7931	177
β-TrNVA[b]	N—H21···O	0.89	1.95	2.826	165

Symmetry code:
[a] 1/2 − *x*, *y* − 1/2, *z*.
[b] *x* + 1/2, −*y* + 1/2, *z*.

non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The maximum and minimum peaks of the final difference Fourier map corresponded to 0.23 and −0.17 $e^-/\text{Å}^3$, respectively. The crystallographic data for the structures in this paper have been deposited with the Chembridge Crystallographic Data Centre as supplementary publication No. CCDC 715860.

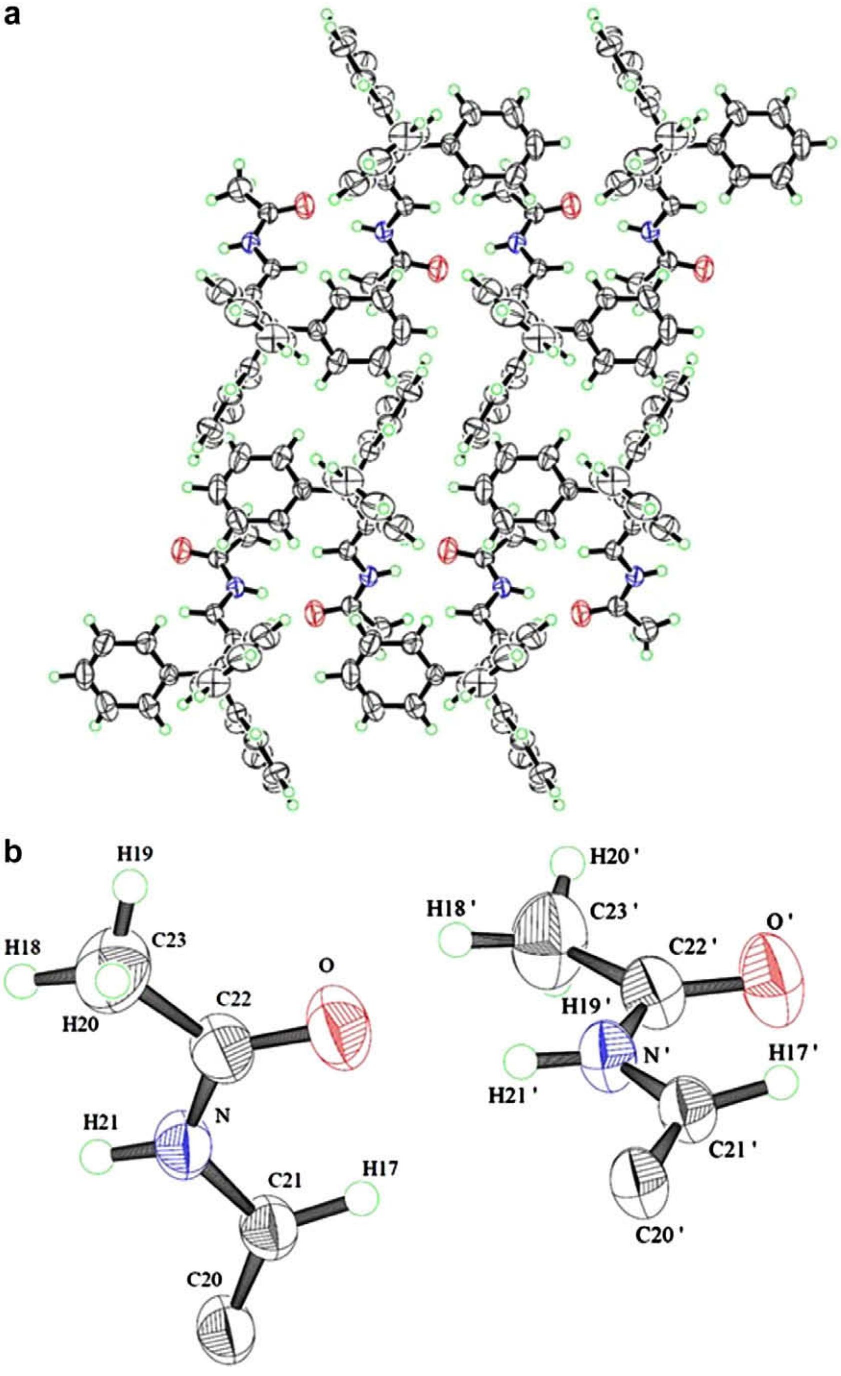

Fig. 3. Crystal packing structure of β-TrNVA.

3. Results and discussion

3.1. Synthesis of N-substituted N-vinylacetamides

An electrophile is usually substituted with hydrogen on the amide group of NVA in DMF solution when NVA is activated with sodium hydride, such as *N*,*N*-5-oxanonamethylene-bis-*N*-vinylacetamide [16]. Therefore, *N*-substituted-*N*-NVA derivatives were initially expected. The results of the syntheses with various alkylhalides were listed in Table 1. As the previous literature [14], 4-methoxybenzyl chloride (**1**) and 3-bromopropylbenzene (**2**) produced the polymerizable vinyl monomers in good yields, however, cyclohexylchloride (**3**) and adamantylbromide (**4**) did not react with NVA. It is suggested that the higher bulkiness of secondary carbon at halogen position prevent the substitution reaction with an amide group.

Similarly, *N*-triphenylmethyl-*N*-vinylacetamide (*N*-TrNVA) was not expected at first, but the substitution reaction has occurred. The mass spectrum and elemental analysis of the purified compound by silicagel chromatography were in good agreement with the predicted structure (Fig. S1 in Supplementary material). However, the N—H bending vibration (1550 cm^{-1}) remained in the IR spectrum after the reaction (Fig. 1). These results imply that the Tr group was substituted with an α- or β-position vinyl group, accompanied with hydrogen transfer [17].

3.2. Structural studies

Fig. 2 is the ORTEP representation of the obtained compound, showing β-triphenylmethyl-*N*-vinylacetamide (β-TrNVA). In accordance with the other analyses, the Tr group was substituted with a hydrogen atom on the vinyl group of NVA. The nitrogen atom and Tr group were placed at the *trans*-position of the vinyl group to avoid intramolecular steric repulsion. The refinement (*R*-factor = 0.046) showed highly reliable structure.

First, angles of phenyl rings are examined, defining plane 1, plane 2, and plane 3 with C1—C6, C7—C12, and C13—C18, respectively (Table S1 in Supplementary material). Three phenyl rings did not stand symmetrically. The angle was 75.52° between plane 1 and plane 2, although that between plane 2 and plane 3 was 99.52°.

The other end position, methyl group was also examined. The calculated H18 position was located in the direction of adjacent O atom. It is noteworthy that the H21, N, C22, C23, and H18 are on the same plane, and the apparently longer distance of C23—H18 (1.00 Å) near the other carboxyl group as compared to the other C23—H19 (0.86 Å) and C23—H20 (0.86 Å) bonds, implies the C23—H18···O hydrogen bond towards the oxygen atom of the adjacent molecule.

It is known that the conjugation nature of carbonyl group and unshared electron pair on nitrogen atom in amide group. Thus, the further conjugation character with vinyl group was investigated. The torsion angles of the amide were described in Table 2. The carbonyl group and N—H are on almost the same plane, including the adjacent vinyl group. The distance C21—N (1.397 (2) Å) was shorter than the normal carbon–nitrogen length, whereas the C—N of the similar crystal of 1-acetamido-1-(1-naphthyl)ethylene (α-NaphNVA) is 1.414 Å [18]. This implies that C20, C21, N, C22, and O possess slightly conjugate properties.

The crystal packing structure was shown in Fig. 3. The linear hydrogen bonds between amides through N—H21···O formed along the *a* axis, similar to α-NaphNVA (Fig. 3a). This crystal packing pattern is different from any other NVA derivatives, which create pairs facing each other and can be regarded as dimer packing [19–21], or which create many other hydrogen bonds with various hetero atoms [22–24]. Both the bond lengths and the angles for N—H21···O were calculated to be typical hydrogen bonding values (Table 3), but the length of the N—H21···O (2.826 Å) bond was slightly longer than the N—H···O (2.793 Å) bond in α-NaphNVA [18], suggesting that the aforementioned C23—H18···O hydrogen bond might be concerned (Fig. 3b). A 2_1 helix was observed perpendicularly to the hydrogen bonding lines, due to the linear hydrogen bonds, differing from usual dimer packing [19–21]. Tr groups surrounded the hydrogen bonding lines and they were present back to back to support the linear structures each other. The directions of the hydrogen bonds build up alternatively, forming aromatic regions intermolecularly. Unfortunately, vinyl group position was far from each other, however, the single crystal structure of β-TrNVA afforded important insights for molecular design for polymerization of *N*-vinyl monomers.

4. Conclusion

In conclusion, the bulky aromatic Tr group was introduced to NVA, which influenced the substituted positions at the β-vinyl proton of NVA, while no reactions were occurred with secondary carbon at halogen position. The crystal structure of β-TrNVA indicated that it crystallized in an orthorhombic system of non-centrosymmetric space group $Pna2_1$. The phenyl rings of the Tr groups flexibly adjusted the packing structure with a different plane angle among the phenyl rings. The C23—H18···O hydrogen bonds are suggested to form chelating with amide hydrogen bonds. In addition, the linear hydrogen bonds are different from the packing patterns that make a pair facing each other with the amide groups, and this may be an advantage in controlling the higher order structure when the compound is a monomer to be polymerized. The demonstrated structural elucidation of β-TrNVA in this study would contribute the molecular design of *N*-vinyl monomers.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2009.11.012.

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