

Mechanochemical Solid-State Polymerization. VI. Quantum Chemical Considerations for Structural Criteria of Mechanically Polymerizable Vinyl Monomers

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To provide the structural criteria for mechanically polymerizable vinyl monomers in metallic vessels, we carried out the MO calculations (AM1 method) of several acrylamide, acrylate and styrene derivatives as model compounds for such reactions. It was found that the nature of LUMO of vinyl monomers is closely related to the capability for initiation of mechanochemical polymerization. The following requisite concerning the nature of LUMO was shown to be a necessary condition for the activity of such reactions: Even if the LUMO energy is lower than 0.166 eV in the AM1 scheme, the LUMO coefficient must be highly localized in the vinyl group. When the monomer does not meet this criterion, the introduction of a saturated group such as an alkyl group to insulate electronically the π -electron system of vinyl group from the rest of the molecules will lead to the mechanically polymerizable monomers.

Keywords mechanochemical polymerization; vinyl monomer; MO calculation AM1; solid-state; LUMO (lowest unoccupied molecular orbital)

The chemotherapeutic utility of polymeric prodrugs has recently been the focus of intense research because of the possible reduction of undesirable side-effects and their utility as a sustained release system.¹⁾ Polymeric prodrugs, however, are usually synthesized in the liquid state, thus the reaction mixture must be worked up by product separation and purification. The mechanochemical polymerization of solid state monomers such as acrylamide (1) and methacrylamide was reported more than 3 decades ago.²⁾ Nonetheless relatively little work has been done with fundamental reaction analyses or with applications of mechanochemical polymerizations in the solid state.³⁻⁷⁾ Simionescu *et al.* speculated that the mechanism by which these polymerizations are initiated involves an electron transfer from the activated metal surface to the vinyl bond of the monomer to produce the corresponding anion radical, followed by propagation through a radical chain polymerization (Chart 1).⁵⁾ But they did not provide the detailed experimental evidence including occurrence of the solid state single electron transfer (SSET).

We have recently reported the first experimental evidence of the occurrence of SSET induced by application of mechanical energy based on the observation of electron spin resonance (ESR) spectra of the reduced form of dipyridinium dications.⁸⁾

We have also reported the first in-depth study of mechanochemical polymerization of specially synthesized

solid state monomers, methacryloyl derivatives of bioactive compounds including the detailed mechanistic implications. Thus, we provided a novel methodology for simple polymeric prodrug syntheses through a totally dry process, and described the nature of the hydrolyses of polymeric prodrugs prepared by mechanochemical polymerization.^{9,10)} Several important conclusions were reached from our series of studies. It was shown that there exists a monomer selectivity for efficiency of the mechanochemical solid state polymerizations, although all the monomers examined underwent conventional radical initiated solution polymerizations. The mechanically polymerizable monomer gave the corresponding polymeric prodrugs essentially quantitatively. Thus, this method eliminates the need for any work up of the reaction mixture, which is required in liquid state. One of the most striking properties observed in such polymers is that the resulting polymeric prodrugs are of very low heterogeneity (narrow molecular weight distribution) represented by M_w/M_n (M_w , weight-average molecular weight; M_n , number-average molecular weight) which is of great value in pharmaceuticals for highly functionalized polymeric prodrugs.⁹⁾

In connection with our work on mechanochemical prodrug syntheses, we felt it would be important and useful to establish the structural criteria of mechanically polymerizable vinyl derivatives. This would allow a full

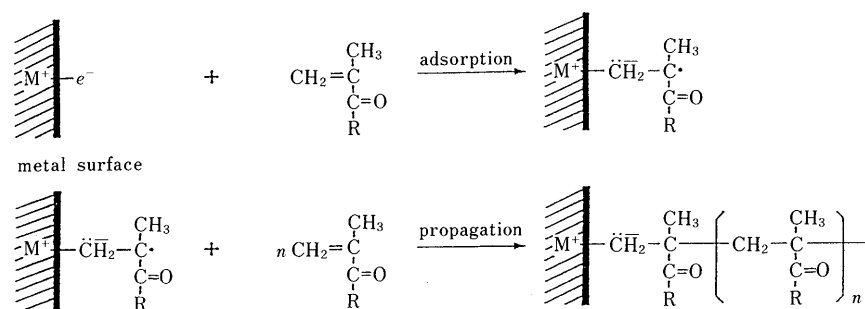


Chart 1. Schematic Representation of Mechanism of Mechanochemical Solid-State Polymerization in a Metallic Vessel

understanding of the factors governing the nature of mechanochemical polymerization for optimal molecular design of the monomer, and further development of the mechanochemical polymerization.

Molecular orbital calculations are particularly useful for such studies since they can provide a great deal of information about the electronic structure prior to experimentation. It is now apparent that nonempirical *ab initio* calculations with extended basis sets must be used to achieve high accuracy on both the molecular and the electronic structures. Yet, for the present purpose, we believe that the semiempirical method can provide sufficient fundamental insight into the reactivity of mechanochemically polymerizable monomers derived from such electronic structures.

In this paper, we describe the scope and limitations of mechanochemical polymerization of vinyl monomers derived from quantum chemical considerations using several acrylamide, acrylate and styrene derivatives as model compounds.

Results and Discussion

Mechanochemical Polymerization of Vinyl Monomers

Phenylacrylamide, phenylacrylate and styrene derivatives shown in Fig. 1 are all solid at room temperature. So, our starting point was to examine the activity of mechanochemical polymerization of these monomers chosen as model compounds.

Mechanochemical polymerizations of these vinyl monomers were carried out in a metallic twin-shell blender for 1h under strictly anaerobic conditions, according to the method described in the previous paper.⁹⁾ The polymer conversion of each fractured mixture was determined by observing the disappearance and appearance of vinyl proton signals and the corresponding alkyl proton signals of the polymer in the ¹H-NMR spectra of the resulting fractured powders.

The results demonstrate that there exists a selectivity for efficiency of the mechanochemical polymerizations;

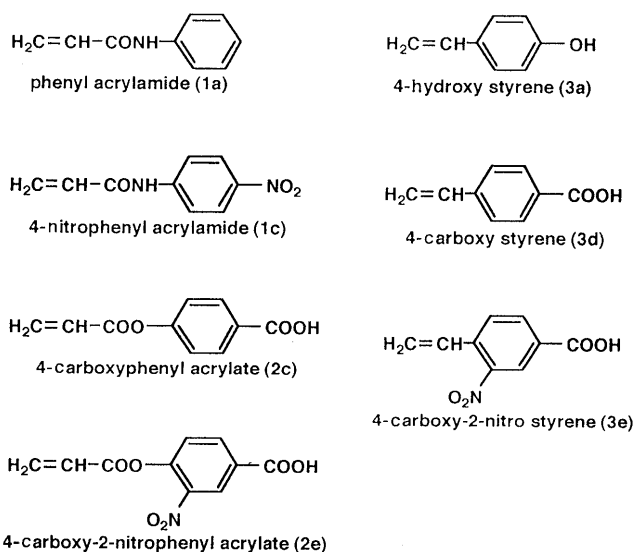


Fig. 1. Structures of Vinyl Monomers Used in Mechanochemical Solid-State Polymerization

phenylacrylamide (1a), 4-carboxyphenyl acrylate (2c) and all styrene derivatives shown in Fig.1 underwent mechanochemical solid-state polymerizations to give the corresponding polymers essentially quantitatively. 4-Nitrophenyl acrylamide (1c) and 4-carboxy-2-nitrophenyl acrylate (2e), however, did not undergo mechanochemical polymerization to a detectable extent. This is in sharp contrast to the fact that all these vinyl monomers have undergone solution polymerizations using conventional radical initiators.¹¹⁻¹⁵⁾

Structures of Vinyl Monomers Since the mechanochemical polymerization of vinyl monomers in a metallic vessel is initiated by the formation of anion radicals produced by SSET from the activated metal surface, an electron affinity (E_a) of the monomers should be a measure of the feasibility of an electron transfer to the molecule, and the E_a can be approximated to the energy of lowest unoccupied molecular orbital (LUMO) in MO terms. Thus, it seems important to understand the nature of LUMO and its capability of anion-radical formation. We therefore carried out MO calculations on several kinds of phenylacrylamide, phenylacrylate and styrene derivatives including the derivatives shown in Fig. 1 by the AM1 method. Table I shows the equilibrium geometry and the energies of LUMO of these model compounds.

As shown in the Table I that phenylacrylamides and styrene derivatives are essentially planar and phenylacrylates are non-planar (θ is *ca.* 40°) in their respective equilibrium geometry. We also inspected the nature of equilibrium geometry for 1a (A) and phenylacrylate (2a) (B).

As shown in Fig. 2, the stability of the two monomers varies with θ , but in a different manner. The result of calculations clearly indicated that the core-core and electron-electron repulsion at A and core-electron attractive force at C decreases as the value of θ increases in

TABLE I. Equilibrium Geometries and Energies of LUMO of Phenylacrylamide, Phenylacrylate and Styrene Derivatives Calculated by the AM1 Method

	X	Y	θ (degree)	LUMO (eV)
	H		5	-0.146
	NH ₂		1	-0.054
	NO ₂		2	-1.095
	H	H	40	-0.190
	NH ₂	H	40	-0.089
	COOH	H	32	-0.666
	NO ₂	H	36	-1.156
	COOH	NO ₂	38	-1.462
	H	H	0	0.017
	OH	H	0	-0.005
	NH ₂	H	0	0.154
	NO ₂	H	0	-1.276
	COOH	H	0	-0.764
	COOH	NO ₂	0	-1.575

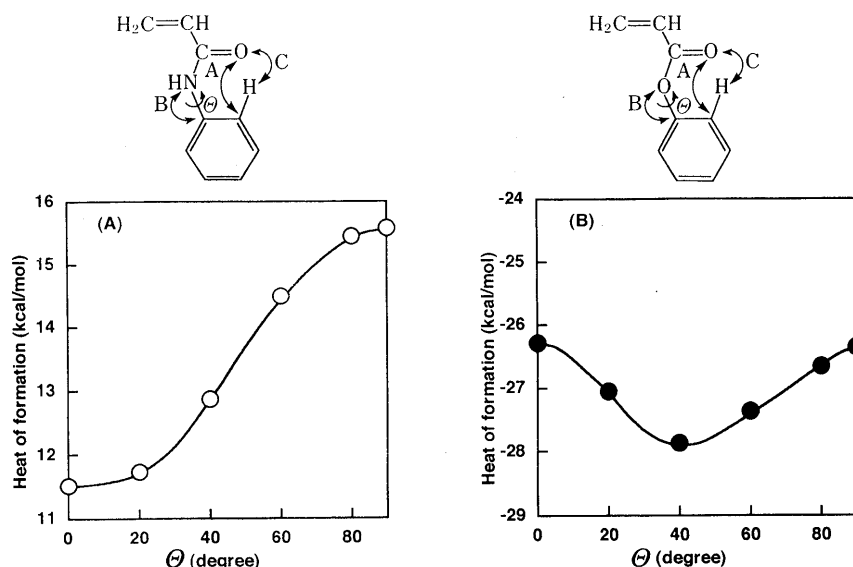


Fig. 2. AM1-Calculated Heat of Formation Shown as a Function of θ
 (A) Phenylacrylamide (1a). (B) Phenylacrylate (2a).

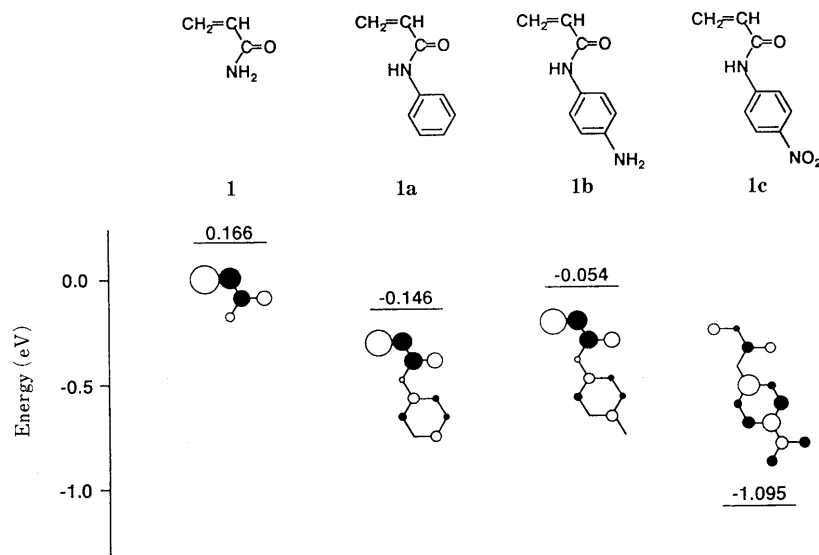


Fig. 3. Energies and Coefficient Distributions of LUMO of Phenylacrylamide Derivatives in the Equilibrium Geometries Calculated by the AM1 Method

both monomers. In contrast, the change of the resonance energy at B with the increase of θ is quite different between the two; this decrease of B in **1a** with the larger value of θ causes a loss of stabilizing energy, so that the planar conformation becomes more stable, despite the fact that the core-core and electron-electron repulsive force at A is rather large in the planar conformation. On the other hand, the resonance energy of B in **2a** is almost unchanged with respect to θ , probably due to the presence of two lone pairs of electrons in oxygen atom. Therefore, the most stable conformation for **2a** is dependent solely on the optimal interatomic energy balance at A and C, which results in the conformation with value of $\theta = 40^\circ$.

It is also seen that the LUMOs of these compounds shown in Table I are lower in energy than that of active **1** (0.166 eV) so that they should have no difficulty in forming the corresponding anion radicals under the

present conditions of vibratory milling in a metallic vessel. Further, it is reasonably assumed that the contribution of the next LUMO (NLUMO) of all these compounds to the formation of anion radical would be negligible, since the NLUMOs lie at a much higher energy level than the LUMOs.

Phenylacrylamides Figure 3 shows the energies and coefficients of LUMO in the equilibrium geometries of phenylacrylamides calculated from the AM1 wave functions, together with those of **1** for comparison.

It is seen that the LUMO's coefficients of **1**, **1a** and **1b** are primarily localized in the acryloyl component. The LUMO's polarizations should correspond to the spin density distribution in the resulting anion radicals, and this has, in fact, been verified by the open-shell unrestricted AM1 (UAM1) calculations of the corresponding anion radicals. Therefore, the anion radical formed should be

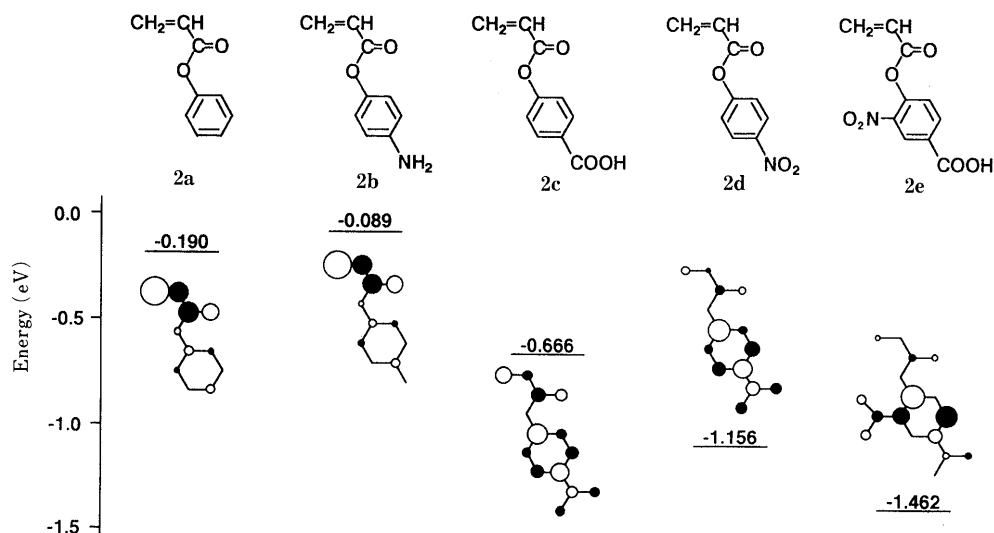


Fig. 4. Energies and Coefficient Distributions of LUMO of Phenylacrylate Derivatives in the Equilibrium Geometries Calculated by the AM1 Method

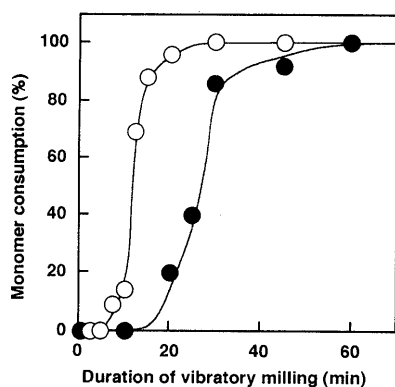


Fig. 5. Progressive Changes in Polymer Conversion (Monomer Consumption) in the Course of Vibratory Milling

○, acrylamide (1); ●, 4-carboxyphenylacrylate (2c).

capable of undergoing the ensuing radical-chain polymerization of the vinyl group, accounting for the occurrence of the mechanochemical polymerizations of **1** and **1a** as experimentally observed. On the other hand, in **1c**, which did not undergo mechanochemical polymerization to a detectable extent, the LUMO's coefficient is largely localized in the phenyl group due to the presence of a strong electron-withdrawing nitro group in the phenyl ring. This may be the result of the anion radical, although being formed, not initiating the subsequent radical-chain polymerization due to the low spin density of the vinyl group.

Phenylacrylates Figure 4 shows the energies and coefficients of LUMO in the equilibrium geometries of phenylacrylates calculated by the AM1 wave functions.

It is immediately seen that **2a**, **2b** and **2c** should undergo mechanochemical polymerization, since the LUMO's coefficients are largely or considerably localized to the acryloyl component. It can be safely said that **2d** and **2e** would be unreactive in the mechanochemical polymerization, since the LUMO's coefficients are localized largely to the phenyl moiety due to the presence of the nitro group. Here, it may be interesting to compare the mechano-

chemical reactivity of **2c** with that of **1**, since the LUMO's coefficients of the vinyl group of **2c**, which corresponds to the spin density in the anion radical, are smaller than those of **1**.

Figure 5 shows plots of the monomer consumption as a function of the duration of the vibratory milling of **1** and **2c**.

Both lines exhibit sigmoidal curves, the apparent time lag of **2c** (*ca.* 15 min) being longer than that of **1** (*ca.* 5 min), although the monomer consumptions have been completed within 60 min in both cases. We earlier reported that the polymerization initiated through the anion radical is only a minor process in the mechanochemical polymerization, though its initiation is essential, and the steep increase in the rate of monomer consumption can be ascribed to the occurrence of a very dominant "mechanoradical-initiated polymerization".⁹⁾ Therefore, the period of the time lag would be associated with the reactivity of anion radical, since the anion reactivity of **2c** is lower than that of **1**, and would demonstrate the importance of LUMO's coefficient distributions of the vinyl group for mechanochemical polymerizations.

We did not carry out the mechanochemical polymerization of **2a**, **2b** and **2d**, because they are liquid at room temperature. It can be predicted from the present calculations, however, that **2a** and **2b** would be active in mechanochemical polymerization if it were carried out at a temperature lower than their freezing points.

Styrenes Figure 6 shows the energies and coefficients of LUMO in the equilibrium geometries of several styrene derivatives similarly calculated. LUMO's coefficients of all styrene derivatives shown in Fig. 6 are seen to be delocalized over the molecules, unlike those of phenylacrylamide and phenylacrylate derivatives, due to the strong π -interaction between the phenyl and vinyl groups.

This suggests that these styrene derivatives do undergo the mechanochemical polymerization. In fact, the experimental results show that **3a**, **3d** and **3e** did undergo the mechanochemical polymerization (*vide supra*).

We have already demonstrated that the introduction

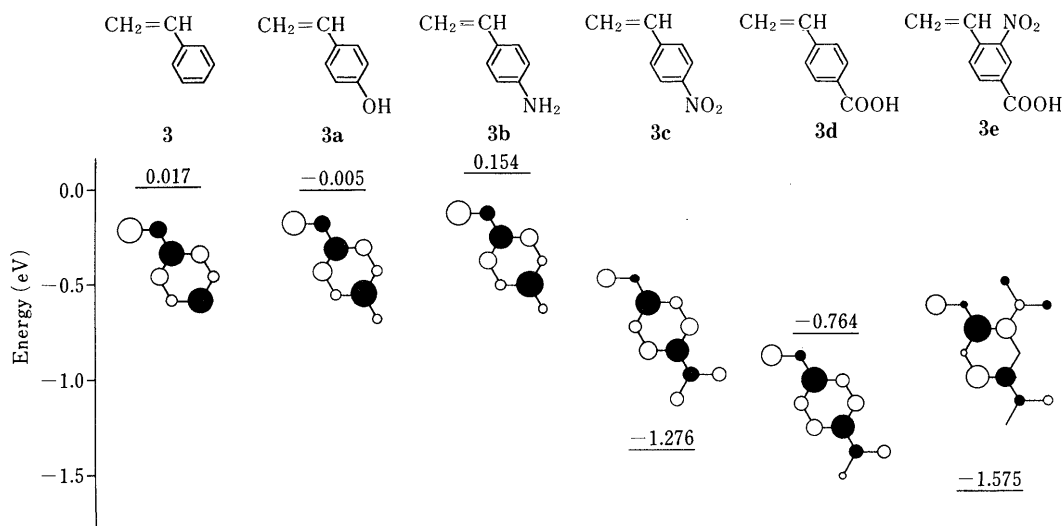


Fig. 6. Energies and Coefficient Distributions of LUMO of Styrene Derivatives in the Equilibrium Geometries Calculated by the AM1 Method

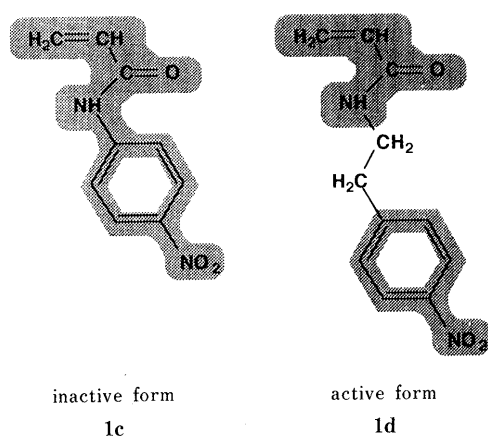


Fig. 7. Illustration of Monomer Structural Features in Inactive and Active Form in Mechanochemical Solid-State Polymerization

of alkyl group between the methacryloyl group and ester substituent (*viz.* drug) made it possible to undergo mechanochemical polymerization of unreactive methacryloyl vinyl monomer possessing π -conjugated substituent.⁹⁾

We emphasize, therefore, that it may always be possible for alkyl-substituted vinyl monomers such as acryl-, methacryl-derivatives to undergo the mechanochemical polymerizations. As illustrated in Fig. 7 using **1c** as a guide example, the acrylamide moiety of **1d** is electronically isolated from the conjugated π -moiety of the phenyl group, so that the electronic structure of the vinyl group is essentially identical with that of **1**, and, in fact, the monomer of **1d** did undergo the mechanochemical polymerization.

Thus, it has been shown that the π -electron system insulating the vinyl group from the rest of the molecules is a necessary condition for monomer activity of mechanochemical polymerization, when the LUMO coefficient is highly localized in a moiety other than the vinyl group.

Conclusion

The conclusions drawn from the present study can be summarized as follows. The nature of LUMO of vinyl monomers is nicely related to the capability for initiation of mechanochemical polymerization induced by the anion radicals. Since the LUMOs of all the compounds examined are lower in energy than that of active acrylamide, **1**, they should produce without any difficulty the corresponding anion radicals under the present operational conditions. Consequently, the prerequisite for the activity of such reactions is that the LUMO must be largely localized in the vinyl group. When the LUMO coefficient is localized to a moiety other than the vinyl group, the introduction of some spacer groups between the vinyl group and ester substituent would make mechanochemical polymerizations possible.

Thus, if one prepares the monomers along the line of such structural criteria as derived from the present study, the mechanochemical polymerizations seem applicable to a wide variety of vinyl monomers of an important class of bioactive compounds with different physicochemical properties.

Since the mechanochemical polymerizations are also controlled by a variety of factors other than the electronic structures of monomers such as the mechanical energies applied and the work function of metallic vessel used, we can not yet provide the further quantitative indices in MO terms for efficiency in such reactions. Nevertheless, the results reported herein provide useful information for a future experimental design for active monomers under the operating conditions used here.

Experimental

Phenylacrylamide (**1a**), 4-hydroxycinnamic acid, 4-hydroxystyrene (**3a**), 4-acetylphenylethyl bromide, 4-(2-bromoethyl)benzoic acid, and 4-carboxystyrene (**3d**) were synthesized according to the literature.^{12-14,16,17)}

4-Nitrophenylacrylamide (1c) To a solution of 4-nitroaniline (0.5 g, 3.6 mmol) in dry benzene (50 ml) was added dropwise acryloyl chloride (0.33 g, 3.6 mmol) at room temperature and the mixture was stirred for 1 h. The content was washed with H₂O (20 ml), dried with MgSO₄, and evaporated in vacuum. The residue was recrystallized from benzene to

give **1c** (0.5 g, 72%). mp 216–217 °C. IR (KBr) cm^{-1} : 1670 (–CONH–), 1530, 1330 (–NO₂). ¹H-NMR (270 MHz, DMSO-*d*₆) δ : 5.85–6.53 (3H, m, H₂C=CH–), 7.90–8.27 (4H, m, Ar-H), 10.75 (1H, s, –CONH–). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 320.5 (17000). MS *m/z*: 192 (M⁺). Anal. Calcd for C₉H₈N₂O₃: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.11; H, 4.23; N, 14.68.

N-(2-(4-Nitrophenyl)ethyl)acrylamide (1d) This compound was synthesized from 4-(2-aminoethyl)nitrobenzene (1 g, 6.0 mmol) in the same way as described for the preparation of **1c**. Yield, 0.45 g (42%). mp 143–144 °C. IR (KBr) cm^{-1} : 1660 (–CONH–), 1620 (H₂C=CH–). ¹H-NMR (270 MHz, CDCl₃) δ : 2.99 (2H, t, *J* = 7.0 Hz, Ar-CH₂–), 3.63 (2H, q, *J* = 7.0 Hz, –CH₂–N), 5.65 (1H, d, *J* = 9.9 Hz, H₂C=), 5.80 (1H, br, –CONH–), 6.06 (1H, dd, *J* = 9.9 and 16.0 Hz, C=CH–), 6.28 (1H, d, *J* = 16.0, H₂C=), 7.37–8.16 (4H, m, Ar-H). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 272.0 (10000). MS *m/z*: 220 (M⁺). Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.26; H, 5.55; N, 12.63.

4-Hydroxy-3-nitrobenzoic Acid To a mixture of 4-hydroxybenzoic acid (0.5 g, 3.6 mmol), NaNO₂ (1 g, 14.5 mmol) and H₂O (1 ml) was added H₂SO₄ (5 ml). The mixture was heated in a steam bath for 30 min, then poured over crushed ice (10 g); the precipitate was filtered, and recrystallized from H₂O to give 4-hydroxy-3-nitrobenzoic acid (0.43 g, 65%). mp 180–181 °C. IR (KBr) cm^{-1} : 1680 (–COOH), 1535, 1335 (–NO₂). ¹H-NMR (270 MHz, DMSO-*d*₆) δ : 7.27 (1H, m, Ar-2), 8.03–8.71 (2H, m, Ar-5 and Ar-6), 11.90 (2H, br, –OH and –COOH). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 350.7 (3700), 236.3 (17000). MS *m/z*: 183 (M⁺). Anal. Calcd for C₇H₅NO₅: C, 45.91; H, 2.75; N, 7.65. Found: C, 46.11; H, 2.79; N, 7.70.

4-Carboxyphenylacrylate (2c) This compound was synthesized from 4-hydroxybenzoic acid (0.5 g, 3.6 mmol) in the manner described for the preparation of **1c**. Yield, 0.5 g (72%). mp 176–177 °C. IR (KBr) cm^{-1} : 1740 (–COO–), 1680 (–COOH). ¹H-NMR (270 MHz, DMSO-*d*₆) δ : 6.18–6.61 (m, 3H, –CH=CH₂), 7.32 (2H, d, *J* = 9.0 Hz, Ar-2 and Ar-6), 8.01 (2H, d, *J* = 9.0 Hz, Ar-3 and Ar-5), 13.04 (1H, br, –COOH). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 234.4 (16000). MS *m/z*: 192 (M⁺). Anal. Calcd for C₁₀H₈O₄: C, 62.50; H, 4.20. Found: C, 62.78; H, 4.07.

4-Carboxy-2-nitrophenylacrylate (2e) To a solution of 4-hydroxy-3-nitrobenzoic acid (0.5 g, 2.7 mmol) and triethylamine (0.3 g, 3.0 mmol) in dry acetonitrile (20 ml) was added dropwise acryloyl chloride (0.3 g, 3.0 mmol) at room temperature. The mixture was stirred at room temperature overnight. After the solvent was evaporated off, CHCl₃ was added to the residue, washed with H₂O, dried over MgSO₄, and evaporated in vacuum. The residue was recrystallized from benzene to give **2e** (0.36 g, 70%). mp 161–162 °C. IR (KBr) cm^{-1} : 1750 (–COO–), 1690 (–COOH), 1530, 1350 (–NO₂). ¹H-NMR (270 MHz, DMSO-*d*₆) δ : 6.22–6.64 (3H, m, H₂C=CH–), 7.45–7.78 (1H, m, Ar-2), 8.36–8.68 (2H, m, Ar-5 and Ar-6), 12.10 (1H, br, –COOH). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 221.3 (25000). MS *m/z*: 237 (M⁺). Anal. Calcd for C₁₀H₇NO₆: C, 50.64; H, 2.97; N, 5.91. Found: C, 50.60; H, 2.99; N, 6.00.

4-(2-Bromoethyl)-3-nitrobenzoic Acid To conc. H₂SO₄ (0.3 g) cooled in an ice bath was added a mixture of 4-(2-bromoethyl)benzoic acid (0.2 g, 0.87 mmol) and sodium nitrate (0.18 g, 2 mmol). The reaction mixture was stirred for 30 min at 5–10 °C, and poured over 10 g of ice. The precipitate was collected, washed with H₂O, and recrystallized from benzene to give 4-(2-bromoethyl)-3-nitrobenzoic acid (0.18 g, 76%). mp 145–146 °C. IR (KBr) cm^{-1} : 1680 (–COOH), 1530, 1360 (–NO₂). ¹H-NMR (270 MHz, CDCl₃) δ : 3.55–3.74 (4H, m, –CH₂CH₂–), 7.59–8.31 (2H, d, Ar-5 and Ar-6), 8.70 (1H, s, Ar-3). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 223.7 (22000). MS *m/z*: 274 (M⁺). Anal. Calcd for C₉H₈BrNO₃: C, 42.96; H, 3.26; N, 4.77. Found: C, 42.79; H, 3.25; N, 4.78.

4-Carboxy-2-nitrostyrene (3e) This compound was synthesized from 4-(2-bromoethyl)-3-nitrobenzoic acid (0.4 g, 1.5 mmol) in the same way as the preparation of **3d**. Yield, 0.2 g (65%). mp 280–281 °C. IR (KBr)

cm^{-1} : 1700 (–COOH), 1530, 1360 (–NO₂). ¹H-NMR (270 MHz, CDCl₃) δ : 5.90–7.30 (3H, m, H₂C=CH–), 8.20–8.80 (3H, m, aromatic proton). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 260.2 (19000). MS *m/z*: 193 (M⁺). Anal. Calcd for C₉H₇NO₄: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.98; H, 3.40; N, 7.02.

Mechanochemical Polymerization Vinyl monomer (100 mg) was mechanically fractured by ball milling according to the method previously reported.⁹⁾

Radical-Initiated Solution Polymerization A solution containing each of vinyl monomer (1 g of **2c**, **2e** and **3e**) with azo-bis-isobutyronitrile (2 mg) in dimethylformamide (10 ml) was carefully degassed and heated for 24 h at 60 °C. The polymer was precipitated into a large amount of methanol and dried in vacuum. Yield, 54% for **2c**, 42% for **2e** and 60% for **3e**.

¹H-NMR Spectral Measurement ¹H-NMR spectra were recorded on a JEOL-JNM-GX270 FT-NMR spectrometer in DMSO-*d*₆. Tetramethyl silane was used as an internal standard. For determination of the polymer conversion, the ¹H-NMR spectra of each of the fractured mixtures were taken after being exposed to air to quench the radicals.

Molecular Orbital Calculation The molecular orbital calculations of vinyl monomers were carried out by the AM1 procedure¹⁸⁾ and the corresponding anion radicals by the UAM1 procedure (AM1 with the UHF formalism¹⁹⁾) with standard parameters as implemented in the MOPAC program (QCPE, No. 549). Full geometry optimization was started with the standard bond lengths and angles.²⁰⁾ The calculations were performed on a FACOM M-780/20 computer at the Computation Center of Nagoya University.

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