A New Development of Mechanochemical Solid-State Polymerization of Vinyl Monomers: Prodrug Syntheses and Its Detailed Mechanistic Study

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ABSTRACT: We describe the first experimental example of mechanochemical polymerization of specially synthesized solid-state monomers, methacryloyl derivatives of bioactive compounds, **1m–3m**. It has been shown, however, that there exists a monomer selectivity for efficiency of such reactions, although all the monomers studied undergo conventional solution polymerizations using radical initiators. The detailed mechanistic implications on the reaction of **1m**, as a representative example, have been clarified based on ESR kinetics on its comparison with that of the corresponding mechanoradical formation of **1p**, the progressive changes in molecular weight distribution including its heterogeneity, and kinetics of the polymer conversion. It has been shown that the mechanochemical polymerization involves a mechanoradical-initiated polymerization as a dominant process, and if one appropriately designs methacryloyl vinyl monomers along the line of the structural criteria derived from the quantum chemical considerations, one can make a variety of solid-state monomers undergo the mechanochemical polymerizations essentially quantitatively. Thus, the present result provides a novel and simple methodology for polymeric prodrug syntheses of low heterogeneity through a totally dry process.

Introduction

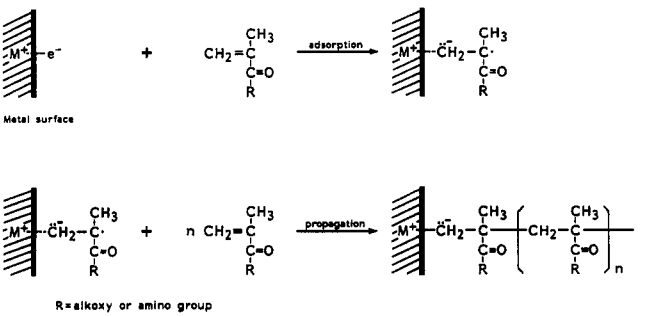
In principle, two distinctly different types of solid-state radical-chain polymerizations are known: radiation-induced polymerization and mechanochemical polymerization. A variety of vinyl monomers undergo radiation-induced solid-state polymerization, but in relatively low yield. One of the noticeable features in these polymerizations is that the monomer crystallinity plays an important role in the efficiency of such reactions, although polymer formation is accomplished by disruption of its crystallinity.[1]

Kargin et al. first reported mechanochemical polymerization of solid-state monomers more than 3 decades ago.[2] Nevertheless, relatively little work has been done with mechanochemical polymerizations in the solid state.[3-7] This may be because most conventional vinyl monomers are liquid at room temperature.[8] Thus, acrylamide (AAm) and methacrylamide (MAAm) are the only well-investigated monomers in such polymerizations, and the earlier investigations were conducted in the presence of inorganic activators such as NaCl, $BaSO_4$, and quartz.[4] It has recently been shown, however, that polyacrylamide (PAAm) and polymethacrylamide (PMAAm) can be obtained in the absence of an activator by vibratory milling in metallic vessels.[5,6] Simionescu et al. have suggested 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 the propagation through a radical-chain polymerization (Scheme I).[5,13]

Most of such research has so far been directed mainly toward synthetic purposes and finding effective operational conditions. The detailed reactions of mechanochemical polymerizations in the solid state have not been worked out, except for our recent work on ESR kinetics in the reaction of AAm,[6] and no attempt has yet been made to obtain functionalized polymers by the mechanochemical polymerization of vinyl monomers.

Development of sustained- and controlled-release systems for drug delivery is one of the most active areas today in the entire field of drug research.[15] Polymeric prodrugs, in which a drug is attached covalently to a polymer backbone and slowly released under appropriate conditions, possess unique properties distinct from those of the corresponding lower molecular weight prodrugs and can be utilized as a sustained-release delivery system. Thus, the chemotherapeutic utility of polymeric prodrugs has been the focus of intense research.[16] The polymeric prodrugs obtained from methacryloyl as well as acryloyl vinyl monomers are especially useful for sustained-release drug delivery, since the drugs are bonded to polymer backbones through hydrolyzable ester and/or amide groups.

Scheme I



We have studied novel mechanochemical polymerizations of several selected specially synthesized vinyl monomers, i.e., methacryloyl derivatives of bioactive compounds such as acetaminophen (**1**; analgesic and antipyretic agent), 7-theophyllineacetic acid (**2**; smooth muscle relaxant), and 5-fluorouracil (5-FU, **3**; antineoplastic agent).

We report for the first time that some appropriately designed methacryloyl derivatives undergo facile mechanochemical solid-state polymerizations to give the corresponding polymeric prodrugs essentially quantitatively. We also provide detailed mechanistic implications of such a reaction of *p*-(methacryloyloxy)acetanilide (**1m**) as a representative example based on the ESR kinetics, molecular weight changes, and rate of monomer consumption as well as the scope and limitations of mechanochemical polymerizations of vinyl monomers derived from the

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quantum chemical considerations.

Experimental Section

p-(Methacryloyloxy)acetanilide (1m). To a solution of acetaminophen (1; 1 g, 6 mmol) and methacryloyl chloride (0.75 g, 7.2 mmol) in dry acetonitrile (60 mL) was added triethylamine (0.73 g, 7.2 mmol). The reaction mixture was stirred for 30 min at room temperature and then evaporated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL). The $CHCl_3$ solution was washed fully with H_2O, dried, and evaporated in vacuo. The residue was recrystallized from benzene to yield 0.8 g (61%) of **1m** as colorless needles: mp 120–121 °C; IR (KBr) 1730, 1660 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 1.99 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 5.88 (s, 1 H, -C=CH-), 6.26 (s, 1 H, -C=CH-), 7.07–7.63 (m, 4 H, phenyl), 10.0 (br, 1 H, amide); UV (ethanol) λ_{max} 273 nm (ϵ 8000); EIMS m/z 219 (M^+). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.53; H, 5.98; N, 6.14.

(Methacryloyloxy)ethyl 7-Theophyllineacetate (2m). To a suspension of potassium theophyllineacetate (2; 0.58 g, 2.1 mmol) in dry dimethylformamide (DMF; 20 mL) was added 1-chloro-2-(methacryloyloxy)ethylene (0.4 g, 2.7 mmol). The reaction mixture was heated at 100 °C for 5 h and then evaporated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL). The solution was washed with H_2O (20 mL), dried, and evaporated in vacuo. The residue was recrystallized from methanol to yield 0.48 g (65%) of **2m** as colorless plates: mp 125–126 °C; IR (KBr) 1745, 1710, 1695, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3 H, CH_3), 3.38 (s, 3 H, CH_3), 3.60 (s, 3 H, CH_3), 4.40–4.46 (m, 4 H, $-OCH_2CH_2O$), 5.12 (s, 2 H, $-NCH_2CO$), 5.61 (s, 1 H, $-C=CH_2$), 6.12 (s, 1 H, $-C=CH_2$), 7.60 (s, 1 H, theophylline ring); UV (ethanol) λ_{max} 244 nm (ϵ 13 500); EIMS m/z 350 (M^+). Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 15.99. Found: C, 51.48; H, 5.24; N, 15.87.

1-[(Methacryloyloxy)methyl]-5-fluorouracil (3m).[17] The mixture of 5-FU (3; 0.5 g, 3.8 mmol) and 37% formalin (0.8 g, 9.6 mmol) was stirred for 30 min at 60 °C, and then excess formalin was evaporated off in vacuo to give 1,3-bis(hydroxymethyl)-5-fluorouracil as viscous oils. To a solution of dry acetonitrile (6 mL) containing crude 1,3-bis(hydroxymethyl)-5-fluorouracil without further purification was added methacryloyl chloride (0.4 g, 3.8 mmol), hydroquinone (20 mg), and triethylamine (0.75 g, 7.4 mmol), and the mixture was stirred at room temperature overnight. After the solvent was evaporated off, methylene chloride (35 mL) was added to the residue, washed with 1 N hydrochloric acid (35 mL) twice and water, and dried over $MgSO_4$. After the solvent was evaporated off, the residue was chromatographed over silica gel (Wakogel C300) in ethyl acetate and *n*-hexane (1:1) as an eluent. The eluated product was further recrystallized from methylene chloride and *n*-hexane (ca. 1:1) to yield 0.2 g (23%) of **3m**: mp 116–117 °C; IR (KBr) 3200 (N-H), 3075 (-CH=CF), 1720 (-OC=O), 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.96 (s 3 H, CH_3), 5.74 (s, 3 H, $-CH_2-$ and =CH-), 6.24 (s, 1 H, =CH-), 7.70 (d, J = 5.5 Hz, 1 H, -CH=CF-), 9.51 (s, 1 H, -CONH); EIMS m/z 220 (M^+). Anal. Calcd for $C_9H_9N_2O_4F$: C, 47.37; H, 3.97; N, 12.28. Found: C, 47.24; H, 4.04; N, 12.18.

1-Methacryloyl-5-fluorouracil (3n).[18] The mixture of 5-FU (3; 0.5 g, 3.8 mmol) and hexamethyldisilazane (3 mL) was refluxed for 5 h. After excess hexamethyldisilazane was evaporated off in vacuo, the viscous residue was rinsed twice with dry benzene (3 mL) and dried in vacuo. To a solution of dry acetonitrile (30 mL) containing 2,4-bis(trimethylsilyl)-5-fluorouracil without further purification was added methacryloyl chloride (1 g, 9.6 mmol), and the mixture was stirred at room temperature for 30 min. After the solvent and excess methacryloyl chloride was thoroughly evaporated off, the residual solid was recrystallized from dry benzene to yield 0.35 g (46%) of **3n**: mp 146–147 °C; IR (KBr) 1730, 1720, 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 2.05 (s, 3 H, CH_3), 5.57 (s, 1 H, $-C=CH_2$), 5.63 (s, 1 H, $-C=CH_2$), 7.86 (d, J = 5.9 Hz, 1 H, -CH=CF-), 12.10 (br, 1 H, -CONH); EIMS m/z 198 (M^+). Anal. Calcd for $C_8H_7N_2O_3F$: C, 48.49; H, 3.61; N, 13.99. Found: C, 48.49; H, 3.56; N, 14.14.

Radical-Initiated Solution Polymerization. For **1p**, a monomer, **1m** (0.65 g, 3.0 mmol), and benzoyl peroxide (5 mg, 0.02 mmol) in dioxane (4 mL) were warmed at 60 °C in a sealed glass-made tube under nitrogen for 40 h. After DMF (2 mL) was added, the content was poured into a large amount of methanol. The precipitated polymer was collected and dried in vacuo to yield 0.23 g (35%) of **1p**: IR (KBr) 3300, 1740, 1665 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (br, 3 H), 2.01 (s, 5 H), 7.00 (br, 2 H), 7.53 (br, 2 H), 9.89 (br, 1 H). For **2p**, a monomer, **2m** (0.5 g, 1.4 mmol), and azobis(isobutyronitrile) (AIBN; 3 mg, 0.02 mmol) in DMF (10 mL) were warmed at 60 °C for 90 h in a manner similar to that described for **1p**. The content was poured into a large amount of methanol to yield 0.14 g (82%) of **2p**: IR (KBr) 1700, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–1.03 (br, 3 H), 1.90 (br, 2 H), 3.30 (s, 3 H), 4.19 (br, 2 H), 4.40 (br, 2 H), 5.17 (br, 2 H), 7.70 (s, 1 H). For **3p**, a monomer, **3m** (0.35 g, 1.53 mmol), and AIBN (6.5 mg, 0.04 mmol) in benzene (30 mL) were heated at 60 °C for 24 h in a manner similar to that described for **1p**. The content was poured into a large amount of methylene chloride. The precipitated polymer was collected and dried in vacuo to yield 0.25 g (71%) of **3p**: IR (KBr) 3450, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.80–1.05 (br, 3 H), 1.90 (br, 2 H), 5.58 (br, 2 H), 8.11 (br, 1 H), 12.00 (br, 1 H).

General Procedure of Mechanochemical Polymerization. Polycrystalline monomer (100 mg) was mechanically fractured by ball milling (stainless steel ball (6.0 mm ϕ, 890 mg) in a stainless steel twin-shell blender (7.8 mm ϕ, 24 mm long) (Vibrating Mill, Shimadzu Co., Ltd.) at room temperature for a prescribed period of time. A prescribed quantity of the resulting fractured powder was transferred to an ESR tube, which was then sealed and submitted to ESR measurements. All operations were carried out under strictly anaerobic conditions (pure nitrogen atmosphere) in a vacuum glovebox (VG-800, Sanplatec Corp.). This experimental device makes it possible to study the ESR kinetics of mechanochemical polymerizations. For the measurements of NMR spectra and molecular weights of fractured mixtures, the resulting powders were exposed to air immediately after milling and then allowed to stand overnight to quench the peroxy radicals formed.

The temperature of the metallic vessel was quickly raised on vibratory milling to ca. 40 °C (within 1 min) but remained at the same temperature even for a longer vibratory milling. The reaction procedure using a Teflon vessel (7.8 mm ϕ, 24 mm long) and ball (6.0 mm ϕ, 290 mg) is the same as that described for the metallic vessel. The mechanoradical formation of each polymer (100 mg), **1p–3p**, was carried out in the same manner as described above.

^1H NMR Spectral Measurement. ^1H NMR spectra were recorded on a JEOL JNM-GX270 FT-NMR spectrometer in either DMSO-d_6 or $CDCl_3$. TMS was used as an internal standard. For determination of the rate of polymer conversion, the ^1H NMR spectra of each of the fractured mixtures were taken after being exposed to air to quench the radicals.

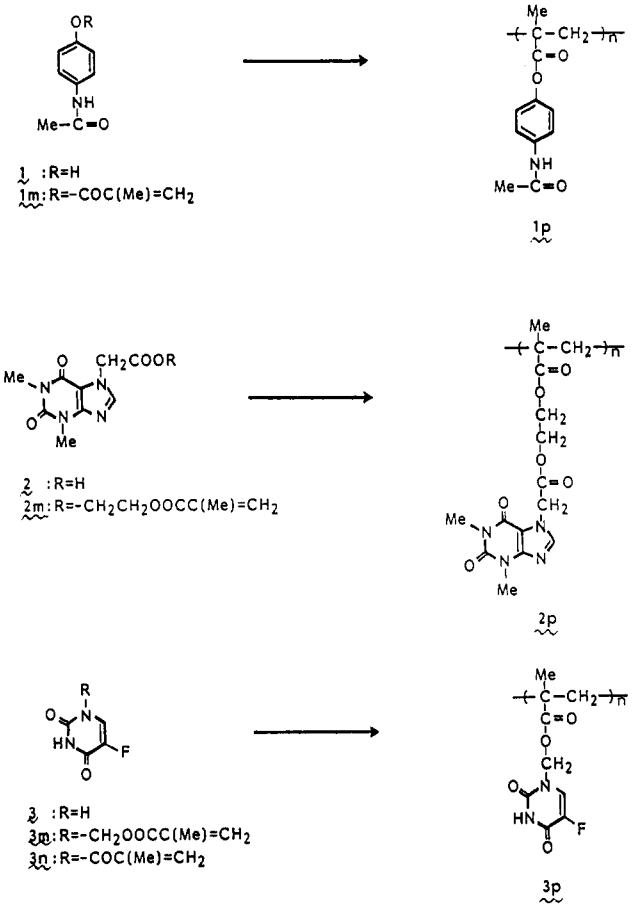
X-ray Diffraction Spectral Measurement. X-ray powder diffraction patterns were measured on Rigaku RAD-IC with Cu Kα radiation.

ESR Measurements. The ESR spectra were recorded on a JEOL JES-RE1X spectrometer with X-band and 100-kHz field modulation, and the microwave power level was kept at less than 0.04 mW, since power levels higher than this began to produce saturation effects in the spectra. The spectral intensity was determined by double integration. The radical concentration (spin number/gram) was calculated from the spectral intensities with the aid of a calibrated line obtained from the spectral intensities of poly(methyl methacrylate) (PMMA) samples impregnated with DPPH. Measurements of g-values were made relative to the fourth signal from the lower magnetic field (g = 1.981) of Mn^{2+} in MgO. The computer simulations were performed according to the method previously reported.[19]

Molecular Weight Measurement. The progressive changes in molecular weight were monitored by a gel permeation chromatograph (GPC; Shimadzu LC-6A) equipped with a refractive index detector (Shimadzu, RID-6A), gel column (Shodex KD-800M and KD-80M), and a data analyzer (Shimadzu, Chromatopac C-R4A), under the following conditions: elution solvent, DMF containing 10 mmol of LiBr; flow rate, 0.7 mL/min; column temperature, 40 °C. Calibration was carried out with a standard specimen of poly(ethylene oxide).

Molecular Orbital Calculation. The molecular orbital calculations of methacryloyl compounds were carried out by the AM1 procedure[20] and the UAM1 procedure (AM1 with the UHF formalism[21]) as implemented in the MOPAC program (QCPE, No.

Scheme II



549). Full geometry optimization was started from the C_s symmetry with the standard bond lengths and angles.[22] The potential energy surface of **1m** was obtained as a function of rotations about two carbon–carbon single bonds within the *s*-trans isomer of the methacryloyl component. The calculations were performed on a FACOM M-780/20 computer at the Computation Center of Nagoya University.

Results and Discussion

Mechanochemical Polymerization. Mechanochemical polymerizations of four kinds of polycrystalline vinyl monomers derived from three types of bioactive compounds, **1**–**3** (Scheme II) were carried out in a metallic twin-shell blender for 45 min at room temperature under strictly anaerobic conditions, according to the method described in the Experimental Section.

The polymer conversion of each fractured mixture was determined by observing the disappearance of vinyl protons and the appearance of the corresponding alkyl protons of the polymer in the ^{1}H NMR spectra of the resulting fractured powders.

The results demonstrate that there exists a selectivity for efficiency of the mechanochemical polymerizations; three vinyl monomers, **1m**–**3m**, underwent mechanochemical solid-state polymerizations to give the corresponding polymers essentially quantitatively. This eliminates the need for any workup such as is required in reactions in the liquid state. The spectroscopic data (IR and ^{1}H NMR) for the polymers thus obtained were identical with those obtained by solution polymerizations using a conventional radical initiator in all cases. The X-ray diffraction of these polymers did not exhibit any peak for the crystallinity shown in the monomers but shows only halo patterns so that the resulting polymers are all amorphous. The monomer **3n**, however, did not undergo mechanochemical polymerization to a detectable extent. This is in sharp contrast to the fact that all these methacryloyl derivatives have been shown to undergo solution polymerizations using conventional radical initiators.

We have also attempted the mechanochemical polymerization of **1m** using a Teflon blender under anaerobic conditions or a metallic blender under aerobic conditions. There was no evidence of polymer formation in either case.

Quantum Chemical Considerations for Mechanically Polymerizable Methacryloyl Monomers. The methacryloyl moieties of **2m** and **3m** are electronically isolated from the conjugated π-moiety of the ester substituent (theophylline in **2m** and 5-FU in **3m**) through alkyl groups, so that they are essentially identical with those of conventional monomers such as AAm and MAAm in structural terms. It is understandable for them to undergo mechanochemical polymerizations as readily as conventional monomers.

Thus, in light of the observed monomer selectivity in mechanochemical polymerizations, we have examined the nature of the electronic structure of monomers, **1m** and **3n**. The monomer of 7-methacryloyltheophylline (**4n**) was also calculated as a structurally related compound of **2m**.

The mechanochemical polymerization of vinyl monomers in a metallic vessel is initiated by the formation of anion radicals produced by an electron transfer from the activated metal surface (vide supra).[5] An electron affinity (E_a) of the molecule is a measure of the feasibility of an electron transfer to the molecule, the E_a can be approximated to the energy of lowest unoccupied molecular orbital (LUMO) in MO terms. Thus, it is important to understand the nature of LUMO for the capability of anion-radical formations.

Figure 1 shows the energies and coefficients (eigenvectors) of lower lying π-type unoccupied molecular orbitals in the equilibrium geometries of **1m**, **3n**, and **4n** calculated from the AM1 wave functions, together with those of methacrylic acid (MAA) and AAm for comparisons with the same level of approximation.

It is seen that the LUMO's are all lower in energy than those of MAA and AAm so that they should have no difficulty in forming the corresponding anion radicals. However, the LUMO's polarizations, which should correspond to the spin density distribution in the resulting anion radicals,[23] vary with compounds due to the very large conformational difference in the equilibrium geometries. The LUMO's coefficient of **1m** (ψ_{43}*) is considerably polarized to the methacryloyl component. As a result, the anion radical formed should be capable of undergoing the ensuing radical-chain polymerization of the vinyl group, accounting for the occurrence of the mechanochemical polymerization of **1m** as experimentally observed. On the other hand, in **3n** and **4n**, in which the six- and five-membered cyclic rings as ester substituents are directly bonded with the methacryloyl carbonyl group, the LUMO's coefficients (ψ_{38}* for **3n** and ψ_{48}* for **4n**) are completely localized to such ester components, as opposed to the situation for **1m**, apparently due to orthogonality between the methacryloyl vinyl bond and the rest of the molecule in their equilibrium geometries. Further, in the lower lying π-type unoccupied molecular orbitals of **3n** and **4n**, the orbitals that are polarized to the methacryloyl vinyl bond with the same nodal property lie at a much higher energy level (ψ_{41}* for **3n** and ψ_{51}* for **4n**) than those of MAA and AAm.

Although it is conceivable from the examination of molecular models that the planar geometry of **3n** could cause severe steric hindrance between the two components, the methacryloyl vinyl hydrogen and the uracil ring (either of 2-carbonyl oxygen or 6-hydrogen), the calculated equilibrium geometry with out-of-plane deformation in the

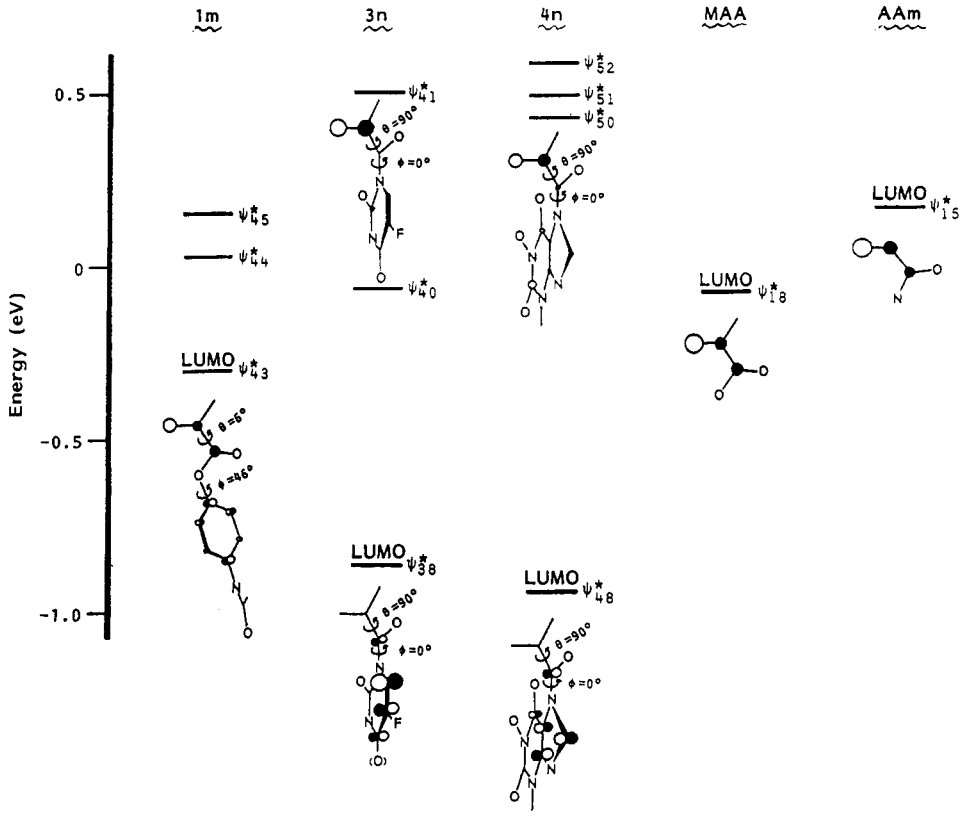


Figure 1. Energies and coefficient distributions of lower lying π-type unoccupied molecular orbitals in the equilibrium geometries calculated by the AM1 method.

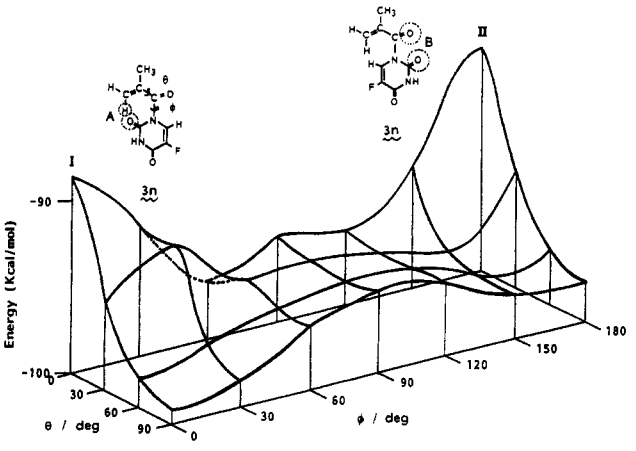


Figure 2. Potential energy surface of **1m** as a function of rotations about two carbon–carbon single bonds evaluated by the AM1 method.

methacryloyl component (Figure 1) is rather unexpected. Therefore, we have further inspected the potential energy surface of **3n** with respect to the rotational conformers within the *s*-trans isomer of a methacryloyl moiety, and the result is shown in Figure 2.

In fact, the planar geometry of either I or II has been shown to be very unstable. The high core-repulsive contribution at A for I and electron-repulsive contribution at B for II (Figure 2) are responsible for their destabilizations, respectively. It also became apparent that an energy optimization in the equilibrium geometry of **3n** is the consequence of greater stabilizing energy gain due to the full π–π interaction between the methacryloyl carbonyl group and a uracil ring ($H_f(\theta=90°$ and $\phi=0°) - H_f(\theta=\phi=90°) = 4.11$ kcal/mol), while the same energy loss due to disruption of planarity of the methacryloyl group was negligible ($H_f(\theta=0°$ and $\phi=90°) - H_f(\theta=\phi=90°) \approx 0$ kcal/mol). A similar situation has also been shown in **4n** from the result of the calculated potential energy surface.[24]

Thus, we believe that this kind of electronic structural feature is the essential reason for the failure of the mechanochemical polymerization of **3n**.[25] It can be predicted that **4n** would also be unreactive in the mechanochemical polymerization. It should be noted, however, that this view does not exclude the reactivity for the radical-initiated solution polymerization of **3n**, as experimentally observed, since the reactivity of a vinyl bond with free radicals should be considered distinct in nature from the formation of the corresponding anion radical by electron transfer.

These results suggest, in turn, that introduction of some spacer groups between the methacryloyl group and ester substituent makes it possible to undergo mechanochemical polymerizations of a wide variety of methacryloyl vinyl monomers.

ESR Spectrum Observed in Mechanochemical Polymerization. In order to gain fundamental insight into the nature of mechanochemical polymerizations of these monomers, the detailed mechanistic implications of **1m** were explored as a representative example.

Figure 3 shows the ESR spectra of the radical produced in the course of mechanochemical polymerization of **1m**. The spectral feature remained unchanged at various stages of vibratory milling, which is most characterized by five major lines with four shoulders ("nine-line spectrum"). Virtually identical spectra were also obtained in polymerizations of the other two monomers, **2m** and **3m**. We believe that this is the first observation of well-defined ESR spectra of the radicals observed in mechanochemical solid-state polymerizations of methacrylic monomers.

Because of the abnormal intensity distribution in the nine-line spectra observed in various types of reactions, such spectra have long been the subject of much discussion.[26] It is now well established that the standard nine-line spectra of the radicals in radiation-induced low-temperature solid-state polymerizations (77 K) of MMA and closely related methacrylic monomers consist of a single end-chain radical, $-CH_2\dot{C}(COOR)(CH_3)$.[27]

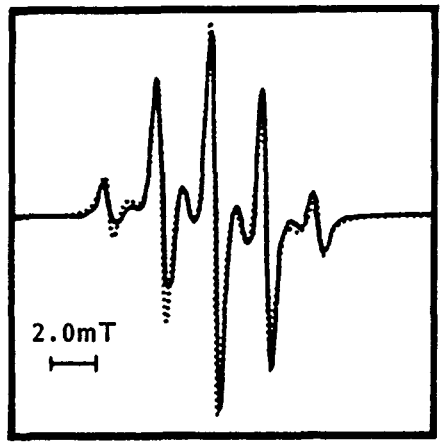


Figure 3. ESR spectrum observed in mechanically fractured **1m** and the corresponding simulated spectrum shown as a dotted line.

We note, however, that the ESR spectra of the radicals produced in plasma-irradiated PMMA and the structurally related polymers have recently been shown to be outlines of multicomponent spectra including the nine-line spectrum.[19]

The present ESR spectrum is essentially identical with those of mechanoradicals obtained from methacrylic polymers such as polymethacrylic acid (PMAA) and its methyl ester (PMMA).[28-30] Furthermore, we have also carried out mechanoradical formation of polymers, **1p**–**3p**, obtained by conventional radical-initiated solution polymerizations of **1m**–**3m**. The ESR spectra of the mechanoradicals thus obtained were all identical with the spectra shown in Figure 3. It is now firmly established from the mechanistic study at 77 K that the mechanism by which mechanoradicals are formed involves main-chain scission to give initially two different radicals.[28] For instance, the mechanical fracture of PMMA gives an end-chain radical, $-CH_2\dot{C}(COOR)(CH_3)$, and a primary alkyl radical, $-C(COOR)(CH_3)\dot{C}H_2$. However, the latter radical has been shown to be quite unstable, undergoing rearrangement above 140 K to the corresponding secondary midchain radical, followed by the termination reactions.[29]

Thus, the radical in the ESR spectra (Figure 3) can be unambiguously assigned to a single end-chain radical (equivalent to a propagating radical) (vide infra). The simulated spectrum shown in Figure 3 as a dotted line also supports this conclusion. It is seen that the observed spectrum has been nicely reproduced by the simulated spectrum, which gives the following spectroscopic parameters: g-value = 2.0037, HSC; $a_{H_\beta}(1) = 1.33$, $a_{H_\beta}(2) = 0.98$, and $a_{Me} = 2.24$ mT.

ESR Kinetics of the Radicals Formed in Reaction of 1m. Figure 4 shows the progressive changes in the radical concentration of the ESR spectra in the course of the mechanochemical polymerization of **1m**, together with those of the mechanoradical formation of the polymer, **1p**.

It is seen that both line features are similar in nature to each other, but the maximum value of **1p** appears earlier than that of **1m**. This is apparently due to the presence of time lag (ca. 5 min) in the case of **1m** (vide infra). After reaching the maximum value, the radical concentrations gradually decrease in both cases. Separate experiments have shown that these radicals are thermally stable for a long period at 40 °C (see the Experimental Section) so that the decrease in the radical concentration must be caused by the vibratory milling.

This is in sharp contrast to the progressive changes in the radical concentration of mechanoradical formation in PAAm[6] and PMAAm.[30] The radical formation in PAAm and PMMAm did not exhibit the maximum value but showed a parabolic increase in the course of vibratory milling. This discrepancy can be rationalized in terms on the basis that the mechanoradicals of PAAm and PMAAm are strongly stabilized by intrinsic inter- and intramolecular doubly hydrogen-bonding interactions among the amide groups directly bonded with the polymer main chain.

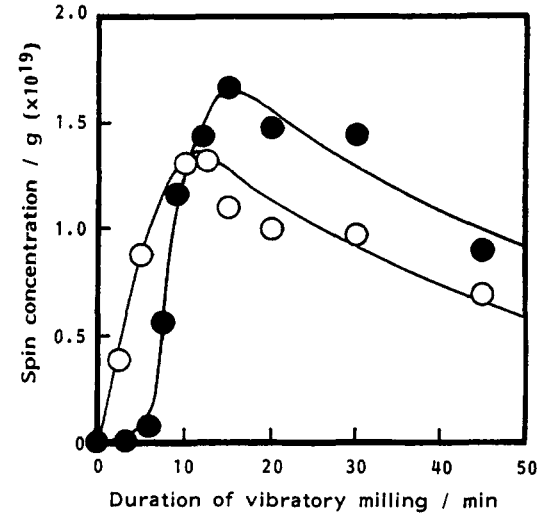


Figure 4. Progressive changes in radical concentration in the course of vibratory milling: (●) mechanochemical polymerization of **1m**; (○) mechanoradical formation of **1p**.

Progressive Changes in Molecular Weight and Its Heterogeneity. Gel permeation chromatograms (GPC) at various stages of vibratory milling of **1m** and **1p** are shown in Figure 5.

It is seen from parts A and B of Figure 5 that the progressive changes in GPC are similar, although undegraded **1p** is of a rather broad molecular weight distribution. We note that GPC of **1p** does not show the bimodal nature of the distribution (such as those having original higher molecular weight and degraded lower molecular weight) in the course of polymer degradation but shows only a broadened one-component curve. This indicates that mechanical fracture of **1p** may cause the rather random polymer main-chain scission.

Figure 6 shows the progressive changes of the number-average molecular weight ($\bar{M}_n$) of the polymer formed in mechanochemical polymerization of **1m**, together with progressive changes of $\bar{M}_n$ in mechanical fracture of **1p**. It is seen that, in the reaction of **1m**, the maximum molecular weight appeared at ca. a 5-min duration of vibratory milling, while the progressive changes in **1p** exhibited a simple decay toward a limiting value.

The heterogeneity ($H = \bar{M}_w/\bar{M}_n$), however, behaves differently as shown in Figure 7. The index H in the reaction of **1m** continues to increase for ca. a 10-min milling ($H = 1.398$ for a 9-min milling) and then tends to decrease toward the limiting value ($H = 1.078$ for 45 min), while the index H ($H = 1.928$) in the reaction of **1p** exhibited a simply decay, due to the broad molecular weight distribution of undegraded **1p**, toward a similar limiting value ($H = 1.100$ for a 45-min milling), which is nearly the same as that of **1m**.

It should be mentioned here that the exceptionally low H values (far less than 2) of fractured polymers from **1m** and **1p** is unusual, though not unprecedented.[31] On the basis of the available data, we cannot provide any definitive reason at present, and even from a theoretical basis, there is no single and simple criterion for random scission of a polymer chain that will cover every situation.[32] It can be assumed, however, that bulky substituents bonded to the main chain of the present polymer (polymer's stereochem-

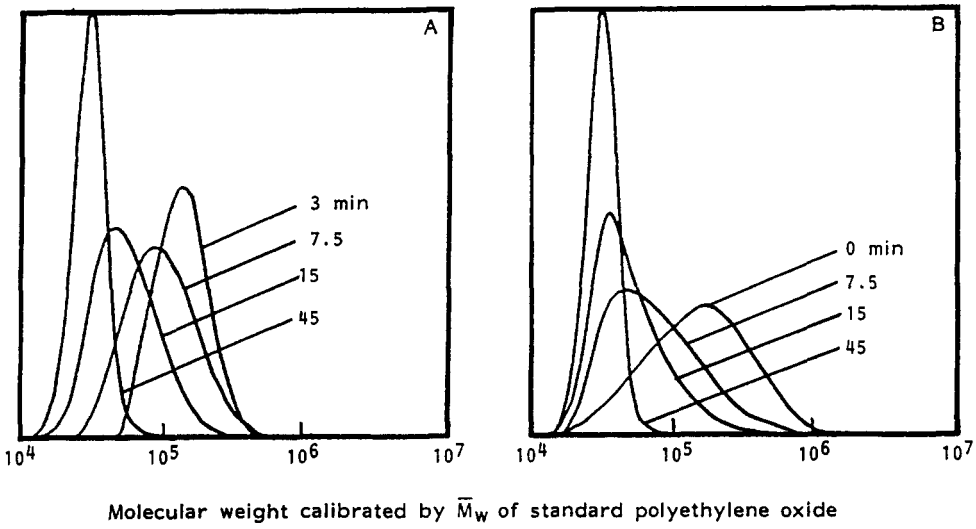


Figure 5. Gel permeation chromatograms (GPC) at various stages of vibratory milling of **1m** (A) and **1p** (B).

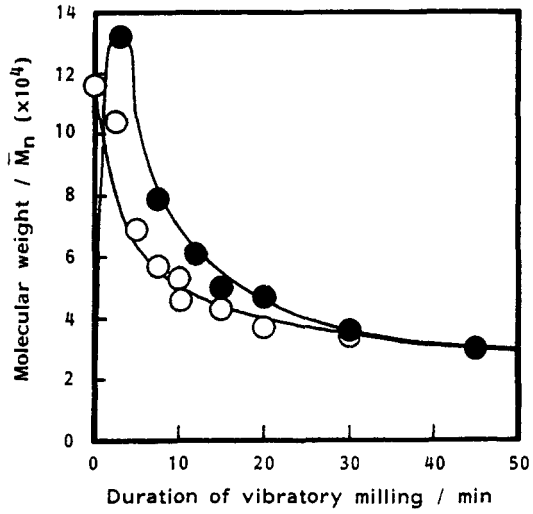


Figure 6. Progressive changes in molecular weight ($\bar{M}_n$) in the course of vibratory milling: (●) mechanochemical polymerization of **1m**; (○) mechanical fracture of **1p**.

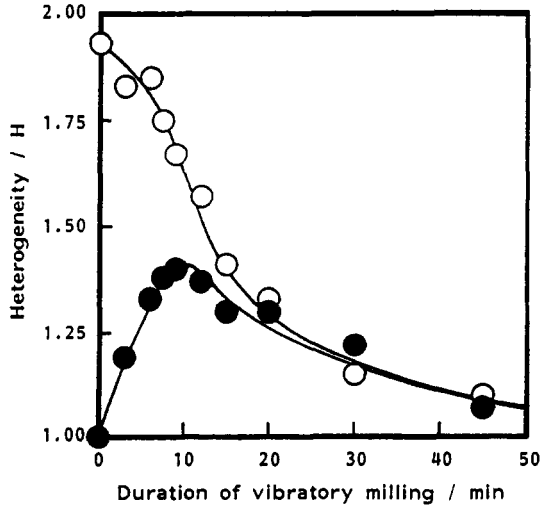


Figure 7. Progressive changes in heterogeneity in the course of vibratory milling: (●) mechanochemical polymerization of **1m**; (○) mechanical fracture of **1p**.

istry) as well as a highly powerful mechanical force may contribute to this specificity.

The appearance of the maximum molecular weight at such a short duration of vibratory milling of **1m** provides an additional insight into the mechanistic implication of mechanochemical polymerizations; i.e., the propagation

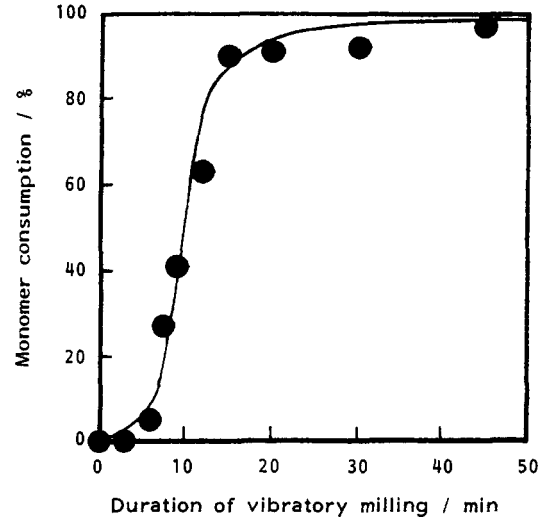


Figure 8. Progressive changes in polymer conversion (monomer consumption) in the course of vibratory milling of **1m**.

rate is very high, and the propagating radicals are rapidly terminated to give polymers of higher molecular weight. This captures the essential reason for the increase in index *H* for an earlier stage of the reaction of **1m** when the unreacted monomer still exists, since the polymer degradation begins to occur immediately after the polymer was formed. Thus, the molecular weight also begins to decrease exponentially toward a limiting value, below which a polymer will not be further degraded.

Therefore, most of radicals observed in the course of the mechanochemical polymerization of **1m** can be considered to be the mechanoradicals in nature, not the propagating radicals (identical with each other in ESR). This concomitantly accounts for the presence of ca. a 5-min time lag followed by the steep increase in the radical concentration in the reaction of **1m** (Figure 4), since the formation of mechanoradicals is a characteristic feature of polymers.

Polymer Conversion. Figure 8 shows plots of the monomer consumption as a function of the duration of the vibratory milling of **1m**. The rate of monomer consumption was monitored by the decay of the olefinic protons of monomers as well as the corresponding growth of the alkyl protons of polymers in the ^{1}H NMR spectra of the fractured mixtures (vide supra).

It is seen that the kinetics of monomer consumption exhibited a sigmoid curve (well fitted with a logistic curve) with ca. a 5-min time lag, and the monomer consumption

has been nearly completed in ca. 15 min of vibratory milling when the radical concentration reaches a maximum value (Figure 4). In other words, the radical concentration increases while the unreacted monomer continues to produce the polymers.

In accord with the conclusion described in a previous subsection, the presence of time lag in Figure 8 also indicates that the polymerization initiated through the anion radical is only a minor process in the mechanochemical polymerization of **1m**, though indispensable to initiate, and the steep increase in the rate of monomer consumption with lowering of the molecular weight of the polymer formed (as well as the same increase in the radical concentration) can be ascribed to the occurrence of a very dominant "mechanoradical-initiated polymerization".[12]

This mechanistic view was further substantiated with the following experimental observations; in the vibratory milling of **1m** in the presence of an equal amount of **1p** using a Teflon twin-shell blender for 45 min under otherwise identical conditions, **1m** did undergo the mechanochemical polymerization.[33] This polymerization is obviously induced by the mechanoradicals formed from **1p**, since **1m** is unreactive in a Teflon blender (vide supra), reinforcing the above-mentioned conclusion.

Conclusions. The conclusion drawn from the present study can be summarized as follows. We have presented the first example of mechanochemical polymerization of solid-state vinyl monomers derived from bioactive compounds, **1m–3m**. A monomer selectivity for efficiency of such reactions has been shown, although all the monomers studied undergo conventional radical-initiated solution polymerizations. Combined data of kinetics on the radical concentrations, molecular weight distribution, and polymer conversion of **1m** studied as a representative example enabled us to clarify the precise nature of this type of reaction. Thus, if one prepares the monomers along the line of the structural criteria derived from the quantum chemical considerations, the present reactions seem applicable to a wide variety of methacryloyl derivatives of an important class of bioactive compounds with different physicochemical properties.

The present result is not only of interest on its own right but also provides a novel methodology for simple polymeric prodrug syntheses through a totally dry process. Of more importance is the fact that the resulting polymers are of lower heterogeneity, which is of great value for highly functionalized polymeric prodrug syntheses, and we believe the result reported here will spark new interest in this research area. The nature of hydrolyses of the resulting polymeric prodrugs will be the subject of a forthcoming paper and is reported elsewhere.

References and Notes

(1) (a) Restaino, A. J.; Mesrobian, R. B.; Morawetz, H.; Ballantine, D. S.; Dienes, G. J.; Metz, D. J. *J. Am. Chem. Soc.* **1956** *78*, 2939. (b) Adler, G.; Ballantine, D.; Baysal, B. *J. Polym. Sci.* **1960**, *48*, 195. (c) Sobue, H.; Tabata, Y. *J. Polym. Sci.* **1960**, *43*, 459. (d) Alder, G.; Petropoulos, J. H. *J. Phys. Chem.* **1965**, *69*, 3712. (e) Morosoff, M.; Morawetz, H.; Post, B. *J. Am. Chem. Soc.* **1965**, *87*, 3035. (f) Shibasaki, Y.; Fukuda, K. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 443. (g) Lando, J. B.; Morawetz, H. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 789. (h) Stannett, V.; Silverman, *J. ACS Symp. Ser.* **1983**, *212*, 435–447 and references therein.

(2) Kargin, V. A.; Plate, N. A. *Vysokomol. Soedin.* **1959**, *1*, 330.

(3) Kargin, V. A.; Kobanov, N. I.; Popoport, N. I. *Vysokomol. Soedin.* **1961**, *3*, 787.

(4) Plate, N. A.; Kargin, V. A. *J. Polym. Sci., Part C* **1963**, *4*, 1027.

(5) Simionescu, C.; Oprea, C. V.; Nicoleanu, J. *Eur. Polym. J.* **1983**, *19*, 525.

(6) Kuzuya, M.; Kondo, S.; Noguchi, A.; Noda, N. *J. Polym. Sci., Polym. Chem. Ed.* **1991**, *29*, 489.

(7) For mechanochemical reactions of AAm and MAAm in solid solutions at high pressures, see also: (a) Ogo, Y.; Nishiguchi, N.; Okuri, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 520. (b) Okuri, Y.; Ogo, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 645. (c) Okuri, Y.; Ogo, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 647.

(8) In fact, the mechanochemical polymerizations of several conventional monomers in the liquid phase are known under a variety of conditions: (a) in the presence of inorganic catalysts by vibratory milling[9] and (b) in the presence of other polymers by either vibratory milling[10] or ultrasonic irradiation.[11] In the case of a, the polymers obtained are paramagnetic (evidenced by ESR) due to inorganic catalysts included in the resulting polymers. In the case of b, the polymers obtained are the block and graft copolymers, since initially presented polymers give the mechanoradicals first, which then initiate the polymerizations of the monomers, i.e., "mechanoradical-initiated polymerization".[12]

(9) (a) Plate, N. A.; Stroganov, L. B.; Uzhinova, L. D.; Golubev, V. B.; Nedorezova, P. M. *Vysokomol. Soedin., Ser. A* **1972**, *14*, 440. (b) Oprea, C. V.; Popa, M.; Dumitriu, S. *Angew. Makromol. Chem.* **1988**, *93*, 268 and references therein.

(10) (a) Neguleanu, C.; Oprea, C. V.; Simionescu, C. I. *Makromol. Chem.* **1974**, *175*, 371. (b) Simionescu, C. I.; Crusos, A. *Rev. Roum. Chim.* **1976**, *21*, 1237. (c) Hon, D. N. S. *ACS Symp. Ser.* **1983**, *212*, 259–279. (d) Simionescu, C. I.; Oprea, C. V. *Mater. Plast. (Bucharest)* **1983**, *20*, 69.

(11) Fujiwara, H.; Goto, K. *Polym. Bull. (Berlin)* **1990**, *23*, 27 and references therein.

(12) Sakaguchi, M.; Sohma, J. *J. Appl. Polym. Sci.* **1978**, *22*, 2915.

(13) Quite an unusual tribopolymerization has been reported on 9-ethyl-3-vinylcarbazole. This polymerization took place by the mechanical stress in air, and the excited singlet state was tentatively considered to be responsible for this polymerization.[14]

(14) Inoue, T.; Tazuke, S. *Chem. Lett.* **1981**, 589.

(15) Sanders, H. J. *C&EN* **1985**, *April 1*, 30.

(16) Sinkula, A. A. In *Design of Prodrugs*; Bundgaard, H., Ed.; Elsevier Science Publishers: Amsterdam, The Netherlands, 1985; pp 157–176.

(17) Ozaki, S.; Nagase, T.; Watanabe, Y.; Onishi, J. Japan Kokai Tokkyo Koho JP0161,467 [8961,467].

(18) Akashi, M.; Tanaka, Y.; Miyazaki, T.; Miyauchi, N. *J. Bioact. Compat. Polym.* **1987**, *2*, 120.

(19) Kuzuya, M.; Noguchi, A.; Ishikawa, M.; Koide, A.; Sawada, K.; Ito, A.; Noda, N. *J. Phys. Chem.* **1991**, *95*, 2398.

(20) Dewar, M. J. S.; Zoebisch, E. G.; Healy, F. E.; Stwart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(21) Pople, J. A.; Nesbet, R. K. *J. Chem. Phys.* **1954**, *22*, 571.

(22) Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970; p 111.

(23) This has been, in fact, verified by the open-shell UAM1 calculations of the corresponding anion radicals.[24]

(24) The detailed account of molecular orbital calculations for more generalized criteria for mechanically polymerizable vinyl monomers will be reported later in a separate paper dealing only with that subject.

(25) The study on the X-ray structure of a crystalline state is in progress.

(26) Kamachi, M. *Adv. Polym. Sci.* **1987**, *82*, 207.

(27) (a) O'Donnel, J. H.; McGarvey, B.; Morawetz, H. *J. Am. Chem. Soc.* **1964**, *86*, 2322. (b) Bowden, M. J.; O'Donnel, J. H. *J. Phys. Chem.* **1968**, *72*, 1577.

(28) Sohma, J.; Sakaguchi, M. *Adv. Polym. Sci.* **1976**, *20*, 109 and references therein.

(29) Pilar, J.; Ulbert, K. *J. Polym. Sci., Polym. Phys. Ed.* **1978**, *16*, 1973.

(30) Kuzuya, M.; Kondo, S.; Noguchi, A.; Noda, N. *J. Polym. Sci., Polym. Phys. Ed.*, in press.

(31) Fukunaga, K.; Kimura, M. *Chem. Lett.* **1987**, 1503.

(32) Scott, K. W. *J. Polym. Sci., Symp.* **1974**, *46*, 321.

(33) The reaction proceeded in only 85% completion for 45-min vibratory milling. This is apparently due to the light weight of teflon ball (see the Experimental Section).