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Antimicrobial Activity of *p*-Hydroxyphenyl Acrylate Derivatives

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To estimate the antimicrobial effect of *p*-hydroxyphenyl acrylate (H5) derivatives on the basis of their molecular structure, the hydroxy and acryl groups of *p*-hydroxyphenyl acrylate were modified. The antimicrobial activity of the resulting compounds was assessed against a Gram-positive bacterium (*Staphylococcus aureus*), a Gram-negative bacterium (*Pseudomonas aeruginosa*), and fungi (*Aspergillus fumigatus* and *Penicillium pinphilum*) by the halo zone and the shake flask test. The antimicrobial activity of H5 was ascribed mainly to the acryl group. Compounds with acryl or acryloxy groups bound to the phenyl moiety were found to exhibit particularly high antimicrobial activities. The activities of phenyl acrylate and phenyl vinyl ketone were excellent as compared to aliphatic acrylates such as cyclohexyl acrylate and hexyl acrylate, indicating that the stereoelectronic effect of the phenyl group was important to the antimicrobial activity.

KEYWORDS: Antimicrobial activity; stereoelectronic effect; phenol group; acryl group

INTRODUCTION

There exist many pathogenic bacteria causing food poisoning and infectious diseases (*1*−*5*). Many spore-forming fungi produce toxic and sometimes carcinogenic metabolites and often provoke allergic diseases.

Recently, the human desire for a better living environment has greatly risen, and human beings are no longer tolerant of black rots on wallpaper and on silicone sealing of kitchens and bathrooms. Antimicrobial functions are requested for food-packaging receptacles, hygienic articles, and household electrical appliances. Antimicrobial agents are also needed for the preservation of products such as cutting fluids, foods and beverages, cosmetics, pharmaceutical formulations, and so on (*6*).

Phenols and cationic compounds are two main groups of compounds used almost exclusively for disinfectants (*7*). Quaternary ammonium compounds with alkyl chains are able to kill microorganisms by interacting with the cell membrane (*8*). Phenols damage the cytoplasmic membrane of microbial cells to cause progressive leakage of intracellular materials and finally loss of structural organization and integrity (*6*).

Park et al. (*9*) reported that *p*-hydroxyphenyl acrylate (H5) showed high antibacterial and antifungal activities. The vinyl group in the α,*β*-position to an electronegative group can react with the nucleophilic entities of a microbial cell to exert its antimicrobial action (*10*). The phenol moiety of H5 should also contribute to the antimicrobial action.

In this study, the substitutent groups of H5 were modified, and then, the resulting compounds were subjected to the halo zone tests and the shake flask tests against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, and *Pencillium pinophilum* to investigate the relationship between the molecular structure and the antimicrobial activity of H5.

EXPERIMENTAL PROCEDURES

Materials. *p*-Hydroquinone (H1), allyloxybenzene (A2), hexyl acrylate (A4), and *N*-phenylacrylamide (A6) were commercially available, and other compounds were found in the literature except *p*-acetoxyphenyl acrylate (A8). Tetrahydrofurane (THF, Junsei, Japan) was refluxed for over 8 h in the presence of sodium and benzophenone and was used after the second distillation. Other chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) spectrometer in $CDCl_3$.

Synthesis of *p*-Allyoxyphenol (H2) (*9*). ^{1}H NMR: δ 4.42−4.46 (m, 2H), 5.24−6.08 (m, 3H), 6.73, 6.89 (ABq, 4H).

Synthesis of *p*-Hydroxyphenyl Acetate (H3) (*11*). To a solution of H1 (5.84 g, 53.0 mmol) and triethylamine (10.7 g, 106 mmol) in THF (50 mL) at −30 °C, acetyl chloride (4.16 g, 53.0 mmol) was added dropwise over 20 min. After the mixture was stirred for 2 h, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The resulting solution was washed with water and brine, dried with $MgSO_4$, and concentrated. The oily residue was purified by column chromatography (10% ethyl acetate/methylene chloride) to give an oil (4.19 g, 52%). ^{1}H NMR: δ 2.12 (s, 3H), 5.90 (s, 1H), 6.92, 6.71 (ABq, 4H).

Synthesis of *p*-Hydroxyphenyl Propanoate (H4) (*12*). H4 was prepared as an oil in 51% yield from H1 and propanoyl chloride using the same method for H3. ^{1}H NMR: δ 1.25 (t, 3H), 2.51−2.63 (m, 2H), 4.89 (s, 1H), 6.73−6.81 (m, 2H), 6.88−6.96 (m, 2H).

Synthesis of *p*-Hydroxyphenyl Acrylate (H5) (*9*). H5 was prepared as an oil in 78% yield from H1 and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 5.90 (s, 1H), 5.98−6.65 (m, 3H), 6.72−6.82 (m, 2H), 6.89−6.97 (m, 2H).

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Synthesis of Phenyl Acrylate (A1) (*13*). A1 was prepared as an oil in 95% yield from phenol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 5.97−6.03 (m, 1H), 6.27−6.41 (m, 1H), 6.58−6.68 (m, 1H), 7.12−7.23 (m, 2H), 7.23−7.29 (m, 1H), 7.36−7.45 (m, 2H).

Synthesis of Cyclohexyl Acrylate (A3) (*14*). A3 was prepared as an oil in 94% yield from cyclohexanol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 1.23−1.83 (m, 10H), 4.69−4.83 (m, 1H), 5.68−5.76 (m, 1H), 5.96−6.10 (m, 1H), 6.26−6.36 (m, 1H).

Synthesis of Phenyl Vinyl Ketone (A5) (*15*). To a solution of 1-phenyl-2-propen-1-ol (1.00 g, 7.45 mmol) in acetone (10 mL) was added Jones reagent (3.8 mL, 30.4 mmol) at 0 °C. After the mixture was stirred for 30 min at ambient temperature, the mixture was quenched with isopropyl alcohol and concentrated *in vacuo*. The residue was dissolved into ether, and the resulting solution was washed with water and brine, dried with $MgSO_4$, and concentrated. The oily residue was purified by column chromatography (10% ethyl acetate/hexane) to give an oil (0.82 g, 83%). ^{1}H NMR: δ 5.87−5.93 (m, 1H), 6.37−6.46 (m, 1H), 7.07−7.21 (m, 1H), 7.45−7.58 (m, 3H), 7.91−7.95 (m, 2H).

Synthesis of *p*-Bisacryloxybenzene (A7) (*16*). A7 was prepared as an oil in 87% yield from H5 and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 5.97−6.64 (m, 6H), 7.04 (s, 4H).

Synthesis of *p*-Acetoxyphenyl Acrylate (A8). A8 was prepared as an oil in 85% yield from H3 and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 2.10 (s, 3H), 5.98−6.65 (m, 3H), 6.71−6.92, (m, 4H).

Synthesis of *p*-Ethylphenyl Acrylate (A9) (*17*). A9 was prepared as an oil in 86% yield from *p*-ethylphenol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 1.20 (t, 3H), 2.60 (q, 2H), 5.88−5.94 (m, 1H), 6.20−6.34 (m, 1H), 6.50−6.59 (m, 1H), 6.98−7.04 (m, 2H), 7.13−7.19 (m, 2H).

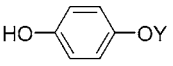
Synthesis of *p*-Dodecylphenyl Acrylate (A10) (*18*). A10 was prepared as an oil in 90% yield from *p*-dodecylphenol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 0.80−1.30 (m, 23H), 2.56−2.69 (m, 2H), 5.92−5.98 (m, 1H), 6.23−6.37 (m, 1H), 6.53−6.63 (m, 1H), 7.03−7.07 (m, 2H), 7.23−7.35 (m, 2H).

Synthesis of Benzyl Acrylate (A11) (*19*). A11 was prepared as an oil in 83% yield from benzyl alcohol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 5.22 (s, 2H), 5.82−5.88 (m, 1H), 6.11−6.25 (m, 1H), 6.42−6.52 (m, 1H), 7.34−7.45 (m, 5H).

Synthesis of 3-Phenylpropyl Acrylate (A12) (*20*). A12 was prepared as an oil in 92% yield from 3-phenyl-1-propanol and acryloyl chloride using the same method for H3. ^{1}H NMR: δ 1.89−2.04 (m, 2H), 2.68 (t, 2H), 4.15 (t, 2H), 5.74−5.80 (m, 1H), 6.03−6.17 (m, 1H), 6.34−6.43 (m, 1H), 7.12−7.29 (m, 5H).

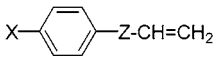
Halo Zone Test. Halo zone tests for microorganisms against the biocides were carried out according to the method of Bauer et al. (*21*). *S. aureus* ATCC 6538P and *P. aeruginosa* ATCC 15522 were subcultured to nutrient agar and incubated overnight at 37 °C. The bacteria were inoculated in 50 mL of nutrient broth medium in a 250 mL flask and cultured for 5 h at 37 °C. Then, the cells were suspended in the same medium to produce a suspension of 10^6 CFU/mL. Agar plates were streaked with a sterile swab moistened with the bacterial suspension. The disks made of filter paper with diameters of 10 mm were exposed to UV for 1 h, and biocides dissolved in dimethyl sulfoxide (DMSO) were spread on the disks in a biosafety cabinet, and then, they were aseptically applied to the surface of the agar plate. All of the test plates were incubated overnight at 37 °C. The susceptibility of microorganisms to the biocides was determined by the size of the growth of the inhibitory zone. The average of three replicates was taken.

Shake Flask Method (*22*). Pure DMSO (0.7 mL) for a control sample or DMSO solution (0.5 g sample/0.7 mL DMSO) was transferred into each wide mouth glass. The number of bacterial cells in the bacteria culture suspension was ca. 3.62×10^6/0.7 mL. After their contact with a sample in diluted phosphate-buffered saline (70 mL), the suspension was incubated at 37 °C for 24 h, and the number of the bacterial cells was calculated by multiplying the number of colonies by the dilution factor. The average of three replicates was taken.



Compound	Y
H1	H
H2	-$CH_2CH=CH_2$
H3	-$C(O)CH_3$
H4	-$C(O)CH_2CH_3$
H5	-$C(O)CH=CH_2$

Figure 1. H1 derivatives.



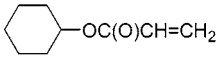
Compound	X	Z
A1	H	-OC(O)-
A2	H	-OCH_2-
A3		
A4	$CH_3(CH_2)_5OC(O)CH=CH_2$	
A5	H	-C(O)-
A6	H	-NHC(O)-
A7	-$OC(O)CH=CH_2$	-OC(O)-
A8	-$OC(O)CH_3$	-OC(O)-
A9	-CH_2CH_3	-OC(O)-
A10	-$(CH_2)_{11}CH_3$	-OC(O)-
A11	H	-$CH_2OC(O)$-
A12	H	-$CH_2CH_2CH_2OC(O)$-

Figure 2. Acryl derivatives.

RESULTS AND DISCUSSION

H5 exhibits not only an antibacterial activity but also an antifungal activity. The vinyl group linked to an electron withdrawing group, which is next to a resonance increasing group such as the phenyl ring, is reported to be responsible for the antimicrobial activity of H5. The phenol moiety of H5 could also contribute to the antimicrobial activity, because phenol kills microbial cells or retards cell growth, by damaging the cell membrane to cause leakage of cellular components.

Some derivatives of *p*-hydroqinone or acrylic acid were prepared as shown in **Figures 1** and **2** to trace the origin of the antimicrobial activity of H5. The antimicrobial activity of the derivatives was assessed through the halo zone test against fungi, *A. fumigatus* and *P. pinophilum*, and against bacteria, *S. aureus* and *P. aeruginosa*.

Because the halo zone test results depend on the solubility and diffusion rate of the compound as well as on its intrinsic antimicrobial activity, the shake flask test was also carried out for H5, A1, and A9, which formed larger halo zones. **Tables 1**−**4** summarize the halo zone test results against the fungi and the bacteria. The shake flask test results are collected in **Table 5**.

H1 did not build up any halo zone against the fungi. In sharp contrast, H2, H3, H4, and H5, which can be synthesized by

Table 1. Antifungal Activity of H1 Derivatives Measured by the Halo Zone Test (Units, mm)[a]

		concentration of compd (μg/mL in DMSO)				
compd	strain	400	200	100	50	10
H1	*P. pinophilum*	×	×	×	×	×
	A. fumigatus	×	×	×	×	×
H2	*P. pinophilum*	41 ± 1.0	36 ± 0.9	35 ± 0.4	–	31 ± 0.6
	A. fumigatus	22 ± 0.6	23 ± 0.8	22 ± 0.0	–	20 ± 0.0
H3	*P. pinophilum*	35 ± 1.6	19 ± 1.6	12 ± 0.8	×	×
	A. fumigatus	×	×	×	×	×
H4	*P. pinophilum*	60 ± 0.0	50 ± 0.0	33 ± 0.0	20 ± 0.0	×
	A. fumigatus	55 ± 0.0	52 ± 0.0	40 ± 0.0	13 ± 0.0	×
H5	*P. pinophilum*	max	max	78 ± 1.0	–	56 ± 1.0
	A. fumigatus	51 ± 1.0	50 ± 0.5	40 ± 1.3	–	27 ± 0.6

[a] Max: clear zone covered all of the agar medium on the Petri dish (diameter, 90 mm); –, not determined; ×, no halo zone was formed.

Table 2. Antibacterial Activity of H1 Derivatives Measured by the Halo Zone Test (Units, mm)[a]

		concentration of compd (μg/mL in DMSO)				
compd	strain	400	200	100	50	10
H1	*P. aeruginosa*	23 ± 3.7	21 ± 2.9	18 ± 1.4	14 ± 2.4	×
	S. aureus	19 ± 0.8	19 ± 1.6	13 ± 2.2	×	×
H2	*P. aeruginosa*	18 ± 0.0	17 ± 0.0	15 ± 0.4	12 ± 0.0	×
	S. aureus	21 ± 0.0	19 ± 0.6	16 ± 0.8	13 ± 0.0	×
H3	*P. aeruginosa*	20 ± 0.8	18 ± 3.6	13 ± 0.8	11 ± 0.8	×
	S. aureus	13 ± 2.4	×	×	×	×
H4	*P. aeruginosa*	23 ± 0.0	22 ± 0.0	15 ± 0.0	×	×
	S. aureus	×	×	×	×	×
H5	*P. aeruginosa*	40 ± 1.0	38 ± 1.0	33 ± 2.0	29 ± 0.0	24 ± 0.8
	S. aureus	45 ± 1.1	41 ± 0.0	36 ± 0.4	30 ± 1.0	26 ± 2.0

[a] ×, no halo zone was formed.

Table 3. Antifungal Activity of Acryl Derivatives Measured by the Halo Zone Test (Units, mm)[a]

		concentration of compd (μg/mL in DMSO)				
compd	strain	400	200	100	50	10
A1	*P. pinophilum*	max	max	max	max	×
	A. fumigatus	max	max	max	max	×
A2	*P. pinophilum*	×	×	×	×	×
	A. fumigatus	×	×	×	×	×
A3	*P. pinophilum*	×	×	×	×	×
	A. fumigatus	×	×	×	×	×
A4	*P. pinophilum*	×	×	×	×	×
	A. fumigatus	×	×	×	×	×
A5	*P. pinophilum*	max	52 ± 0.0	50 ± 0.0	28 ± 0.0	16 ± 0.0
	A. fumigatus	max	42 ± 0.0	42 ± 0.0	28 ± 0.0	13 ± 0.0
A6	*P. pinophilum*	37 ± 2.8	38 ± 4.3	34 ± 6.4	26 ± 2.9	×
	A. fumigatus	27 ± 2.8	26 ± 4.3	19 ± 4.3	16 ± 4.3	×
A7	*P. pinophilum*	35 ± 2.8	32 ± 1.4	32 ± 0.8	28 ± 0.8	×
	A. fumigatus	35 ± 4.1	32 ± 2.2	31 ± 0.8	28 ± 1.4	20 ± 0.8
A8	*P. pinophilum*	40 ± 1.4	38 ± 1.6	33 ± 2.2	27 ± 1.4	23 ± 2.4
	A. fumigatus	41 ± 1.6	40 ± 1.4	37 ± 3.7	33 ± 1.4	20 ± 0.8
A9	*P. pinophilum*	max	max	30 ± 3.6	32 ± 2.2	22 ± 2.8
	A. fumigatus	max	max	30 ± 3.6	30 ± 0.8	21 ± 2.8
A10	*P. pinophilum*	×	×	×	×	×
	A. fumigatus	×	×	×	×	×
A11	*P. pinophilum*	53 ± 2.9	×	×	×	×
	A. fumigatus	max	13 ± 0.0	×	×	×
A12	*P. pinophilum*	29 ± 2.9	20 ± 0.0	×	×	×
	A. fumigatus	23 ± 2.4	18 ± 0.0	×	×	×

[a] Max: clear zone covered all of the agar medium on the Petri dish; ×, no halo zone was formed.

replacing one of the hydroxyl groups of H1 with allyloxy, acetoxy, propanoyloxy, and acryloxy groups, respectively, manifested a potent antifungal activity, and the size of the halo zone increased in the order of H3 < H4 < H2 < H5.

The halo zone test results against the bacteria were not in accord with those against the fungi, in that the halo zone

Table 4. Antibacterial Activity of Acryl Derivatives Measured by the Halo Zone Test (Units, mm)[a]

		concentration of compd (μg/mL in DMSO)				
compd	strain	400	200	100	50	10
A1	*P. aeruginosa*	max	max	45 ± 0	30 ± 0	21 ± 0
	S. aureus	max	65 ± 0	40 ± 0	20 ± 0	14 ± 0
A2	*P. aeruginosa*	11 ± 0.0	×	×	×	×
	S. aureus	12 ± 0.0	×	×	×	×
A3	*P. aeruginosa*	×	×	×	×	×
	S. aureus	×	×	×	×	×
A4	*P. aeruginosa*	×	×	×	×	×
	S. aureus	×	×	×	×	×
A5	*P. aeruginosa*	max	54 ± 0.0	33 ± 0.0	23 ± 0.0	16 ± 0.0
	S. aureus	max	70 ± 0.0	53 ± 0.0	53 ± 0.0	36 ± 0.0
A6	*P. aeruginosa*	13 ± 2.2	×	×	×	×
	S. aureus	15 ± 1.6	15 ± 1.6	×	×	×
A7	*P. aeruginosa*	28 ± 2.2	28 ± 1.6	25 ± 0.8	24 ± 0.8	21 ± 1.4
	S. aureus	25 ± 1.6	20 ± 1.4	18 ± 2.4	16 ± 2.4	×
A8	*P. aeruginosa*	30 ± 3.7	29 ± 2.4	28 ± 1.4	27 ± 3.7	18 ± 0.8
	S. aureus	20 ± 3.6	19 ± 0.8	19 ± 1.6	17 ± 2.2	×
A9	*P. aeruginosa*	max	max	21 ± 2.2	17 ± 1.6	15 ± 1.6
	S. aureus	max	max	78 ± 4.5	57 ± 2.2	34 ± 3.7
A10	*P. aeruginosa*	×	×	×	×	×
	S. aureus	×	×	×	×	×
A11	*P. aeruginosa*	13 ± 1.4	×	×	×	×
	S. aureus	14 ± 0.8	×	×	×	×
A12	*P. aeruginosa*	×	×	×	×	×
	S. aureus	13 ± 2.2	×	×	×	×

[a] Max: clear zone covered all of the agar medium on the Petri dish; ×, no halo zone was formed.

Table 5. Antibacterial Activity of H5, A1, and A9 against *S. aureus* and *P. aeruginosa* Based on the Shake Flask Test[a]

strain	compd	CFU/mL	reduction rate (%)
S. aureus	control	3.62×10^6	
	H5	0.0	100
	A1	1.34×10^3	99.96
	A9	7.10×10^3	99.80
P. aeruginosa	control	7.90×10^6	
	H5	0.0	100
	A1	8.90×10^2	99.98
	A9	3.98×10^5	94.96

[a] CFU, colony forming unit; concentration of the biocides, 0.2 μg/L.

diameter increased in the following order: H3, H4 < H2 ≈ H1 < H5. It is worth noting that H1 was effective against the two bacteria. It formed a larger halo zone than H3 and H4 did. The halo zone formed by H2 was similar in size to that formed by H1.

Phenol permeates through the microbial cell wall and cell membrane to disturb the transmembrane pH gradient and membrane integrity. Thus, it accelerates leakage of intracellular materials such as inorganic phosphates, amino acids, nucleotides, and proteins to provoke autolysis. 2-Phenylethanol, ethylphenol, and 2-phenoxyethanol kill microorganisms by way of the same mechanism as that for phenol (*6*). However, curiously enough, H1 was not active at all against the fungi and it was only weakly active against the bacteria.

Because H2 showed a similar antimicrobial effect to H3 or H4, an elctronic effect of the substituents might not be important. The phenol moiety played a certain role in the antimicrobial activity because H2, H3, and H4 formed nonnegligible halo zone in the halo zone tests. As the antimicrobial activities of H2, H3, and H4 were lower than that of H5, the acryl group should make a significant contribution to the antimicrobial activity of H5.

A1 exhibited an excellent antimicrobial activity not only against the fungi but also against the bacteria. As expected, A2

had a negligible activity. A3 and A4 were prepared in the reaction of acryloyl chloride with cyclohexanol and 1-hexanol instead of phenol, respectively. A3 and A4 were not active at all both against the fungi and against the bacteria.

Paulus reported that a vinyl group situated in the α- and β-position to an electronegative group exhibited antimicrobial virtue by interacting with electrophilic sites of microbial cells (*10*). The antimicrobial virtue became more prominent when a resonance promoting group was bound to the electronegative group. The importance of the resonance promoting group for the antimicrobial virtue can be confirmed by comparing the halo zone test results of A5 and A6 with those of A1. A5 was as competent for the antimicrobial activity as A1, while A6 had much less activity, although the nucleophilicity of the acryl group and the resonance increasing effect of the phenyl group of the latter are expected to be similar to those of A1.

Although A7 has two acryl groups, A7 was less active than A1. One of the acryl groups in A7 acts like the acetyl one in A8. Alkyl substituents in the phenyl ring differently affected the antimicrobial activity. Ethyl in A9 slightly lowered the activity, while dodecyl made A10 completely inactive. In general, both the intrinsic activity and the diffusion rate of the antimicrobial agent affect the halo zone test results, which depend therefore on the molecular weight and the hydrophilicity as well as on the electrophilicity.

The lower antimicrobial activity of A11 as compared to that of A1 is attributed to the lack of the resonance increasing effect of the phenyl group. It is curious to observe that A11 exhibits some antimicrobial activity against both the fungi and the bacteria, despite the resonance deficiency. In addition, A12 showed almost the same activity as A11, completely different from A3 and A4 in terms of the resonance increasing effect. Therefore, the stereoelectronic effect of the phenyl group in acryl derivatives might play a certain role in their antimicrobial activities.

Shake flask tests were carried out for H5, A1, and A9 that formed lager halo zones in the halo zone tests. Viable cells of *S. aureus* were reduced by 100, 100, and 99.8%, and those of *P. aeruginosa* were reduced by 100, 100, and 95.0%, respectively, in the presence of H5, A1, and A9. The results from the shake flask tests were in accord with those from the halo zone tests.

The present study confirms that the acryl group plays a crucial role in the antimicrobial activity of H5 and that a compound with a vinyl electron withdrawing group and a resonance promoting group is an excellent antimicrobial agent, as reported by Paulus (*10*). However, an exception to this rule was discovered in that A6 was far less active than A1.

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