Notes

Circular Reasoning about Linear Free-Energy Relationships

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Solvolysis rates of aryl-substituted tertiary carbinyl *p*-nitrobenzoates in 80% aqueous acetone at 25 °C have been extensively documented.[1] When log $k_{4\text{-OMe}}/k_{\text{H}}$ (where $k_{4\text{-OMe}}$ is the rate constant of the *p*-anisyl derivative and k_{H} that of the phenyl derivative in a given series) is plotted against the reaction constant, ρ, a straight line results of slope −0.81 closely similar to the σ^+ value of the 4-methoxy substituent.[2] This correlation is presented as "a critical, sensitive and unequivocal test of the extended selectivity principle[3]/Yukawa–Tsuno[4] treatments". We believe it to be simply an example of circular reasoning.

With one exception (see below) the ρ values quoted are Brown's[5] and are based mainly on four substituents with well-established σ^+ values: 4-OMe, H, 4-CF_3, and 3,5-$(CF_3)_2$. In some cases, however, the last point is found to deviate from the correlation[5e] or is inaccessible;[5d–f] the ρ value is then calculated from the three others.[6] Consequently, the difference between the *p*-anisyl and the phenyl derivatives weighs heavily in the evaluation of ρ, since it constitutes on average more than 50% of the available information. It is, therefore, *inevitable* that a straight line of slope $\sigma^+_{4\text{-OMe}}$ will be obtained when log $k_{4\text{-OMe}}/k_{\text{H}}$ is plotted against ρ.

One point, that for the aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates,[7] lies off the line. The reason for this is simple: the ρ value was calculated from a correlation with Hammett's σ values.[8] It will therefore lie on a line of slope $\sigma_{4\text{-OMe}}$ not $\sigma^+_{4\text{-OMe}}$. A more appropriate datum, given by extrapolation[9] of results for 70% aqueous acetone[10] to 25 °C, is situated at log $k_{4\text{-OMe}}/k_{\text{H}} = 0.88$ and $\rho = -1.51$ (from σ^+ values), i.e., only 0.3 log units below Johnson's line. His approach, if applied consistently, is rather *insensitive* to even quite large steric effects; deviations only indicate that the rate–σ^+ correlation is less than perfect. A much better procedure for detecting mechanistic variants or steric effects in a particular system is to apply the Yukawa–Tsuno equation first to meta-substituted compounds (to find ρ) and then to para-substituted derivatives (to find r), but this requires more data.

The small values of both ρ and r found in the solvolysis of aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates have been discussed in terms of an early transition state and steric hindrance to resonance.[8,10,11] The two parameters are not necessarily related.[4] Geometric constraints are known to produce low r values even when ρ is normal,[12] though other factors may be involved.[13]

References and Notes

(1) For an excellent summary see: H. C. Brown, "The Nonclassical Ion Problem", with comments by P. v. R. Schleyer, Plenum Press, New York, 1977.

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(5) (a) H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, **99,** 505 (1977); (b) H. C. Brown, M. Ravindranathan, E. N. Peters, C. G. Rao, and M. M. Rho, *ibid.*, **99,** 5373 (1977); (c) H. C. Brown, M. Ravindranathan and E. N. Peters, *J. Org. Chem.*, **42,** 1073 (1977); (d) H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, **97,** 7449 (1975); (e) H. C. Brown and E. N. Peters, *ibid.*, **97,** 7442 (1975); (f) K. Takeuchi and H. C. Brown, *ibid.*, **90,** 2693 (1968); (g) H. C. Brown and E. N. Peters, *ibid.*, **97,** 1927 (1975); (h) H. C. Brown, M. Ravindranathan, and M. M. Rho, *ibid.*, **98,** 4216 (1976); (i) E. N. Peters and H. C. Brown, *ibid.*, **97,** 7454 (1975).

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(8) The fact that the data are for acetic acid at 85 °C (J. S. Lomas and J. E. Dubois, *J. Org. Chem.*, **40,** 3303 (1975)) while all the others are for 80% aqueous acetone at 25 °C is irrelevant. *Any reaction under any conditions whatsoever will fall on the σ^+ line provided that the rates correlate with σ^+ constants.*

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On Using the Tool of Increasing Electron Demand to Evaluate the Yukawa–Tsuno Equation and for Identifying Nonclassical Carbocations

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A test of the validity of the Yukawa–Tsuno equation[1] was described very recently by Johnson.[2] The values of log $k_{p\text{-OMe}}/k_{\text{H}}$ derived (by Brown and coworkers) from S_N1 solvolyses of compounds of the general type ArCRR′OPNB were plotted against the reaction ρ values; these latter varied from −3.2 to −5.0.[3] This gave a line of slope −0.824 (cf. −0.78 expected) which was interpreted as showing that the Yukawa–Tsuno equation is invalid, i.e., only the Hammett–Brown[4] equation applies. In principle this test (if carried out over a wide enough ρ range) is a sound one. However, detailed analysis of the manner in which the data were obtained show it in fact to be inapplicable, for in every case *the parameter which the analysis was intended to derive was incorporated in the original data.* Consequently an excellent fit to the Hammett–Brown equation was unavoidable. The following evidence supports this latter statement.

(i) The data for compounds **19** (the numbers are those used in Johnson's paper) are meaningless. Rate coefficients were obtained *only for* the *p*-OMe and unsubstituted compound.[6] A rate coefficient was then created[6] for the nonexistent *p*-CF_3 compound[6] and was chosen assuming perfect application of the Hammett–Brown equation. Thus the perfect line through the points for the *p*-OMe, H, and *p*-CF_3 compounds inevitably gives a value of −0.78 for $\sigma^+_{p\text{-OMe}}$ since this value was chosen in the first place. Clearly the data for compounds **19** cannot be included.

(ii) For compounds **1** and **6** in the original paper, the data are barely more meaningful. For these ρ was determined from three compounds only,[5,6] *one of which was the p-OMe compound.* Consequently ρ was chosen to fit the *p*-OMe point, so again the derived σ^+ value is almost exactly that (−0.78)

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Table I. Solvolysis of *p*-$\mathrm{NO_2C_6H_4COOR}$ in 80% Aqueous Acetone at 25 °C

No.	R	$-\log k$	$-\rho$	ref
1	1-aryl-1-(2,2′-dichlorocyclopropyl)-1-ethyl	7.745	4.60	5
2	1-arylcylobutyl	8.735	4.87	9
3	1-aryl-1-isopropyl-1-ethyl	8.022	4.65	5
4	1-aryl-1-methyl-1-ethyl	7.143	4.79	9
5	1-aryl-1-ethyl-1-propyl	7.827	5.04	9
6	2-aryl-5-methyl-*endo*-2-norbornenyl	8.138	4.55	6
7	2-aryl-*endo*-2-norbornenyl	8.220	4.37	7
8	2-aryl-*endo*-2-norbornyl	7.276	3.87	8
9	3-aryl-3-nortricyclyl	6.438	3.26	9
10	1-aryl-1-phenyl-1-ethyl	6.105	3.17	9
11	1-arylcyclohexyl	7.836	4.38	9
12	2-aryl-*exo*-2-norbornenyl	5.907	4.14	7
13	2-aryl-*exo*-2-norbornyl	5.122	3.67	8
14	1-aryl-1-cyclobutyl-1-ethyl	7.264	4.32	9
15	1-arylcyclopent-3-enyl	6.198	3.95	9
16	1-arylcycloheptyl	6.124	4.39	9
17	1-arylcyclooctyl	5.124	3.84	9
18	1-arylcyclopentyl	5.585	3.82	9
20	1-aryl-1-cyclopropyl-1-ethyl	3.618	2.83	5
21	1-aryl-1-(2,2′-dimethylcyclopropyl)-1-ethyl	2.542	2.10	5
22	1-aryl-1-cyclopentyl-1-ethyl	7.456	4.46	11
23	1-aryl-1-cyclohexyl-1-ethyl	7.719	4.73	11
24	1-aryl-1-(Δ^1-cyclohexenyl)-1-ethyl	3.909	2.38	11
25	1-aryl-1-(Δ^2-cyclohexenyl)1-ethyl	8.380	4.76	11
26	2-aryl-2-bicyclo[2.1.1]hexyl	6.812	4.23	13
27	7-aryl-7-norbornyl	10.678	6.65	25
28	9-aryl-9-pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonyl	6.910	1.89	14
29	7-aryl-7-*anti*-norbornenyl	9.060	1.89	25
30	1-aryl-1-(*exo*-2-norbornyl)-1-ethyl	7.436	4.65	12
31	1-aryl-1-(*endo*-2-norbornyl)-1-ethyl	6.842	4.38	12
32	2-aryl-*exo*-2-benzonorbornenyl	6.556	4.53	26
33	2-aryl-*endo*-2-benzonorbornenyl	10.013	4.50	26
34	2-aryl-*exo*-2-(6-methoxybenzonorbornenyl)	5.866	3.15	26
35	2-aryl-*endo*-2-(6-methoxybenzonorbornenyl)	10.030	3.54	26

chosen in the first place. The effect of this technique is to cause $\sigma^+_{p\text{-OMe}}$ to converge upon the mean value by 0.06 units in each case. A proper evaluation of the Yukawa–Tsuno equation evidently must exclude consideration of compounds **1** and **6**.

(iii) The data for compounds **7** and **8** appear at first sight to be marginally more valid, with rate coefficients included for the m,m'-$(\mathrm{CF_3})_2$ and p-$\mathrm{NO_2}$ derivatives, respectively. Alas this is illusory since these compounds have not been made either, the quoted "rate coefficients" being merely calculated assuming that the Hammett–Brown equation applies perfectly.[7,8] Again the derived $\sigma^+_{p\text{-OMe}}$ values will be virtually those chosen in the first place, and compounds **7** and **8** cannot be considered further.

(iv) For the remaining compounds, data were obtained for the p-OMe, H, p-$\mathrm{CF_3}$, and m,m'-$(\mathrm{CF_3})_2$ compounds. Even if these data were perfectly acceptable [and they are not for reasons given in (v) and (vi)] it would follow that the derived $\sigma^+_{p\text{-OMe}}$ values will be almost exactly those used to derive the ρ values, since the latter are derived from so few data points. For some of the reactions, correlation coefficients of 0.999 were quoted. To appreciate the meaning of these numerical values it may be noted that four-point plots with $\sigma^+_{p\text{-OMe}}$ values which vary from −0.65 to −0.91 give correlation coefficients greater than 0.999.

(v) For compounds **11–19**, no rate data were in fact obtained for the p-OMe-substituted p-nitrobenzoates.[6-9] Instead, rate coefficients for the benzoates were multiplied by a constant factor of 20.8 (the difference in the rate coefficients for the benzoate and p-nitrobenzoate derivatives of the unsubstituted compound **8**).[10] Now while this may be an acceptable means of obtaining *approximate* ρ factors, there are nevertheless two objections to this approach insofar as detailed data analysis is concerned. The first is that applying this factor to the p-OMe compounds assumes (as noted by Johnson) that the ρ factors for benzoate and p-nitrobenzoate solvolyses are equal, which is unlikely. Secondly, there is no reason to suppose that the value of 20.8 which applies only to the unsubstituted compounds **8** is relevant to other series of compounds *which are up to 200 times less reactive!* The calculated rate coefficients for the p-OMe-substituted compounds **11–19** may therefore be substantially in error, and the data are inappropriate to any evaluation of the Yukawa–Tsuno equation. The same arguments exclude consideration of more recent data for 1-aryl-1-cyclopentyl,[11] -1-cyclohexyl-,[11] -1-Δ^1-cyclohexenyl-,[11] and -1-*exo*- and *endo*-norborn-2-yl-1-ethyl[12] p-nitrobenzoates.

(vi) Thus we are left only with data for compounds **2–5, 9,** and **10** and to these may be added more recent solvolytic data for 1-aryl-1-(Δ^2-cyclohexenyl)-1-ethyl,[11] 2-aryl-2-bicyclo[2.1.1]hexyl,[13] and 9-aryl-9-pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]nonyl[14] p-nitrobenzoates. However all of these are unsatisfactory because (a) they suffer from the statistical objection noted under (iv) and (b) like most of the other data they include rate coefficients calculated at 25 °C from extrapolations of up to 125 °C. A simple calculation shows that an error of ±2% in rate coefficients measured at two temperatures and only 25 °C apart (as in this work) will produce an error of ±24% in the derived rate coefficient and an error of 0.1 in ρ.[15,16] (An additional complication is that some rate coefficients by extrapolation are miscalculated from the data given at higher temperatures.)

Thus while solvolysis data may provide good material for testing the Yukawa–Tsuno equation, the data presently available are insufficient for such an analysis. We believe it would be appropriate to select a limited number of reactions with divergent ρ factors and obtain accurate values of the latter by using a large number of substituents, and minimum

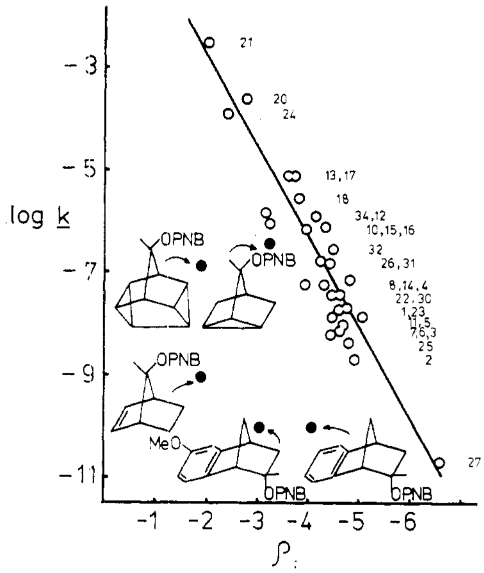
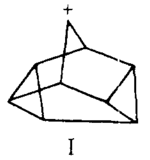


Figure 1. Correlation of log *k* vs. ρ for solvolysis of 1-X-1-arylethyl *p*-nitrobenzoates. For identication of points see Table I.

extrapolation of rate data. Each series should preferably include the *p*-MeS substituent since this is even more polarizable than *p*-MeO.[18] The systems would have to be carefully chosen to minimize steric hindrance to solvation, an important factor in these side-chain solvolyses.[19] Differences in solvation will require differing net amounts of stabilization of the carbocation by the methoxy substituent. (An extreme example of this effect is provided by the pyrolysis of 1-arylethyl acetates, which proceeds via partial formation of a carbocation at the side-chain α position. The ρ factor for this gas-phase reaction is equivalent to only −1.3 at 25 °C, yet $\sigma^{+}_{p\text{-OMe}}$ is −0.755; there is a high demand for substituent stabilization of the carbocation, relative to the charge on the cation, because of the total absence of solvent.[20])

The shortcomings in the available data preclude their use in the manner described by Johnson, so that there is no evidence at this time to suggest abandoning the Yukawa–Tsuno equation. Nevertheless it must be borne in mind that the primary object of these solvolyses studies was to evaluate the *general* parallel between the ρ factors and the electron release of the group attached to, or forming part of, a carbocation (and for this, high precision in ρ is less important). Thus the plausibility of the intervention of nonclassical carbocations could be ascertained, and the following conclusions have been revealed. (1) σ-Participation stabilizes Coates cation (I), i.e., it is a nonclassical carbocation.[21] (2) π-Participation stabilizes the 7-norbornenyl cation (II) (derived from the anti precursor),[22] and it seems very probable that a symmetrical π-bridged cation is an intermediate. (3) Cyclopropyl rings provide very strong stabilization especially when they are in the bisected conformation [as in the 3-nortricyclyl cation (III)];[23] the mechanism by which they do this is unclear, though steric- and strain-assisted carbon–carbon hyperconjugation is likely to be a major factor.



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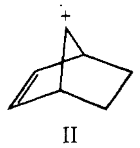

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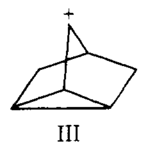
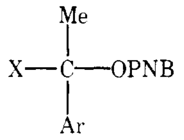


III

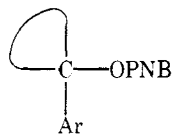
These conclusions have however been based on subjective assessments of the meaningfulness (or otherwise) of the differences in ρ factors for solvolysis of compounds of similar structure. We here propose what may be a more rigorous method.

Since both ρ factors and the reactivities of the molecules are a function of the charge on the cation, one would expect that there would be a correlation between log *k* and ρ. Figure 1,[24] which relates to compounds of types IV and V,[5–9,11–14,25,26] shows that this is largely true with deviations within one order of magnitude of that predicted for a given ρ value. (It follows from the foregoing discussion that part of this deviation may derive from inaccuracy of the ρ values.) The linear regression line, log *k* = 1.74ρ + 0.52 (correlation coefficient 0.913), was calculated with exclusion of the five most deviant points (solid circles).[27] What is the most significant is that these *latter points relate either to the compounds described under (1–3) and which are atypically stabilized, through extensive delocalization, or to those compounds for which steric hindrance to ionization is generally accepted as occurring.* Thus evaluation of the status of a point obtained for a particular solvolysis in relation to the regression line may in future provide a surer footing for identifying these phenomena. Two points require comment.



$$\text{X}-\overset{\text{Me}}{\underset{\text{Ar}}{\text{C}}}-\text{OPNB}$$

IV



V

First it is arguable that the regression line is not meaningfully located, since most of the solvolyses will be affected by differential solvation effects, *i.e.*, the line should be drawn through the points of highest reactivity. (Steric hindrance to solvation etc. is likely to cause diminished rates rather than enhanced ones). If this is done, 17 points are within 0.5 ρ units of the line, including that for solvolysis of the *exo*-2-aryl-2-norbornyl ester, *i.e.*, this is normal and that for the corresponding endo compound is deviant arising from low reactivity. This therefore confirms Brown's view that solvolysis of the latter (tertiary compounds) is subject to steric hindrance to ionization, and this is of course more emphatically confirmed by the very low rates of the (more hindered) *endo*-2-aryl-2-benzonorbornenyl esters.

Secondly, why do reactions which proceed via cations which are extensively delocalized give very low ρ factors compared to the observed reaction rate? A reasonable explanation is that this extensive delocalization leaves relatively little net charge at the reaction site for stabilization by the aryl group. Since very recent calculations indicate that specific solvation becomes less favorable with increasing charge delocalization,[28] one could expect a better log *k*–ρ relation for solvolyses carried out in less polar media.

References and Notes

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(3) The plot contained additional points which appeared to extend the range down to −2.0. However, these relate to nonexistent compounds[5] whose rates of solvolysis have consequently never been measured.

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(10) The reason for this is not entirely clear. Many of the calculated rate coefficients are substantially *lower* than for the other *p*-methoxy-substituted *p*-nitrobenzoates whose rates *have* been measured directly.

(11) H. C. Brown, M. Ravindranathan, and C. G. Rao, *J. Am. Chem. Soc.*, **100**, 1218 (1978).

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(14) H. C. Brown and M. Ravindranathan, *J. Am. Chem. Soc.*, **99**, 299 (1977).
(15) It appears from the rate data that the temperature range could be extended to at least 50 °C without difficulty, thereby substantially reducing the error probability.
(16) Unfortunately, quotation of the ρ values to within ±0.2% has implied an accuracy greater than that which is evident. Thus, for example, the ρ factor for solvolysis of *exo*-2-aryl-2-benzonorbornenyl *p*-nitrobenzoate is quoted as −4.50, and a value of −4.51 for the corresponding *endo* compound is quoted,[16] yet the rate spread is *greater* for the former compounds.
(17) H. C. Brown, "The Non-Classical Carbonium Ion Problem", Plenum Press, New York, 1977, p 168.
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(21) Reference 17, p 277.
(22) Reference 17, pp 16–17.
(23) Reference 17, p 75.
(24) The ρ factors were estimated from the rate data for the *p*-CF_3 and unsubstituted *p*-nitrobenzoates *only*, in order to overcome the objections noted above; it follows that the error in ρ may be of the order of ±0.5. The log *k* values are for the phenyl derivatives, since these were derived by minimal extrapolation of rate data; rate coefficients for solvolysis of the 7-phenyl-7-norbornyl and 7-phenyl-7-norbornenyl *p*-nitrobenzoates obtained in 70% aqueous dioxane[25] were multiplied by 0.206[14] in order to obtain the approximate values for 80% aqueous acetone.
(25) P. G. Gassman and A. G. Fentiman, *J. Am. Chem. Soc.*, **92**, 2549 (1970).
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(27) The reactivities cover 14 orders of magnitude and range from the least reactive 7-norbornyl cation (which is sterically precluded from stabilization by either C–H or C–C hyperconjugation) to the 2,2-dimethylcyclopropylcarbinyl cation.
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Synthesis and Properties of *trans*-3-(1,4-Cyclohexadienyl)acrylic Acid[1]

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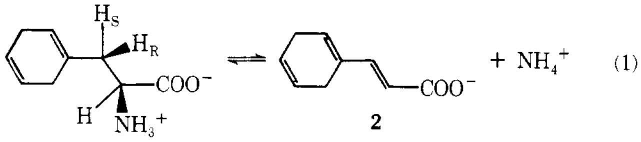
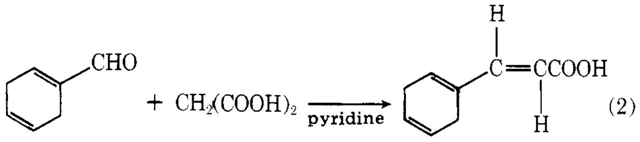
A recent study[3] examined the phenylalanine analogue 3-(1,4-cyclohexadienyl)-L-alanine (1)[4] as a substrate for L-phenylalanine ammonia-lyase (EC 4.3.1.5) (eq 1) in order to investigate electronic effects of β substituents on the elimination reaction with L-phenylalanine (3). The enzymic reaction with L-phenylalanine had been established to be an anti elimination of the (pro-3*S*)-H and NH_3 to give *trans*-cinnamate (4).[5] The new enzyme product accordingly was assigned the structure *trans*-3-(1,4-cyclohexadienyl)acrylic acid (2,5-dihydrophenylacrylic acid, 2). Elemental analysis and the ^1H NMR spectrum were fully consistent with this structure.



1 2 (1)

To confirm the structure and to make this previously unknown dihydrocinnamate more readily available, synthesis of 2 was undertaken and is described herein.

An initial attempted route to 2 was analogous to a stereospecific synthesis of ethyl *trans*-cinnamate.[6] Ethyl 2-diazo-3-(2,5-dihydrophenyl)propionate, derived from ethyl 3-(2,5-dihydrophenyl)alaninate, was decomposed with sodium alkoxide. After treatment with an equivalent of base in MeOH, the tarry product afforded less than 1% of solid material with the ^1H NMR spectrum and melting point of 2. In another attempt, a Wittig-type condensation[7] of 2,5-dihydrobenzaldehyde[8] and triethyl phosphonoacetate appeared to form an ethyl ester of 2. However, it was complicated by a strong tendency toward aromatization and difficulty in isolation of the product after the subsequent hydrolysis step. Presumably the strongly alkaline conditions in both experiments were disadvantageous. The Doebner modification of the Knoevenagel reaction was expected to give almost exclusively an α,β-unsaturated compound with the desired substituted *trans*-acrylate structure[9,10] and to yield the free acid directly. This route in which 2,5-dihydrobenzaldehyde (6) and malonic acid are condensed in pyridine (eq 2) proved to be reasonably satisfactory, although some aromatization again took place.



6 2 (2)

The condensation reaction was examined under a variety of conditions of temperature, time, and molar ratios of reactants and base as well as with several different catalysts. A maximal yield of about 40% was attained after 3 h at 100 °C with a threefold excess of malonic acid and 1.4 equiv of pyridine on a 37-mmol scale. The crude product was an almost colorless crystalline solid. As determined by ^1H NMR, it consisted of a mixture of the desired 3-(1,4-cyclohexadienyl)-acrylic acid and cinnamic acid in a ratio of 75:25.

The dehydrogenation side reaction producing cinnamic acid was not investigated in detail. However, it was noted that when 2,5-dihydrobenzaldehyde only was heated with pyridine for the customary reaction time and temperature, the ratio of 2,5-dihydrobenzaldehyde/benzaldehyde was similar to the ratio of 2/4 in reaction 2. At least part of the dehydrogenation, therefore, can take place at the aldehyde stage and appears to be pyridine catalyzed. Decreasing the amount of pyridine to 0.2 equiv increased dehydrogenation and decreased the yield, possibly as a result of a decrease in condensation rate. It is likely that the formyl group of dihydrobenzaldehyde and the acrylate side chain of 2 could each promote base-catalyzed C-3 proton ionization that would favor dehydrogenation. In keeping with this, addition to the reaction mixture of cyclohexadiene lacking these groups did not lead to a product with significantly improved composition.

Preliminary attempts to purify 2 by a variety of techniques were unpromising. These included fractional crystallization of the mixture of 2 and 4 both as free acids and as dicyclohexylamine salts, sublimation, and thin-layer chromatography on silica gel sheets in ten solvent systems. Zone electrophoresis on paper was useful for analytical purposes. Partition chromatography with benzene on buffered silica gel columns also separated 2 and 4 but was unwieldy for preparative work.[3] High pressure liquid chromatography (LC) with μ Bondapak reverse-phase support proved to be highly satisfactory for analytical and semipreparative separations. The product was purified in this way and then recrystallized.

Assignment of the ^1H NMR signals of 3 was aided by comparison with reported spectra for *trans,trans*-sorbic acid, *trans*-cinnamic acid, and various 3-(2,5-dihydrophenyl)alanine (1) derivatives. The trans configuration of the substituted acrylate double bond of 2 was confirmed by the magnitude of the $J_{b,c}$ coupling constant. Synthetic 2 and the enzyme product agreed closely in ^1H NMR and infrared spectra and melting points.

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