247. *Reaction Kinetics and the Walden Inversion. Part XII.*[1] *Steric Course of Bimolecular Nucleophilic Substitution of an Initially Positively Charged Leaving Group by a Neutral Nucleophile.*

By H. M. R. HOFFMANN and (the late) E. D. HUGHES.

It is shown that an S_N2 reaction of charge-type 4 (neutral nucleophile, initially positively charged leaving group), namely that of thiourea with the dimethyl-1-phenylethylsulphonium ion to give the 1-phenylethylthiouronium salt, proceeds with substantially complete inversion. Methyl 1-phenylethyl sulphide can be methylated in high yield, using methyl toluene-*p*-sulphonate without a solvent. Dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate undergoes unimolecular elimination in acetonitrile. The disturbance to the stereochemical investigation that might have been thus created was suitably dealt with.

So far, we do not know of any example to support the S_N2 rule [2] for reactions of charge-type 4, *i.e.*, displacements of an initially positively charged leaving group by a neutral nucleophile.[2] Although the reaction

$$\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{N}Me_3 + AcOH \xrightarrow{130^\circ} Me{\cdot}CHPh{\cdot}OAc + H\overset{+}{N}Me_3}$$

has been reported to entail 98—100% inversion,[3] it is difficult to see why this acetolysis should be stereospecific. Solvolyses of 1-phenylethyl compounds are known to be close to the limiting S_N1 mechanism, and racemisation exceeding 70% has been observed independently by a number of workers for a variety of solvents and leaving groups; [2,4] in particular, the acetolysis of 1-phenylethyl chloride involves at least 85% racemisation and at best 15% inversion.[5] Similarly, solvolyses in methanol, ethanol, and 80% aqueous acetone proceed with only a very small percentage of inversion.[2] Therefore, the cited observation [3] should perhaps be regarded with some reserve.

As an example of a substitution of charge-type 4, the 1-phenylethyl system was again chosen as the alkyl structure, and, by further analogy with earlier work,[1,6] thiourea was taken as the neutral nucleophile and the dimethylsulphonium group as the initially positively charged leaving group. The compounds reacted, apart from an $E\,1$ reaction of the substrate, according to the equation:

$$\mathrm{(H_2N)_2CS + Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2 \xrightarrow[MeCN]{59{\cdot}8^\circ} Me{\cdot}CHPh{\cdot}S{\cdot}C(NH_2)_2{}^+ + SMe_2} \qquad (1)$$

No methyl 1-phenylethyl sulphide was detectable. The optical purity of sulphonium ion relative to thiouronium ion was determined as shown in Scheme 1.

$$\mathrm{R{\cdot}S{\cdot}C(NH_2)_2{}^+ \xrightarrow{step\ 1} RSH \xrightarrow{step\ 2} RSMe \xrightarrow{step\ 3} RSMe_2{}^+}$$

$$\mathrm{[R = Me{\cdot}CHPh]}$$

Scheme 1.

Steps 1 and 2 had been carried out stereospecifically in Parts XI [1] and IX,[7] respectively. Therefore, the missing link in the correlation was step 3, *i.e.*, the formation of the sulphonium salt, a reaction which does not disturb the bonds around the asymmetric centre. Methylation with methyl toluene-*p*-sulphonate was preferred to the more common

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[1] Part XI, Hoffmann and Hughes, preceding paper.
[2] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953.
[3] Snyder and Brewster, *J. Amer. Chem. Soc.*, 1949, **71**, 291; cf. *ibid.*, p. 4165.
[4] Summarised by Streitwieser, jun., "Solvolytic Displacement Reactions," McGraw-Hill, New York, 1962, p. 59.
[5] Steigman and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 2536.
[6] Harvey, Hoye, Hughes, and Ingold, *J.*, 1960, 800.

method in which methyl iodide in nitromethane is used,[6] because, unlike the sulphonium iodide, dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate was non-hygroscopic, crystallised readily, and was stable at room temperature. Furthermore, the yields were higher than 80%. Since methyl toluene-*p*-sulphonate melts at 28°, it was unnecessary to use any solvent; methyl 1-phenylethyl sulphide was simply mixed with a 3-fold excess of methyl toluene-*p*-sulphonate and kept at 35°.

Complete preservation of optical purity was confirmed experimentally by isolating three successive fractions of product, for which the rotation remained practically unchanged. From a sample of methyl 1-phenylethyl sulphide having α_D^{20} $-106{\cdot}1°$,* the dimethyl-1-phenylethylsulphonium salt was obtained, with an average molecular rotation $[M]_D^{20}$ $-143{\cdot}6°$ in ethanol. This relation is in good agreement with earlier work[6] where methyl 1-phenylethyl sulphide with α_D^{20} 22·66° gave dimethyl-1-phenylethylsulphonium iodide with $[M]_D^{20}$ 31·4° in ethanol. Steps 1, 2, and 3 of Scheme 1 can be summarised as follows. Dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate with $[M]_D^{20}$ 265° in ethanol (or $[M]_D^{20}$ 243° in acetonitrile) has the same configuration and optical purity as 1-phenylethylthiouronium toluene-*p*-sulphonate with $[M]_D^{20}$ 342° in water (or, with slightly less accuracy, $[M]_D^{20}$ 354° in acetonitrile); and, more specifically, both compounds are optically pure when possessing these rotations.

The kinetics of the substitution of charge-type 4 (equation 1) were in practice complicated by the lability of the sulphonium salt under conditions where it reacted readily with thiourea. A variety of solvents and solvent mixtures were tested. Best results were obtained in acetonitrile, which is non-solvolysing and a fairly good cation solvator. In this solvent one side-reaction occurred, the decomposition of the sulphonium salt, by the *E* 1 mechanism:

$$\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2 \xrightarrow{k_1} CH_2{:}CHPh + H^+ + SMe_2}$$

as summarised in Table 1. The reaction was followed by titration of the acid liberated. The values for k_1 were calculated from initial rates, *i.e.*, up to 20% reaction. If the reaction was followed beyond this point the rates fell off because of interaction of the liberated acid with the solvent. Added toluene-*p*-sulphonate ion had no effect on the rate of elimination, *i.e.*, this anion in acetonitrile is not sufficiently nucleophilic to interfere with the course of the reaction, and 1-phenylethyl toluene-*p*-sulphonate, although probably formed in a small amount by mechanism S_N1, eliminates even more rapidly by the same reaction path, or can be titrated under the experimental conditions. Independently, the elimination was measured polarimetrically (Table 2). These rates are slightly higher

TABLE 1.

First-order rate constants (k_1 in sec.$^{-1}$) for the elimination of dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°, followed titrimetrically.

$[\mathrm{Me{\cdot}CHPh{\cdot}SMe_2^+}]_0$ (moles l.$^{-1}$)	0·047	0·071	0·071	0·097
$[\mathrm{OTs^-}]$ (moles l.$^{-1}$)	0·047	0·127	0·299	0·154
$k_1 \times 10^5$	2·68	2·81	2·70	2·82

$\mathrm{OTs^-} = p\text{-}\mathrm{Me{\cdot}C_6H_4{\cdot}SO_3^-}$

TABLE 2.

First-order rate constants (k_1 in sec.$^{-1}$) for the elimination of dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°, followed polarimetrically.

$[\mathrm{Me{\cdot}CHPh{\cdot}SMe_2^+OTs^-}]_0$ (moles l.$^{-1}$)	0·0255	0·0581
$k_1 \times 10^5$	3·09	3·14

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* The values for α in this paper refer to neat liquids and l 1 dm., unless stated otherwise.

than the titrimetric values. This is probably best explained by assuming that dissociation is preceded by ionisation to form an ion-dipole:

$$\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2} \rightleftharpoons \underset{\text{(ion-dipole)}}{\mathrm{Me{\cdot}CHPh^{+}SMe_2}} \rightleftharpoons \underset{\text{(dissociated ion)}}{\mathrm{Me{\cdot}CHPh^{+} + SMe_2}}$$

Apart from the elimination, no other side-reaction could be detected. Moreover, thiourea cannot have acted as a base in an $E\,2$ reaction because no additional acid was produced.

In order to suppress elimination, runs were carried out with a 4- to 7-fold excess of thiourea, the limit imposed being the solubility of thiourea in acetonitrile at room temperature (0·19 mole l.$^{-1}$). Under these conditions, the bimolecular substitution, during its first half-life, was about ten times faster than the unimolecular elimination, and reactions were followed over 30—40% of their paths. Unfortunately, it proved difficult to isolate the product during the initial stages of the reaction. Therefore inversion has to be demonstrated in a different way. It is shown in the Appendix that the second-order rate law,

$$\frac{1}{a-b}\ln\frac{b(a-x)}{a(b-x)} = k_2t,$$

has its stereochemical counterpart in the second-order polarimetric rate law,

$$\frac{1}{a-b}\ln\frac{b}{a}\cdot\frac{\frac{b}{a}(\alpha_\infty-\alpha_0)+\alpha_0-\alpha}{\alpha_\infty-\alpha} = k_2t,$$

provided that the S_N2 rule is fulfilled.

Both equations are derived on the assumption of a purely bimolecular reaction. Using this approximation for both equations, k_2 was determined from the first equation by estimating unreacted thiourea, and from the second by measuring the change in optical rotation of the reaction solution. The titration of thiourea (cf. Analytical Methods section) gave fairly accurate results, as the blue coloration of the iodine–starch complex could be easily recognised.* However, it was not found possible to estimate the liberated acid from the elimination simultaneously, as the amount was too small, and no satisfactory end-points could be obtained. The measurement of optical rotation was straightforward; since α changes owing to the S_N2 reaction as well as the unimolecular elimination, which is titrimetrically undetectable, a small correction has to be applied for the latter (see Table 3).

TABLE 3.

The reaction of thiourea with dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°, followed titrimetrically and polarimetrically.

Time (min.)	10	15	20	25	30
$[\mathrm{Me{\cdot}CHPh{\cdot}S{\cdot}C(NH_2)_2^+}]$ moles l.$^{-1}$	0·0106	0·0140	0·0154	0·0170	0·0196
α (obs. rotation)	−1·01	−0·83	−0·64	−0·46	−0·34
α (corr.)	−1·03	−0·86	−0·68	−0·51	−0·40

This is done by calculating the unimolecular decomposition of dimethyl-1-phenylethylsulphonium salt numerically from point to point, using the equation $\ln \alpha_t = \ln \alpha_0 - k_1t$, and taking the mean concentration for each step. The effect of this correction is not very significant during the initial stages of the reaction, *e.g.*, for the run quoted in Table 3, with a relatively high concentration of substrate, the uncorrected rate constants, k_2, is $1{\cdot}17 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$, as compared with the corrected value k_2 (corr.) of $1{\cdot}09 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. A summary of results is given in Table 4. Both sets of

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* The concentration, x, of the thiouronium salt formed, which is calculated from the difference of two relatively large values, is subject to some error, especially at the beginning of the reaction when x is small. Nevertheless, plots of $\ln[(a-x)/(b-x)]$ against t gave satisfactory straight lines.

TABLE 4.

Titrimetric and corrected polarimetric rate constants (k_2 in l. mole^{-1} sec.$^{-1}$) for the reaction of thiourea with dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°.

$[(H_2N)_2CS]_0$ (moles l.$^{-1}$) ...	0·142	0·185	0·185	0·183	0·191	0·188	0·186	0·180	
$[RSMe_2{}^+OTs^-]_0$ moles l.$^{-1}$	0·026	0·027	0·027	0·028	0·028	0·041	0·052	0·052	
$k_2 \times 10^3$ (titr.)	1·03	—	—	—	1·01	0·97	—	1·05	(Mean 1·02)
$k_2 \times 10^3$ (pol, corr.)	—	0·93	1·01	0·94	1·06	1·11	1·11	1·09	(Mean 1·04)

independently obtained rate constants are in satisfactory agreement. Therefore the stereochemical path of this nucleophilic substitution of charge-type 4 leads to complete inversion of configuration.

EXPERIMENTAL

Materials.—The preparation and purification of most of the compounds has been described.[1,7]

Analytical Methods.—*Thiourea*.[8] Aqueous solutions (50 ml.) of thiourea were acidified with 50% sulphuric acid (30 ml.), and a 1% potassium iodide solution (5 ml.) was added together with a few drops of a freshly prepared 1% starch solution. This mixture was titrated at 35° with 0·1N-potassium bromate–potassium bromide (standardised with a thiourea solution of known concentration) until a distinct blue colour appeared. The solution was then decolourised by dilution to 250 ml. with water at 35°, and titrated to the final blue end-point. 1-Phenylethylthiouronium salts do not interfere. Some experience was required as regards the stage to which decolorisation was to be carried out. *Sulphonium and thiouronium salts*. These salts were analysed by use of the cation-exchange resin Zeo-Karb 225(H).[1]

Dimethyl-1-*phenylethylsulphonium Toluene*-p-*sulphonate*.—*From optically inactive methyl* 1-*phenylethyl sulphide*. Methyl 1-phenylethyl sulphide (20 g.) and liquid methyl toluene-*p*-sulphonate (56 g.) were seeded with a few crystals of product and kept at 35° for 17 hr. (However, it was not proved that both the seeding and the 3-fold excess of methyl toluene-*p*-sulphonate were necessary.) The resulting crystalline cake was thoroughly shaken with dry ether, filtered off, and washed with ether. The combined filtrate was freed from ether, and, on keeping at 35° for a further 10 hr., gave a second fraction. The combined product was quickly dissolved in ethanol at 40°, filtered from dust, and reprecipitated with ether, giving *dimethyl*-1-*phenylethylsulphonium toluene*-p-*sulphonate* (40 g., 90%), m. p. 110—111°. The compound was analysed for toluene-*p*-sulphonate ion as described in the Analytical Methods section (Found: OTs^- 50·0. $C_{17}H_{22}O_3S_2$ requires OTs^- 50·6%).

From optically active methyl 1-*phenylethyl sulphide*. The method was essentially the same as above except that three fractions were isolated. From (−)-methyl 1-phenylethyl sulphide[7] (2·73 g.), having α_D^{20} −106·1°, and methyl toluene-*p*-sulphonate (6·93 g.), the following fractions were obtained: (*a*) 0·90 g., α_D^{20} −1·36 (*l* 4 dm., *c* 0·7976) in ethanol ($[\alpha]_D^{20}$ −42·6°); (*b*) 2·20 g., $[\alpha]_D^{20}$ −42·3°; and (*c*) 1·64 g., $[\alpha]_D^{20}$ −42·0° [combined yield, 4·74 g. (80% of theory); m. p. (not sharp) 105°, sintering above 95°]. The average molecular rotation in ethanol is therefore $[M]_D^{20}$ −143·6°. In acetonitrile the compound showed $[M]_D^{20}$ −131·6°.

1-*Phenylethylthiouronium Toluene*-p-*sulphonate*.—1-Phenylethylthiouronium chloride[1] (10·8 g.) and a slight excess of toluene-*p*-sulphonic acid (8·6 g.) were dissolved in ethanol (80 ml.). The solution was evaporated to dryness, the residue redissolved in ethanol, and the solvent again evaporated. This procedure was repeated twice to remove all hydrogen chloride. The product was washed with dry ether and recrystallised from acetonitrile containing 5% of ethanol, giving bushy needles of 1-*phenylethylthiouronium toluene*-p-*sulphonate*, m. p. 179°. Tests for chloride ion and acid were negative (Found: OTs, 48·3. $C_{16}H_{20}N_2O_3S$ requires OTs, 48·5%).

A small sample of (+)-1-phenylethylthiouronium chloride[1] was dissolved in water. One portion had $[\alpha]_D^{20}$ 30·9° (*l* 4 dm., *c* 0·0356). A second portion of the aqueous solution was evaporated, and the salt obtained was dissolved completely in acetonitrile and its rotation measured under the same conditions, giving $[\alpha]_D^{20}$ 32·0°. It is assumed that the molecular

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[7] Part IX, Hoffmann and Hughes, *J.*, 1964, 1244.

[8] Mahr, *Z. analyt. Chem.*, 1939, **117**, 93.

rotations of 1-phenylethylthiouronium chloride and 1-phenylethylthiouronium toluene-*p*-sulphonate are identical in acetonitrile, *i.e.*, they are independent of the anion, as established previously for water as solvent.[1]

TABLE 5.

Rate of elimination of dimethyl-1-phenylethylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°, followed titrimetrically.

Initially, $[\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2}]$ = 0·0705 mole l.$^{-1}$, and $[\mathrm{OTs^-}]$ = 0·1270 mole l.$^{-1}$; $[\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2}]$ is expressed in ml. of 0·02N-NaOH per 5·23 ml. solution.

Time (min.)	0	10	30	50	70	90	100
$[\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2}]$	18·22	17·91	17·34	16·72	16·19	15·60	15·14

*The Elimination of Dimethyl-*1*-phenylethylsulphonium Toluene-*p*-Sulphonate in Acetonitrile at* 59·8°.—*Titrimetric procedure.* The reaction solution was prepared from a weighed amount of the sulphonium salt and a standard solution of tetraethylammonium toluene-*p*-sulphonate in acetonitrile. Samples were quenched in ice-cold water and titrated immediately with 0·02N-sodium hydroxide. A sample run is shown in Table 5. $k_1 = 2{\cdot}81 \times 10^{-5}$ sec.$^{-1}$ was evaluated from the best straight line of a plot of the equation $\ln(a - x) = \text{Const.} - k_1t$. The values of k_1 for all runs are compiled in Table 1.

Polarimetric procedure. The sealed-tube technique was used. Timed samples were quenched, allowed individually to reach 20°, and their rotation measured in a polarimeter tube (l 2 dm.). A sample run is shown in Table 6.

TABLE 6.

Rate of elimination of dimethyl-1-phenylsulphonium toluene-*p*-sulphonate in acetonitrile at 59·8°, followed polarimetrically.

Initially, $[\mathrm{Me{\cdot}CHPh{\cdot}\overset{+}{S}Me_2OTs^-}]$ = 0·0581 mole l.$^{-1}$.

Time (min.)	0	30	40	60	100	120	180
α_t	1·56	1·47	1·46	1·39	1·29	1·24	1·11

$k_1 = 3{\cdot}14 \times 10^{-5}$ sec.$^{-1}$ was determined graphically from a plot of the equation $\ln \alpha_t = \ln \alpha_0 - k_1t$.

*The Reaction of Thiourea with Dimethyl-*1*-phenylethylsulphonium Toluene-*p*-sulphonate in Acetonitrile at* 59·8°.—*Product check.* Thiourea (0·784 g.) and dimethyl-1-phenylethylsulphonium toluene *p*-sulphonate (1·00 g.) were dissolved in acetonitrile (50 ml.) and kept at 59·8° for 2 hr. The solvent was pumped off, and the residue was washed with dry ether, dissolved in hot acetone (10 ml.) and acetonitrile (30 ml.), and filtered. After 6 hr. at room temperature, needles of 1-phenylethylthiouronium toluene-*p*-sulphonate separated. A mixed m. p. with a sample prepared by exchange of chloride for toluene-*p*-sulphonate ion (see above) gave no depression.

The ether washings were collected, concentrated, and analysed by gas–liquid chromatography. No methyl 1-phenylethyl sulphide was detectable.

Kinetic procedure. The sealed-tube technique was used. Samples (5 ml.) were partitioned between carbon tetrachloride (50 ml.) and water (50 ml.), and the aqueous layer was titrated for thiourea.

The measurements of rotation were carried out as described for the elimination. For the calculation of the polarimetric rate constants, eqn. (5) was employed (cf. Appendix); the molecular rotation of the reactant, *i.e.*, the sulphonium salt, was $[M_r]_D^{20}$ −132° in acetonitrile, corresponding to a molecular rotation of $[M_p]_D^{20}$ +192° for the thiouronium salt in acetonitrile. A sample run is shown in Table 3.

APPENDIX

The Second-order Polarimetric Rate Law. The reaction under consideration is:

$$\underset{(a-x)}{\mathrm{N}} + \underset{(b-x)}{(+)\text{-}\mathrm{RX}} \longrightarrow (-)\text{-}\underset{x}{\mathrm{RN}} + \underset{x}{\mathrm{X}}$$

(electrical charges are omitted for the sake of simplicity). The reaction obeys the integrated second-order rate law:

$$\frac{1}{a-b}\ln\frac{b(a-x)}{a(b-x)} = k_2t \tag{2}$$

The specific rotation is defined by $[\alpha] = 100\alpha/lc$, where α = observed rotation, c = concentration of optically active substance in g./100 ml. solution, and l = length of polarimeter tube in dm.; hence

$$\alpha = [\alpha]lc/100. \tag{3}$$

The concentrations (in moles $l.^{-1}$) of the species causing rotation are

$$[(+)\text{-RX}] = b - x = 10c_r/M_r, \text{ and } [(-)\text{-RN}] = x = 10c_p/M_p,$$

provided that every single bimolecular displacement proceeds with inversion of configuration. Here, M_r = molecular weight of reactant, (+)-RX, M_p = molecular weight of product, (−)-RN, c_r = concentration of (+)-RX, and c_p = concentration of (−)-RN.

The observed total rotation follows from eqn. (**3**):

$$\alpha = \{[\alpha_r]c_r + [\alpha_p]c_p\}l/100,$$

where $[\alpha_r]$ = specific rotation of reactant, (+)-RX, and $[\alpha_p]$ = specific rotation of product, (−)-RN. Therefore

$$100\alpha/l = [\alpha_r](b-x)M_r/10 + [\alpha_p]\,xM_p/10$$

Introducing molecular rotations which are, by definition:

$$[M_r] = [\alpha_r]M_r/100;\ [M_p] = [\alpha_p]M_p/100$$

one obtains:

$$10\alpha/l = [M_r](b-x) + [M_p]x$$

therefore,

$$x = m\alpha - n, \tag{4}$$

where $m = 10/l\{[M_p] - [M_r]\}$, and $n = [M_r]b/\{[M_p] - [M_r]\}$.

From (**4**) and (**2**) one obtains:

$$\frac{1}{a-b}\ln\frac{b}{a}\cdot\frac{\dfrac{a+n}{m}-\alpha}{\dfrac{b+n}{m}-\alpha} = k_2t \tag{5}$$

Alternatively, since $\alpha = \alpha_0$ for $x = 0$, and $\alpha = \alpha_\infty$ for $x = b$:

$$m = b/(\alpha_\infty - \alpha_0);\ \text{and}\ n = b\alpha_0/(\alpha_\infty - \alpha_0).$$

Therefore,

$$\frac{1}{a-b}\ln\frac{b}{a}\,\frac{\dfrac{a}{b}(\alpha_\infty-\alpha_0)+\alpha_0-\alpha}{\alpha_\infty-\alpha} = k_2t.$$

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WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON W.C.1.

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